Mayo Clinic Cancer Center

Phase II Trial of Lenvatinib in Metastatic or Advanced Pheochromocytoma and Paraganglioma

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*No waivers of eligibility allowed

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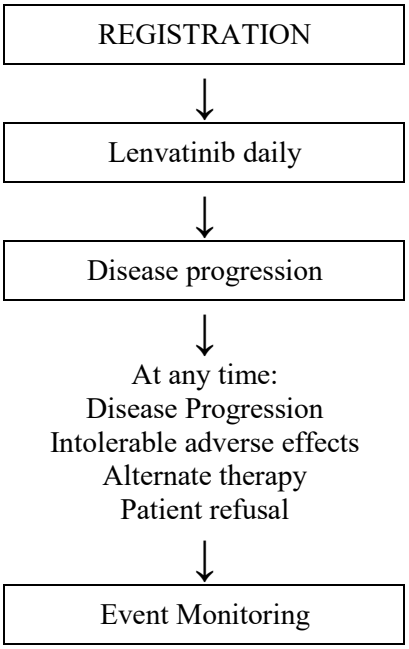
SCHEMA



Cycle = 28 days

Generic name: lenvatinib Brand name(s): Lenvima® Mayo Abbreviation: LENVATINIB Availability: Eisai Inc

1.0 BACKGROUND

1.1 Pheochromocytoma and Paraganglioma

1.11 Clinical epidemiology of pheochromocytomas and paragangliomas

Pheochromocytomas are tumors arising from chromaffin cells of the adrenal medulla. Paragangliomas on the other hand are tumors arising from extra-adrenal chromaffin cells of the sympathetic ganglia. Although paragangliomas are classically present in the head and neck (e.g. carotid bodies) they are also seen in the abdomen and pelvis and also sometimes in the thorax. Since both pheochromocytomas and paragangliomas arise from chromaffin cells they share many common clinicopathologic characteristics and treatment strategies, and for that reason they have historically been grouped and studied together.

Both pheochromocytomas and paragangliomas are rare tumors. The prevalence of adrenal pheochromocytomas is not precisely known and estimates range from 1-2 per 100,000 patients to 1.9% depending on the method of detection (Beard, Sheps et al. 1983; Stenstrom and Svardsudd 1986; Smythe, Edwards et al. 1992; McNeil, Blok et al. 2000). In general 10% of pheochromocytomas are malignant (Sinclair, Isles et al. 1987; Anderson, Blakeman et al. 1994; Goldstein, O'Neill et al. 1999; Omura, Saito et al. 2004). Extra-adrenal paragangliomas (paragangliomas) are less frequent, comprising 10-23% of catecholamine secreting tumors. Paragangliomas may also have a higher chance of being malignant, estimated at 20% (O'Riordain, Young et al. 1996; Bravo and Tagle 2003). Similarly, tumors with SDH-B mutation also have a higher probability of being malignant (Amar, Baudin et al. 2007). Histopathologically, however, it is impossible to distinguish benign from malignant pheochromocytomas or paragangliomas - and the diagnosis of malignant disease relies solely on the demonstration of tumors in non-chromaffin tissue (Eisenhofer, Bornstein et al. 2004; Tischler, Kimura et al. 2006).

1.12 Presentation and clinical course

The presentation of malignant pheochromocytomas and paragangliomas depends mainly on their location and their ability to secrete catecholamines. Pheochromocytomas generally have longer overall survival than paragangliomas. However, in patients with metastatic disease from either pheochromocytoma or paraganglioma, the overall survival appears similar (Ayala-Ramirez, Feng et al. 2011).

Adrenal or extra-adrenal tumors of the abdomen and thorax frequently secrete catecholamines. They present either as an intraabdominal or a thoracic mass, or they are discovered due to catecholamine secreting complications (i.e. secondary or malignant hypertension). On the contrary, paragangliomas arising in the head and neck sympathetic ganglia rarely secrete catecholamines. Their most frequent location is along the carotid body, but can also be seen in the middle ear, jugular bulb or along the vagus nerve.(Neumann, Bausch et al. 2002; Boedeker, Ridder et al. 2005). The clinical course of malignant pheochromocytomas is extremely heterogeneous (Sisson, Shulkin et al. 2006; Huang, Chung et al. 2007). While survival of patients with metastatic disease is approximately 5 years (Schlumberger, Gicquel et al. 1992; John, Ziegler et al. 1999; Eisenhofer, Bornstein et al. 2004); half the patients have an indolent course with survival up

to 20 years - while the other half presents with aggressive disease and survival limited to 1-3 years (Remine, Chong et al. 1974; Scott, Reynolds et al. 1982; van Heerden, Sheps et al. 1982; Lewi, Reid et al. 1985).

1.13 Surgical management of pheochromocytomas and paragangliomas

Surgical management of the disease, which is most frequently located in the abdomen and thorax, is the mainstay of treatment. Pheochromocytomas and paragangliomas can metastasize to the lung, liver, bone, lymph nodes and other locations. While surgical resection of metastatic lesions is desirable, this is not always possible. External beam radiation therapy has been successfully utilized to treat skeletal metastasis and other symptomatic disease. Other local modality treatments that have been employed successfully include radiofrequency ablation and hepatic artery embolization (Pacak, Fojo et al. 2001; Bianchi, Marchetti et al. 2009).

Issues pertaining to peri-operative management of the catecholamine secreting syndrome, which is frequently encountered in intrathoracic and intra-abdominal disease, is of the utmost importance, as hypertensive crisis can be triggered by surgical intervention. The surgical management of head and neck paragangliomas is also challenging, not usually due to catecholamine secretion, since this is infrequently encountered, but due instead to the location of the tumors along the carotid artery or the base of the skull. Treatment of localized paragangliomas of the head and neck requires a multidisciplinary approach in experienced centers and frequently requires involvement of surgery, tumor embolization, radiation therapy, and aggressive postoperative rehabilitation. Postoperative cerebrovascular accidents and cranial nerve abnormalities are a significant risk.

1.14 Systemic management of pheochromocytomas and paragangliomas

Metaiodobenzylguanidine (MIBG) is a norepinephrine analogue that concentrates in the adrenal medulla and some tumors of neuroectodermal origin. Tumor irradiation with therapeutic doses of 131I-MIBG has been used to treat non-head and neck paragangliomas and pheochromocytomas with partial and durable responses seen in a third of patients (Shapiro, Sisson et al. 1991; Loh, Fitzgerald et al. 1997; Rose, Matthay et al. 2003; Safford, Coleman et al. 2003). High dose 131I-MIBG with autologous stem cell rescue has also been used in selected patients with a tumor response rate of 22%, minor response of 34%, biochemical response rate up to 74% and 5 year OS of 64%, which is thought to be better than historical controls (Gonias, Goldsby et al. 2009). However, this approach can have significant hematologic and pulmonary toxicities - and responses are not durable. Consequently, radiotherapeutic MIBG is an option of last resort in many centers, especially as hematological toxicities can obviate or delay safe alternative administration of other proven-effective cytotoxic therapies.

Chemotherapy is generally reserved for recurrent/refractory or surgically inoperable progressive and/or symptomatic disease. Traditionally, a combination of cyclophosphamide, vincristine, and dacarbazine (CVD) has been used to treat these patients. One study has reported a tumor response rate 57% and biochemical response rate of 79% (cyclophosphamide 750 mg/m^2 and vincristine at 1.4 mg/m^2 on Day 1, and dacarbazine 600 mg/m^2 on Day 1 and 2, every 21 to 28 days) (Averbuch, Steakley et al. 1988). A long term follow up of that study

reported a median duration of response of 20 months, and a median overall survival of 3.3 years, broken down to 3.8 years for responders and 1.8 years for non-responders, a difference however which is not statistically significant likely due to the small number of patients (Huang, Abraham et al. 2008). Another single institution cohort with different chemotherapy regimens also showed similar results where median overall survival for responders was 6.4 years versus 3.7 years for nonresponders (Ayala-Ramirez, Feng et al. 2012). While treatment with CVD is generally well tolerated and can be administered for long periods of time, (Averbuch, Steakley et al. 1988; Huang, Abraham et al. 2008; Ayala-Ramirez, Feng et al. 2012) better systemic therapies are clearly needed, since the majority of patients ultimately succumb to their disease despite therapy.

There is relatively little experience with other chemotherapeutic regiments, generally limited to case reports or small series and include the combination cisplatin and 5-FU (Srimuninnimit and Wampler 1991), lomustine and 5-FU or capecitabine (Chrisoulidou, Kaltsas et al. 2007), carboplatin (Cairnduff and Smith 1986), etoposide and cisplatin (Mertens, Grignon et al. 1993; Chrisoulidou, Kaltsas et al. 2007), etoposide, carboplatin, vincristine, cyclophosphamide and doxorubicin (Jirari, Charpentier et al. 1999), modifications of CVD with doxorubicin (Patel, Winchester et al. 1995; Nakane, Takahashi et al. 2003; Ayala-Ramirez, Feng et al. 2012), MAID (Fitoussi, Debled et al. 1999), gemcitabine (Pipas and Krywicki 2000), paclitaxel (Kruijtzer, Beijnen et al. 2000), and temozolomide and thalidomide (Kulke, Stuart et al. 2006). At least 2 case series have reported very poor results with various chemotherapeutic regiments including cisplatin, etoposide, doxorubicin, cyclophosphamide and dacarbazine (Massey and Wallner 1992; Schlumberger, Gicquel et al. 1992). Recently, temozolomide (an oral prodrug of dacarbazine, an agent used in the CVD regimen above) was reported to have 33% partial response rate in a single center case series (Hadoux, Favier et al. 2014). Some targeted therapies have also been tried with imatinib mesylate being ineffective in 2 patients (Gross, Munter et al. 2006) and everolimus (RAD001) being also ineffective (Chrisoulidou, Kaltsas et al. 2007; Oh, Kim et al. 2012).

1.15 Pathophysiology and molecular characteristics of pheochromocytomas and paragangliomas

Pheochromocytomas and paragangliomas are highly hypervascular tumors as suggested by immunohistochemical studies of vascular density (Liu, Djuricin et al. 1996; Ohji, Sasagawa et al. 2001). Quantitative as well as architectural differences between benign and malignant tumors have been demonstrated (Liu, Djuricin et al. 1996; Favier, Plouin et al. 2002; Zielke, Middeke et al. 2002). In addition, several angiogenic growth factors and their receptors are overexpressed in malignant pheochromocytomas and paragangliomas (Zielke, Middeke et al. 2002; Salmenkivi, Heikkila et al. 2003; Favier, Igaz et al. 2012). From these, vascular endothelium growth factor (VEGF), the most potent factor of vascular development, is the most studied, and consistent overexpression at both the genetic and protein expression level has been demonstrated (Favier, Plouin et al. 2002; Zielke, Middeke et al. 2002; Salmenkivi, Heikkila et al. 2003). Several other key angiogenic factors are also overexpressed such as the hypoxia induced transcription factor EPAS1, and the endothelin receptors type A (ETA) and type B (ETB) (Favier, Plouin et al. 2002). Anti-VEGF antibodies have been shown to

inhibit angiogenesis in experimental pheochromocytomas (Zielke, Middeke et al. 2002).

The genetics of pheochromocytomas and paragangliomas are very complex (Dahia 2006). Adrenal pheochromocytoma is strongly associated with multiple endocrine neoplasia 2A and 2B, von Hippel-Lindau disease (VHL), and familial paraganglioma syndrome (Neumann, Bausch et al. 2002; Boedeker, Ridder et al. 2005), and is less commonly seen with neurofibromatosis type 1 (NF 1) or MEN 1. However, malignant adrenal pheochromocytoma is only infrequently seen in association with these genetic syndromes. On the contrary, extra-adrenal malignant paragangliomas are most frequently seen in association with familial paraganglioma syndrome (PGL), an autosomal dominant disorder presenting with paragangliomas in the head and neck, but also in the thorax, abdomen, and urinary bladder (Neumann, Bausch et al. 2002; Boedeker, Ridder et al. 2005). Most cases are caused by mutations in the succinate dehydrogenase gene (SDH) subunits B, C and D even in apparent "sporadic" cases. Extra-adrenal malignant paraganglioma is strongly associated with mutations of the B subunit of the gene (SDHB) (Amar, Baudin et al. 2007).

Global gene expression profiles of large series of sporadic pheochromocytomas and paragangliomas have generated 2 unique transcription signatures (Eisenhofer, Bornstein et al. 2004; Dahia, Ross et al. 2005). In the first cluster are mutations of the VHL, SDHB and SDHD genes known to be associated to VHL and PGL syndromes; in the second cluster are mutations in the RET and NF1 genes associated with the MEN syndromes. Both VHL and SDH mutations are known to dysregulate the hypoxia response (Dahia, Ross et al. 2005). VHL mutations lead to hypoxia inducible factor (HIF) mediated hypoxia response with activation of genes involved in angiogenesis, proliferation, cell survival and death (Semenza 2002; Semenza 2002). Mutations in the SDH gene, an intergral enzyme of the Krebs cycle, also lead to activation of HIF mediated hypoxia signals likely through accumulation of Krebs cycle intermediates, mitochondrial complex II inhibition, and HIF1a over-expression (Gimenez-Roqueplo, Favier et al. 2001; Gimenez-Roqueplo, Favier et al. 2002; Gottlieb and Tomlinson 2005; Pollard, Briere et al. 2005; Selak, Armour et al. 2005; Dahia 2006).

1.2 Kinase inhibitors as therapeutics in pheochromocytoma and paraganglioma

1.21 Sunitinib

Sunitinib is an oral multikinase inhibitor of VEGFR1-3, platelet-derived growth factor receptor (PDGFR)-α and -β, stem cell factor receptor (c-Kit), FLT3, and RET. Case studies and a case series from MD Anderson suggested benefit from this agent in patients with advanced metastatic pheochromocytomas and paragangliomas (Jimenez, Cabanillas et al. 2009; Joshua, Ezzat et al. 2009; Ayala-Ramirez, Chougnet et al. 2012; Jimenez, Rohren et al. 2013).

1.22 Pazopanib

A phase II trial was conducted at our institution (Bible, PI) to evaluate the effects of another oral multikinase inhibitor, pazopanib, in patients with metastatic pheochromocytomas and paragangliomas, initiated after observing promising results in patients with metastatic differentiated thyroid cancers including

Medullary thyroid cancer (Bible, Suman et al. 2010; Bible, Suman et al. 2014). Interim results indicated clinical efficacy in paraganglioma and pheochromocytoma, with some patients experiencing profound and sustained responses as illustrated below in Figure 1. Unfortunately, it has not been possible to continue or complete our pazopanib study due to sparse governmental funding for this initially NCI-sponsored trial. No kinase inhibitor has yet been subject to regulatory (FDA) approval for use in adrenal cancers, paragangliomas and pheochromocytomas.

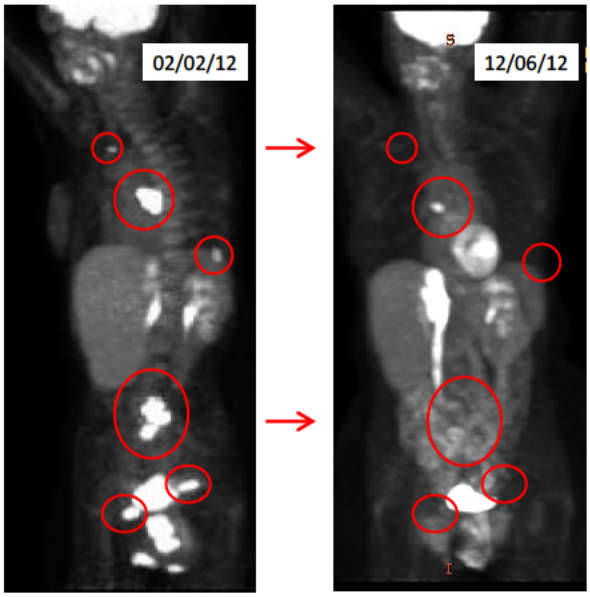


Figure 1. FDG-PET imaging showing near-complete response to pazopanib in a patient with widely metastatic paraganglioma who had experienced progressive disease despite prior cytotoxic chemotherapy (cyclophosphamide, vincristine, dacarbazine "CVD").

1.23 Lenvatinib

1.231 **Mechanism of action**

Lenvatinib is an orally available potent inhibitor of the split-kinase family of transmembrane growth factor receptors including Flt-1/VEGFR-1 and KDR/VEGFR-2 (Matsui, Yamamoto et al. 2008). Lenvatinib also inhibits vascular endothelial growth factor receptor 3, fibroblast growth factor receptor (FGFR)-1,2,3,4 and platelet-derived growth factor receptor beta tyrosine kinases(Glen, Mason et al. 2011; Tohyama, Matsui et al. 2014).

1.232 **Clinical efficacy**

The largest experience is reported in a phase 3, randomized, double-blind, multicenter study involving patients with progressive thyroid cancer that was refractory to iodine-131 (SELECT study) (Schlumberger, Tahara et al. 2015). The study enrolled 492 patients in 2:1 randomization scheme to lenvatinib or placebo. The primary end point was progression-free survival. Secondary end points included the response rate, overall survival, and safety. The median progression-free

survival was 18.3 months in the lenvatinib group and 3.6 months in the placebo group (hazard ratio for progression or death, 0.21; 99% confidence interval, 0.14 to 0.31; P<0.001). The overall response rate (ORR) was 64.8% in the lenvatinib group and 1.5% in the placebo group (P<0.001).

A phase 2 trial with medullary thyroid cancer (MTC) patients also showed promising results (Schlumberger, Jarzab et al. 2016). Fifty-nine patients with unresectable progressive MTC who demonstrated progressive disease within the prior 12 months received lenvatinib at 24 mg daily dose. Prior anti-VEGFR therapy was permitted. The primary endpoint was ORR. Lenvatinib ORR was 36% [95% confidence interval (CI), 24%-49%]. ORR was comparable between patients with (35%) or without (36%) prior anti-VEGFR therapy. Among responders, median time to response (TTR) was 3.5 months (95% CI, 1.9-3.7). Median progression-free survival (PFS) was 9.0 months (95% CI, 7.0-not evaluable).

Lenvatinib has not been concertedly yet investigated in paraganglioma and pheochromocytoma. We have, however, recently observed a very promising response to lenvatinib therapy in a patient with widely metastatic malignant paraganglioma noted as soon as after only two 24 mg doses of lenvatinib were administered (Jasim Sina 2016). In particular, clinical regression of adenopathy was observed beginning only 24h after initial dosing. Therapeutic response was so prompt and profound that it was associated with (easily remediable) features suggestive of early tumor lysis syndrome. Anatomical response in this patient is indicated in Figure 2 below. We have subsequently treated 3 more patients who have tolerated therapy but who have not yet undergone response assessment. All of these patients required careful close monitoring for adverse events including hypertension, including daily supervision via phone calls to provide dose modification advice and to assist in remediation of induced adverse effects.

There is no ongoing clinical trial assessing the efficacy of lenvatinib in patients with pheochromocytoma or paraganglioma. We now thus propose studying lenvatinib in these patient groups.

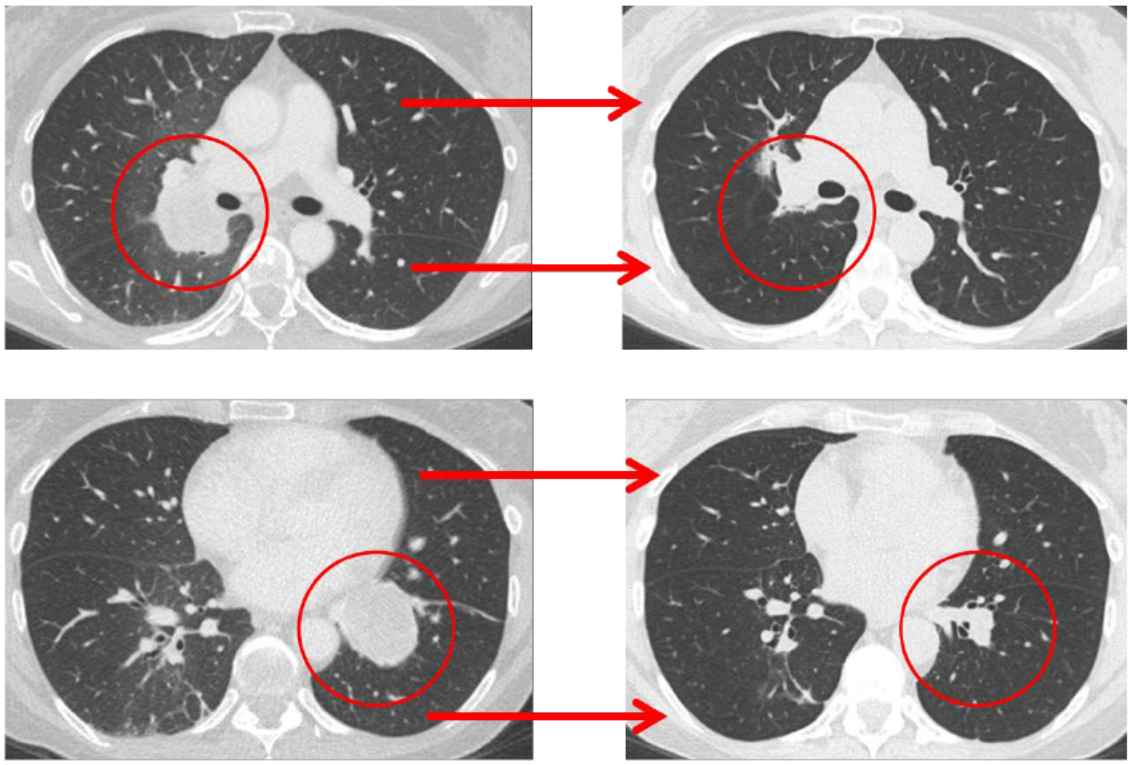


Figure 2. CT imaging showing response to lenvatinib in a patient with widely metastatic paraganglioma who had previously experienced disease progression despite prior cytotoxic ("CVD") and kinase inhibitor (pazopanib) therapy.

1.233 Safety profile

The phase 1 study in patients with solid tumors was conducted to determine the safety, tolerability and pharmacokinetics of three different regimens of oral lenvatinib, including continuous once daily dosing, and an intermittent schedule of twice daily dosing for 2 weeks of a 3 week cycle(Yamada, Yamamoto et al. 2011; Boss, Glen et al. 2012). For the phase 3 trial with differentiated thyroid cancer the 24 mg orally daily schedule was chosen. Pharmacokinetic analysis has demonstrated that lenvatinib is rapidly absorbed with maximum concentrations observed from 1 to 3 hours post-dose. The drug half-life is approximately 28 hours and steady state is achieved within 5 days. Food intake does not seem to affect the exposure much but absorption might be delayed (Shumaker, Aluri et al. 2014).

In the SELECT phase 3 trial (Schlumberger, Tahara et al. 2015), hypertension was most common observed adverse effect. It was seen in 68% of the enrolled subjects and grade ≥3 hypertension was seen in 42%. Other commons adverse effects included fatigue (59%), diarrhea (59%), decreased appetite (50%), decreased weight (46%), nausea

(41%), stomatitis (36%), palmo-plantar erythrodysesthesia (32%) and proteinuria (31%). With the limited experience of using lenvatinib in paraganglioma/pheochromocytoma patients, we postulate that some patients may experience profound and quick response to therapy that may result in mild tumor lysis-like syndrome (Jasim Sina 2016).

1.234 Quality -of –Life (QOL) Measurements for use of Lenvatinib

As described above kinase inhibitors have been used previously for the treatment of advanced paraganglioma and pheochromocytoma patients (Ayala-Ramirez, Chougnet et al. 2012). Ayala-Ramirez et al. have described the largest cohort of patients treated with sunitinib for advanced and progressive metastatic pheochromocytoma/ and paraganglioma, however, data on QOL was unfortunately missing

Clinical efficacy data on lenvatinib are derived from phase III, randomized, double-blind, multicenter study involving patients with progressive thyroid cancer that was refractory to iodine-131 (SELECT study) described above (Schlumberger, Tahara et al. 2015). This study, however, lacked the data on patient reported QOL during and after therapy.

Data on QOL with other kinase inhibitors are variable. For instance, there was no reported change in QOL in renal cell carcinoma treated with sorafenib (Bukowski, Cella et al. 2007). While mild but detectable impact on health-related quality of life was noticed in patients with thyroid cancer (Schlumberger 2013).

1.3 Rationale

Based on information presented above, agents implicated in inhibition of angiogenesis have been for long postulated as possible therapies for pheochromocytomas and paragangliomas (Jimenez, Cabanillas et al. 2009; Joshua, Ezzat et al. 2009; Ayala-Ramirez, Chougnet et al. 2012; Jimenez, Rohren et al. 2013). To date, however, no clinical trials of tyrosine kinase inhibitors have been undertaken in pheochromocytoma/paraganglioma.

In order to more rigorously assess the efficacy of tyrosine kinase inhibition in pheochromocytoma/paraganglioma, we plan to evaluate the tyrosine kinase inhibitor lenvatinib in these diseases in a phase II trial. Both patients with secretory and non-secretory pheochromocytoma or paraganglioma will be permitted in the study as there is no substantial evidence to suggest that these tumor types are expected to have a differential response to lenvatinib—but we will examine this possibility in exploratory analyses as feasible.

It is also not known whether patients with prior exposure to tyrosine kinase inhibitors may a have differential rate of response to lenvatinib compared to patients without such prior exposure. However, accumulating clinical evidence and experience in renal cell carcinoma and in thyroid cancer would suggest that tyrosine kinase inhibitors in general appear active even after prior exposure to anti-angiogenic therapy. Moreover, the patient response described in Figure 2 was observed in a patient who had previously received both CVD, and later, pazopanib therapy. As a result, and in consideration of the rarity of pheochromocytoma and paraganglioma requiring therapy as outlined in the clinical trial, we feel that there is greater disadvantage than advantage to developing independent patient cohorts based upon presence/absence of prior tyroisine kinase inhibitor therapy.

In assessing safety and efficacy of lenvatinib in patients with pheochromocytoma or paraganglioma, and given the wide range and seriousness of reported side effects, we plan to incorporate QOL data while treating our patient cohort in correlation with response outcomes. QOL data will be collected at baseline and every two months on therapy. We propose to use EQ-5D-5L descriptive questionnaire system designed by EuroQol group as well as FACT-G (Functional Assessment of Cancer Therapy-General).

The usual starting dose for Lenvatinib in DTC is 24 mg per day (Schlumberger, Tahara et al. 2015). Hypertension is one of the most common side effects seen with lenvatinib use. Hypertension and its complications are usual in catecholamine secreting tumors like paragangliomas and pheochromocytomas. Therefore, a reduced starting dose of 20 mg daily is being proposed for this trial.

1.4 Hypotheses

Hypothesis 1: Lenvatinib treatment of patients with advanced malignant pheochromocytoma and paraganglioma may lead to attenuated tumor growth and/or tumor regression (as defined by RECIST criteria – see Section 11.0).

Hypothesis 2: Lenvatinib-induced changes in plasma and urinary catecholamine and/or metanephrine levels in patients with advanced, catecholamine secreting pheochromocytoma and paraganglioma may be observed and be predictive of patient objective response to lenvatinib therapy (per RECIST criteria – see Section 11.0).

Hypothesis 3: Somatic mutational status (presence of SDHD, SDHB, RET, VHL, neurofibromatosis type-1 in archival tumors) may predict response to lenvatinib therapy.

Hypothesis 4: Germline mutational status (detection of SDHD, SDHB, RET, VHL, neurofibromatosis type-1 in patient's PBMCs) may predict response to lenvatinib therapy.

Hypothesis 5: There is no significant deleterious net change in patient reported quality of life during lenvatinib therapy.

2.0 OBJECTIVES

2.1 Primary objective

To determine the anti-tumor activity of lenvatinib (overall response rate; ORR) in patients with metastatic or advanced unresectable pheochromocytomas and paragangliomas

2.2 Secondary objectives

2.21 To determine progression-free survival (PFS)

2.22 To determine overall survival (OS)

2.23 To determine duration of tumor response

2.24 To determine safety and tolerability of lenvatinib

2.25 To assess patient reported quality of life using EQ-5D-5L and FACT-G

2.3 Correlative objectives

2.31 For patients with secretory tumors,

2.311 To examine changes in plasma metanephrine levels and urinary catecholamine and/or metanephrine levels.

2.312 To examine whether lenvatinib-induced changes in plasma metanephrines and urinary catecholamine and/or metanephrine levels during the first cycle of treatment may be associated with objective tumor response.

2.32 To examine associations between tumor response and somatic mutational status in archived tumors, or germline mutational status (presence of SDHD, SDHB, RET, VHL, neurofibromatosis type-1).

3.0 ELIGIBILITY

3.1 Inclusion Criteria

3.11 Age ≥18 years.

3.12 Histologically or cytologically confirmed malignant secretory or non-secretory pheochromocytoma or paraganglioma that is unresectable and deemed inappropriate for alternative local regional therapeutic approaches.

3.13 Measurable disease as defined in Section 11.0.

3.14 ECOG Performance Status (PS) 0, 1, or 2 (Appendix I).

3.15 Life expectancy >24 weeks.

3.16 The following laboratory values obtained ≤14 days prior to registration.

- Absolute neutrophil count (ANC) ≥1500/mm^3
- White blood cell (WBC) count ≥3,000/mm^3
- Platelet count ≥100,000/mm^3
- Hemoglobin ≥9.0 g/dL (5.6mmol/L)
  NOTE: Transfusions are not allowed ≤7 days prior to registration
- Total bilirubin ≤1.5 X upper limit of normal (ULN)
  (or total bilirubin ≤3.0 X ULN with direct bilirubin ≤1.5 X ULN in patients with well-documented Gilbert's Syndrome)
- Aspartate transaminase (AST/SGOT) ≤2.5 X ULN
- Creatinine ≤1.5 X ULN
- Urine protein/creatinine ratio ≤1 OR 24-hour urine protein <1.5 gram

3.17 Negative pregnancy test done ≤7 days prior to registration, for women of childbearing potential only.

3.18 Blood pressure (BP) <150 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 <150/90 mmHg.

NOTE: All patients with secretory pheochromocytoma or paraganglioma are REQUIRED to: 1) be evaluated in consultation by a hypertension specialist with specific experience in the management of hypertension in the setting of catecholamine-secreting tumors (usually an endocrinologist, nephrologist, or a cardiologist), and in the setting of hormone-associated hypertension) receive α- and β-adrenergic blockade for at least 7-14 days prior to initiation of lenvatinib (see Appendix IV for guidelines regarding proper α- and β-blockade). The hypertension specialist of record for each patient should be committed to closely following the patient during the clinical study with evaluation by said specialist required at Cycle 1 and 2 and thereafter on an as needed basis. Please see Appendix IV for guidelines on hypertension evaluation, follow up and management.

Please note that this is a critical patient safety issue and that no exceptions to this approach are permitted.

3.19a Provide written informed consent.

3.19b Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.19c Ability to complete questionnaire(s) by themselves or with assistance.

3.2 Exclusion Criteria

3.21 Any of the following because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects:
- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.22 Chemotherapy/systemic therapy, radiotherapy, immunotherapy or surgery ≤21 days prior to registration or kinase inhibitor therapy ≤14 days prior to registration or failure to recover from toxicities (to Grade 1 or below) from treatment.

NOTE: Concurrent therapy with octreotide is allowed providing that tumor progression on this therapy has been demonstrated. Concurrent therapy with bisphosphonates (e.g. zoledronic acid) or denosumab is also allowed.

NOTE: An unlimited number of prior chemotherapeutic or biologic therapies for malignant pheochromocytoma or paraganglioma is permitted. This includes prior anti-angiogenesis therapies such as tyrosine kinase inhibitors.

3.23 Active or uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.24 Receiving any other investigational agent

3.25 Current use of warfarin for any reason.
NOTE: If patient can be safely transitioned to another anticoagulant, they may be eligible provided other criteria are satisfied.

3.26 Any of the following:
- QTc prolongation (defined as a QTc interval ≥500 msecs)
- LVEF < institutional LLN
- frequent ventricular ectopy
- evidence of ongoing myocardial ischemia

3.27 Receiving any medications or substances with risk of torsades de pointes (see Appendix V for partial list).
NOTE: Medications or substances with known Risk of Torsades de Pointes are prohibited. Consult pharmacist for review if needed.

3.28 Known active and/or untreated brain metastases.

3.29a Known severe allergic or other prohibitive reactions to other tyrosine kinase inhibitors (TKI).

3.29b Prior treatment with lenvatinib.

3.29c Any of the following conditions:
- Active peptic ulcer disease
- Inflammatory bowel disease (e.g., ulcerative colitis, Crohn's disease) or other

gastrointestinal conditions which increase the risk of perforation
- History of new abdominal fistula, gastrointestinal perforation or intra-abdominal abscess ≤84 days prior to registration
  NOTE: Enrollment of patients with chronic/canalized fistulous tracts (present for >84 days) is allowed.
- Serious or non-healing wound, ulcer, or bone fracture
- History of familial QTc prolongation syndrome

3.29d Any of the following conditions ≤6 months prior to registration:
- Cerebrovascular accident (CVA) or transient ischemic attack (TIA)
- Serious or unstable cardiac arrhythmia
- Admission for unstable angina or Myocardial infarction
- Cardiac angioplasty or stenting
- Coronary artery bypass graft surgery
- Pulmonary embolism, untreated deep venous thrombosis (DVT) or DVT which has been treated with therapeutic anticoagulation ≤30 days
- Arterial thrombosis
- Symptomatic peripheral vascular disease

3.29e Other active malignancy ≤2 years prior to registration.
EXCEPTIONS: Non-melanotic skin cancer or carcinoma-in-situ of the cervix.
NOTE: If there is a history of prior malignancy, they must not be receiving other specific treatment for their cancer.
NOTE: Adjuvant anti-estrogen/hormonal therapy for breast cancer is allowed

4.0 STUDY CALENDAR

4.1 Test Schedule

Tests and procedures[1]	≤28 days prior to registration	≤14 days prior to registration	≤7 days prior to registration	Active Treatment: Cycle 1 D1	Cycle 1 D3	Cycle 1 D10[2]	Prior to Day 1 of subsequent cycles[3]	Every 2 months	End of Treatment
Window:							±3 days	±7 days	±14 days
Clinical Procedures									
Vital signs, history (including personal/family history for prolonged QTc) and exam, weight, PS		X		X	X	X	X		X
Height		X							
Review of concurrent medications[4]		X					X		
Pregnancy test[5]			X						
Blood pressure monitoring[6]		X		X	X	X	X		
Adverse event assessment		X		X	X	X	X		X
Consultation with endocrinologist, cardiologist, or nephrologist for blood pressure management		X					X		
Hematology: CBC/diff[7]		X					X		X
Chemistry Panel[8]		X					X		X
TSH		X					X		
24 hr urine catecholamine and metanephrines		X					X		
Plasma fractionated metanephrines		X					X		
Urinalysis[9]		X					X		
Urine protein/creatinine ratio		X					X		
Genetic counseling and testing at discretion of patient and counselor[10]	X								

[1] All tests and procedures are clinically indicated, unless noted with an R to indicate funding by research

[2] May be omitted at discretion of treating provider and replaced with telephone call contact.

[3] If patient is tolerating treatment well, return visits may be performed over the phone for non-imaging cycles (starting with cycle 3, 5, 7 etc.). During these phone visits the patient status, treatment information, and Adverse Event Assessments must be assessed and recorded. Labs may be done locally and transmitted to Mayo Clinic.

[4] Concurrent/concomitant medications are reviewed every cycle. Only requested medications are recorded in the study case report forms.

[5] For women of childbearing potential only. Must be done ≤7 days prior to registration

[6] Note: 1) daily monitoring of blood pressure is REQUIRED and must be recorded in patient diaries throughout the entire duration of therapy; 2) any systolic BP >150 mm Hg and/or diastolic BP >100 mm Hg must be brought to the attention of treating provider <24h after noted; 3) any systolic BP >200 mm Hg and/or diastolic BP >110 mm HG should prompt immediate cessation of lenvatinib therapy maintained until remediation to <150 mm Hg systolic is accomplished.

[7] Must include: hemoglobin (hgb), MCV, leukocyte count, neutrophils (ANC), monocyte count, lymphocyte count, and platelet count (PLT)

[8] AST, alk phos, total bilirubin (direct if TBili is elevated), creatinine (and calculated creatinine clearance), albumin, glucose, calcium (Ca), sodium (Na), potassium (K), magnesium (Mg), phosphorus (P), uric acid, LDH,

[9] Urinalysis for protein, glucose, blood

[10] Only if not performed previously (optional); can be performed anytime during study. Testing should include SDHD, SDHB, RET, VHL, neurofibromatosis type-1 genes.

Tests and procedures[1]	≤28 days prior to registration	≤14 days prior to registration	≤7 days prior to registration	Active Treatment: Cycle 1 D1	Cycle 1 D3	Cycle 1 D10[2]	Prior to Day 1 of subsequent cycles[3]	Every 2 months	End of Treatment
Window:							±3 days	±7 days	±14 days
PET-CT or CT (Chest, Abdomen and pelvis), or MRI abdomen/MRI neck, if needed	X							X	X[11]
ECG		X					X[12]		
2D-ECHO	X								
Blood or Tissue- Analysis performed by Research Lab									
Optional tissue sample for correlatives (see Section 17.0)[13]			X						
Optional research blood will be collected under IRB 13-005838[14]		X							
Quality of Life assessment									
Patient Questionnaire Booklet: EQ-5D-5L/FACT-G			X[15]				X		

Cycle = 28 days

4.2 Event Monitoring/Survival Follow-up

	Event Monitoring Phase[1]				
	q. 3 months until PD	At PD	After PD q. 6 months	Death	New Primary
Event Monitoring	X	X	X	X	At each occurrence

1. If a patient is still alive 5 years after registration, no further follow-up is required.

[11] Repeat imaging needed within 4 weeks of documentation of disease recurrence per RECIST (see Section 11.0).
[12] Only for Cycle 2 and 3
[13] Request archived tissue if patient has consented to release of tissue.
[14] Contact [redacted] for specifics.
[15] Baseline booklet must be completed after patient has consented and prior to first treatment

5.0 STRATIFICATION FACTORS: None

6.0 REGISTRATION PROCEDURES

6.1 Registration

6.11 Mayo Clinic Sites

To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the remote registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at [redacted] between the hours of 8 a.m. and 5:00 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page [redacted] 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 MCCC 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 registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [redacted]. If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.12 Non-Mayo Clinic sites

To register a patient, fax [redacted] a completed eligibility checklist to the Mayo Clinic Cancer Center (MCCC) Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

6.2 Verification

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

- IRB approval of the study
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.3 Documentation of IRB approval

Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office (fax: [redacted]. 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.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.4 Correlative studies

An optional correlative component is part of this study. There will be an option to select if the patient is to be registered onto this component (see Section17.2).

- Patient has/has not given permission to use his/her tissue sample for research testing

At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her sample(s) for future research of cancer at Mayo.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
- Patient has/has not given permission for MCCC to give his/her sample(s) to researchers at other institutions.

6.5 Treatment on protocol

Treatment on this protocol must commence at enrolling institution under the supervision of a medical oncologist or endocrinologist

6.6 Treatment start

Treatment cannot begin prior to registration and must begin ≤14 days after registration.

6.7 Pretreatment

Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.8 Baseline symptoms

All required baseline symptoms (see Section 10.0) must be documented and graded.

6.9a Study drug availability

Study drug is available on site for this patient.

6.9b Booklet availability

Patient questionnaire booklet is available on site for this patient; copies are not acceptable for this submission.

6.9c Consultation with hypertension specialist

A hypertension specialist (endocrinologist, or cardiologist, or nephrologist) at enrolling institution has seen this patient and confirms the patient is a suitable candidate for this study ≤14 days prior to registration.

7.0 PROTOCOL TREATMENT

7.1 Treatment Schedule

Treatment will be administered on an outpatient basis. Reported AEs and potential risks are described in Sections 9 and 10. No other investigational or commercial agents or therapies may be administered with the intent to treat the subject's malignancy.

Subjects will receive lenvatinib on an outpatient basis at a dose of 20 mg/day (two 10-mg capsules; dose modification will be accomplished by combining 10-mg and 4-mg capsules as necessary). Subjects are instructed to swallow capsules once a day (preferably in the morning) with or without food with about 1 cup (240 mL) water. Capsules should be swallowed whole; they must not be chewed, broken, or crushed. Treatment continues until progression, excessive toxicity, or patient refuses to continue study medication. Missed and/or withheld doses of lenvatinib (whether intentional or not) are to be reported in the Medication Diary, but not made up.

- Patients will be provided with a Medication Diary for lenvatinib (Appendix II). Patient should bring the diary back at the end of each cycle of treatment.
- Any blood pressure medications patients is already taking or started during the treatment period should be listed in the CRF.

Study drug lenvatinib will be administered at a dose of 20 mg daily by mouth on a 28 day cycle for a maximum of 5 years.

7.11 Treatment medication table

Agent	Dose Level	Route	Day	ReRx
Lenvatinib	20 mg daily	oral	1-28	Q4w

7.2 Criteria for Continuing Treatment

Subjects 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, lenvatinib will be held or the dose adjusted according to the dose modification criteria stated in Section 8.

To continue therapy, subjects must meet the following criteria:

- Absolute neutrophil count (ANC) $\geq$1,000/mm^3 (1 X 10^9/L),
- Platelet count $\geq$50,000/mm^3 (50 X 10^9/L),
- Blood pressure, if elevated, should be controlled with antihypertensive medication(s),
- Grade $\leq$3 proteinuria or (urinary protein $\leq$3.5 g/24 hrs),
- QTc interval <500 msec,
- hypokalemia or hyperkalemia $\leq$Grade 1 or within institutional limits of normal,
- hypocalcemia or hypercalcemia is $\leq$Grade 2,
- hypomagnesemia or hypermagnesemia is $\leq$Grade 2; Medical judgment should be exercised in deciding whether an AE of greater than or equal to grade 2 requires dose interruption or modification (see Section 8.0 for Dose Modification guidelines).

7.3 Self-administration statement

Patients can be instructed in administration techniques and granted treatment independence with nursing staff approval.

7.4 Return to consenting institution

For this protocol, the patient must return to the consenting institution for evaluation at least every 28 days during treatment.
NOTE: If patient is tolerating treatment well, return visits to Mayo Clinic may be reduced to once every 56-60 days at PI discretion. Required laboratory testing may be done locally and transmitted to Mayo Clinic.

7.5 Treatment by local medical doctor

Treatment by local medical doctor (LMD) is not allowed and patients will be treated only at Mayo clinic.
NOTE: For patients who are tolerating treatment well, safety assessments including labs may be done locally and transmitted to Mayo Clinic at PI discretion.

7.6 Duration of Therapy

In the absence of treatment delays due to adverse event(s) or intolerable toxicity, treatment will continue for a maximum of 5 yearsor until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable AE(s),
- Subject decides to withdraw from the study, or
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator.
- Patients who discontinue treatment for any of above reasons will proceed to event monitoring.

7.7 Duration of follow up

- If a patient discontinues treatment due to progression within 5 years of registration, submission of an event monitoring form is required every 6 months thereafter until death or a maximum of 5 years post-registration.
- If a patient discontinues treatment due to reasons other than progression or death within 5 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 5 years post-registration.
- If a patient is deemed ineligible after receiving treatment, all study-related materials including biospecimen data up until the point of confirmation of ineligibility must be submitted. The patient will proceed to event monitoring phase per Section 4.2 of the protocol.
- If a patient does not receive treatment, On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further follow-up information is necessary.

8.0 DOSAGE MODIFICATIONS

Strictly follow the modifications in Table 8.1 for the first two cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

8.1 Dose Modification Table

If patient is able to tolerate the starting dose of 20 mg daily for the first 2 cycles and if patient shows stable disease (SD) or objective response (OR) by RECIST 1.1 (see Section 11.0), then dose can be escalated to 24 mg daily at the physician's discretion.

Otherwise follow the dose modifications below:

Dose Level	Lenvatinib
+1	24 mg daily
0*	20 mg daily
-1	14 mg daily
-2	10 mg daily

*Dose level 0 refers to the starting dose.

ALERT: ADR reporting may be required for some adverse events (See Section 10.0)

8.2 Dose Modifications Based on Adverse Events

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Blood and lymphatic system	Anemia* Grade ≥3	lenvatinib	Hold treatment until event is ≤Grade 2; reduce one dose level If no recovery to ≤Grade 2 or recurrent Grade 3 or 4, discontinue lenvatinib and enter event monitoring. However, if the subject is benefiting from therapy, contact the PI to discuss course of action.
Cardiac disorders	Acute coronary syndrome Grade ≥3		Discontinue lenvatinib and enter event monitoring
Gastrointestinal disorders	Diarrhea Grade ≥3		Grade 3, hold lenvatinib until it resolves to Grade 1 or less and resume at one reduced dose level Grade 4, discontinue lenvatinib and enter event monitoring
	Nausea/vomiting Grade ≥3 despite antiemetics		Grade 3, hold lenvatinib until it resolves to Grade 1 or less and resume at one reduced dose level Grade 4, discontinue lenvatinib and enter event monitoring

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Gastrointestinal disorders	Weight loss Grade ≥3	lenvatinib	Discontinue lenvatinib and enter event monitoring However, if the subject is benefiting from therapy, contact the PI to discuss course of action
General disorders and administration site conditions	Fatigue Grade ≥2		Grade 2, hold lenvatinib until it resolves to Grade 1 or less and resume at one reduced dose level Grade 3, discontinue lenvatinib and enter event monitoring
Endocrine disorders	Hypothyroidism Grade ≥3		Grade 3 and 4, hold lenvatinib and replace with levothyroxine until TSH is normalized and resume lenvatinib at same dose
Investigations	Neutrophil count decreased Grade ≥3		Hold treatment until event is ≤Grade 2; reduce one dose level If no recovery to ≤Grade 2 or recurrent Grade 3 or 4, discontinue lenvatinib and enter event monitoring However, if the subject is benefiting from therapy, contact the PI to discuss course of action
	Platelet count decreased Grade ≥3		Hold treatment until event is ≤Grade 2; reduce one dose level If no recovery to ≤Grade 2 or recurrent Grade 3 or 4, discontinue lenvatinib and enter event monitoring However, if the subject is benefiting from therapy, contact the PI to discuss course of action
Infections and infestations	Any infection Grade ≥3		Hold lenvatinib; resume when AE is Grade 1 or less
Metabolism and nutrition disorders	Tumor lysis Grade ≥3		Hold lenvatinib until it resolves and resume at one reduced dose level
Renal and urinary disorders	Proteinuria Grade ≥3		Grade 3, hold lenvatinib until it resolves to Grade 2 or less and resume at one reduced dose level (see Section 8.33) Grade 4, discontinue lenvatinib and enter event monitoring
Skin and subcutaneous tissue disorders	Palmoplantar erythrodysesthesia Grade ≥2		Grade 2, hold lenvatinib until it resolves to Grade 1 or less and resume at one reduced dose level Grade 3, discontinue lenvatinib and enter event monitoring

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Skin and subcutaneous tissue disorders	Maculopapular-rash Grade ≥2	lenvatinib	Grade 2, hold lenvatinib until it resolves to Grade 1 or less and resume at one reduced dose level Grade 3, discontinue lenvatinib and enter event monitoring
Vascular disorders	Hypertension Grade ≤3		Dose adjust and/or hold lenvatinib and continue to manage per Appendix IV; consultation with expert recommended Grade 4, discontinue lenvatinib and enter event monitoring
Other non-hematologic adverse events (excluding alopecia)	Grade ≥3		Grade 3, hold lenvatinib until AE resolves to Grade 1 or less and resume at one reduced dose level Grade 4, discontinue lenvatinib and enter event monitoring

NOTE: If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered for that entire subsequent cycle. If that cycle is completed with no further adverse events >Grade 2, then the dose may be increased, at the investigator's discretion, one level at a time, in the following cycles.

NOTE: Adverse events requiring a dose-reduction step for any or all drugs beyond the two dose-reduction steps (levels –1 and –2) will be at the discretion of the treating physician, if the decision is made for the patient to be kept on study. These dose reductions must be clearly recorded in reported clinical data.

8.3 Management of Specific Adverse Events

8.31 Electrolyte abnormalities with or without tumor lysis syndrome

Management of Grade 2 or higher hypokalemia and hyperkalemia, management of Grade 3 or higher hypomagnesemia and hypermagnesemia, Grade 3 or higher hypophosphatemia and Grade 3 or higher hypocalcemia and hypercalcemia.

Management of Abnormal Laboratory Assessments	
Hypokalemia or hyperkalemia ≥Grade 2 Hypocalcemia or hypercalcemia ≥Grade 3 Hypophosphatemia ≥Grade 3 or Hypomagnesemia or hypermagnesemia ≥Grade 3	• Hold treatment and ECG must be performed • Laboratory values should be corrected as soon as possible in a manner consistent with good medical judgment • Lenvatinib may be re-administered when – hypokalemia or hyperkalemia is Grade 1 or within institutional normal limits – hypocalcemia or hypercalcemia is ≤Grade 2 – hypophosphatemia is ≤Grade 2 – hypomagnesemia or hypermagnesemia is ≤Grade 2

8.32 Management of QTc Prolongation

Table below outlines the management of QTc prolongation of 500 msec and management of QTc prolongation of 60 msec or more from baseline.

Management of QTc Prolongation	
If ECG reveals an increase in the QTc to >500 msec or an increase in the QTc by at least 60 msec from baseline	Hold lenvatinib and repeat ECG ≤7 days and before re-administration of lenvatinib
If repeat ECG shows QTc interval is ≥500 msec	Discontinue lenvatinib and patient enters the event monitoring
If on repeat ECG, QTc remains at least 60 msec longer than baseline but is <500 msec	Consider discontinuing lenvatinib or increase monitoring after discussion with PI

8.33 Management of Proteinuria

If, at any time, a subject has a urine protein/creatinine ratio greater than 1, a 24 hour urine collection must be performed. If a subject develops the nephrotic syndrome, treatment must be discontinued.

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

Management of Proteinuria	
UPC >1and <3	Obtain 24-hr urine protein and if <3.4 g, continue at current dose and monitor as clinically indicated
UPC ≥3 or 24-h urine protein ≥3.5g	Step 1: Hold lenvatinib Step 2: Weekly UPC or 24-hr urine protein monitoring until UPC is <3 or 24-hr urine protein is <3 grams Then restart lenvatinib one dose level less Step 3: If UPC >3 or 24-h urine protein ≥3g recurs, repeat Steps 1 and 2 Step 4: If UPC ≥3 or 24-hr urine protein ≥3 recurs and the lenvatinib dose can no longer be reduced, discontinue lenvatinib and remove subject from study

8.34 Management of Subjects with Elevations in AST, ALT and/or Bilirubin

Management of AST, ALT and/or Bilirubin Elevations	
Isolated AST/ALT elevations between 3X ULN and 8X ULN	Continue lenvatinib, but monitor weekly until AST/ALT returns to ≤2.5 or baseline
AST/ALT >8 X ULN	Hold lenvatinib until AST/ALT returns to ≤2.5 X ULN or baseline If the potential benefit of reinitiating lenvatinib treatment is considered to outweigh the risk for hepatotoxicity, then consider reintroducing lenvatinib at one dose level less and measure serum liver tests weekly for 8 weeks only after discussion with the PI If AST/ALT elevations >3 X ULN recur, then lenvatinib should be permanently discontinued and patient enters event monitoring phase
AST/ALT >3 X ULN and	Discontinue lenvatinib and enter event monitoring phase

concurrent direct bilirubin elevations >2 X ULN	
Mild indirect hyperbilirubinemia, known or suspected Gilbert's syndrome, and elevation in ALT >3 X ULN	Continue lenvatinib, but monitor weekly until ALT returns to Grade 1 (NCI CTCAE v4) or baseline

8.35 Management of Other Adverse Events

CTCAE SOC	Adverse Event	Grade	Treatment Modification
Respiratory, thoracic and mediastinal disorders	Broncho-pulmonary hemorrhage	Grade 1	Hold therapy if hemoptysis is in excess of 2.5 mL (1/2 teaspoon) per day until resolved, otherwise maintain current dose.
		Grade 2	Hold lenvatinib unless resolved to ≤Grade 1; reduce dose to next lower dose level, and continue treatment. If Grade 2 or greater hemorrhage/ bleeding recur following dose reduction, discontinue lenvatinib and patient enters event monitoring phase
		Grades 3 or 4	Discontinue lenvatinib and patient enters event monitoring study phase
Vascular disorders	Thrombo-embolic event	Grade 1	No interruption in treatment; maintain current dose
		Grade 2, 3	Hold lenvatinib until subject is receiving a stable dose of Low Molecular Weight Heparin (LMWH). Concurrent warfarin will not be allowed, if patient needs warfarin, stop the study drug and enter event monitoring. Treatment may resume during the period of full-dose anticoagulation if all of the following criteria are met: • The subject must be have been treated with an anticoagulant at the desired level for at least one week • The subject must not have had a Grade 3 or 4 or significant Grade 2 hemorrhagic event while on anticoagulant Subject should be monitored as clinically indicated during anticoagulation treatment and after resuming study treatment.
		Grade 4 or pulmonary embolus	Discontinue lenvatinib and patient enters event monitoring

9.0 ANCILLARY TREATMENT/SUPPORTIVE CARE

9.1 Full supportive care

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.2 Blood products and growth factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the Journal of Clinical Oncology, Vol 24, No 18 (June 20), 2006: pp. 2932-2947.

9.3 Antiemetics

Antiemetics may be used at the discretion of the attending physician.

9.4 Diarrhea

Diarrhea could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of Grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

9.5 Hypertension

Please see Appendix IV for guidelines regarding management of hypertension. They should be seen by an expert in management of hypertension before they are started on the study drug. During the therapy patients will experience worsening of hypertension especially the secretory tumors and repeat consultation with the expert in recommended for concurrent management.

9.6 Tumor lysis syndrome

Patients may experience tumor lysis-like syndrome if they get profound, rapid response to therapy. Tumor lysis is characterized by hyperkalemia, hypocalcemia, elevated uric acid, renal failure and ECG abnormalities. Please see Section 8.2 for dose modification. If there are changes in the electrolytes they should be managed as per the Section 8.31. If there is suspicion of tumor lysis or tumor lysis-like syndrome then therapy should be held, Allopurinol 300 mg daily should be instituted. EKG, laboratory examination, history and physical examination should be repeated in 1 week. If EKG and laboratory values have normalized, and patient is clinically stable then therapy can be re-instituted.

9.7 Precautions/Warnings

9.71 Drug-Drug Interactions

There have been few completed human studies, at present, specifically evaluating drug-drug interactions with lenvatinib. The weak inhibitory effect on CYP P450

enzymes (in vitro) exhibited by lenvatinib suggests a low risk of lenvatinib interference with the pharmacokinetics of other drugs coadministered in usual clinic practice (Shumaker, Aluri et al. 2015). However, preliminary preclinical studies identify CYP3A4 as an important enzyme responsible for human hepatic metabolism of lenvatinib. Caution should be exercised when administering drugs metabolized by CYP3A4 or drugs that are inhibitors or inducers of CYP3A4 (including herbal supplements or grapefruit), as administration of such drugs could affect the metabolism of lenvatinib. Please refer to Appendix III.
Other medications have potential to increment risks to patients when combined with lenvatinib. These include: i) agents that increase bleeding risks (Warfarin is specifically prohibited, whereas heparin and NSAIDS/anti-platelet agents should be used with caution), and ii) bisphosphonates and denosumab (as there is potential that combined therapy with lenvatinib may further increase the risks of jaw osteonecrosis and other bone liabilities due to combined antiangiogenic effects).

9.72 Hypertension

Hypertension is an important AE associated with lenvatinib (Schlumberger, Tahara et al. 2015). Frequent blood pressure (BP) monitoring is important in subjects receiving lenvatinib. In addition patients with secretory pheochromocytomas and paragangliomas are at risk for hypertension and hypertensive crisis by virtue of disease. Patients will be provided with a diary in which to record their daily BP readings (see Appendix VI) for fist three cycles. Daily readings should be taken. If the systolic reading is >140 mmHg OR the diastolic reading is >90 mmHg OR any combination of elevated systolic and diastolic readings, patients will be instructed to retake their blood pressure within 1-4 hours. If a second consecutive reading is elevated patient 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). In addition, expert consultation and follow-up for patients with secretory tumors will be required prior to enrollment, and during the study. Experience to date suggests that increases in BP may occur following dosing with lenvatinib 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 holding therapy with lenvatinib. Considering the potential of this adverse event we will monitor patients closely in the initial weeks with frequent measurement of blood pressure in clinic on Day 1, 3 and 10. Recommendations for hypertension monitoring and management are presented in Appendix IV.

9.73 QTc prolongation and Torsades de Pointes

QTc prolongation was not seen in the healthy volunteers studied with lenvatinib (Shumaker, Zhou et al. 2014). But QTc prolongation and Torsades de Pointes are rare but possible serious adverse event associated with tyrosine kinase inhibitors. Therefore, the following is required:

- Intensive QTc monitoring. A baseline ECG is required prior to study registration, and subjects with QTc≥500 msec are excluded. Repeat ECG

performed at the completion of Cycle 1 and 2. See Section 8.32 for dose modification related to QTc prolongation.
- Subjects must be questioned about family history of prolonged QTc, personal history of prolonged QTc, relevant cardiac disease, and concomitant medications which are associated with a high risk of causing QTc prolongation prior to study registration.
- Potassium, calcium, phosphate, and magnesium levels must be obtained before administration of the first dose of lenvatinib and as described in the study calendar, thereafter.

9.74 Tumor Lysis Syndrome

Tyrosine kinase inhibitors have been previously used in the treatment of paraganglioma and pheochromocytoma. Mayo Clinic Phase 2 Consortium (P2C) was conducting a phase 2 trial with pazopanib. Seven patients were enrolled before the trial was closed due to lack of funding by National Cancer Institute. Another case series of 17 patients was also (Ayala-Ramirez, Chougnet et al. 2012) published by the MD Anderson group and treatment was well tolerated. There were no reported cases of tumor lysis syndrome in both cohorts. However, one patient that was treated at Mayo Clinic with lenvatinib experienced transient fever, and a mild elevation of uric acid. Other laboratory parameters including potassium and creatinine were normal. Considering the potential of this milder form a tumor lysis we will monitor patients closely in the initial week with frequent measurement of electrolytes and clinic visits on Day 1, 3 and 10.

9.75 Proteinuria

Urinary protein/creatinine ratio should be frequently monitored to screen for proteinuria as it is a known adverse event associated with antiangiogenic agents including lenvatinib. Specific guidelines for management of proteinuria are presented in Section 8.2 and Section 8.33.

10.0 ADVERSE EVENT (AE) REPORTING AND MONITORING

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Summary of SAE Reporting for this study
(please read entire section for specific instructions):

WHO:	WHAT form:	WHERE to send:
All sites	Pregnancy Reporting [redacted]	Mayo Sites – attach to MCCC Electronic SAE Reporting Form Non Mayo sites – complete and forward to [redacted]
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form: [redacted]	Will automatically be sent to [redacted]

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest

Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

Unanticipated Adverse Device Event (UADE)
Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. 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/protocolDevelopment/electronic_applications/ctc.htm)

a. Identify the grade and severity of the event using the CTCAE version 4.0.
b. Determine whether the event is expected or unexpected (see Section 10.2).
c. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).
d. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).
e. Determine if other reporting is required (see Section 10.5).
f. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

NOTE: A severe AE is NOT the same as a serious AE, which is defined in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

NOTE: *The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure. Refer to protocol or IB for reporting needs.

10.3 Attribution to agent(s) or procedure

When assessing whether an adverse event (AE) is related to a medical agent(s) medical or procedure, the following attribution categories are utilized:

Definite - The AE *is clearly related* to the agent(s)/procedure.
Probable - The AE *is likely related* to the agent(s)/procedure.
Possible - The AE *may be related* to the agent(s)/procedure.
Unlikely - The AE *is doubtfully related* to the agent(s)/procedure.
Unrelated - The AE *is clearly NOT related* to the agent(s)/procedure.

10.31 EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.6).*

*Report any clinically important increase in the rate of a serious suspected adverse reaction (at your study site) over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event.

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be reported in an expedited manner[1]
Blood and lymphatic system disorders	Anemia	≤Grade 4
Investigations	Lymphocyte count decreased	≤Grade 4
	Neutrophil count decreased	≤Grade 4
	Platelet count decreased	≤Grade 4
	White blood cell count decreased	≤Grade 4
General disorders and administrations site conditions	Fatigue	≤Grade 3
	Malaise	≤Grade 3
Gastrointestinal disorders	Nausea	≤Grade 3
	Vomiting	≤Grade 3
	Diarrhea	≤Grade 3
Renal and urinary disorders	Proteinuria	≤Grade 2
Skin and subcutaneous tissue disorders	Alopecia	≤Grade 2
	Rash	≤Grade 3
Vascular disorders	Hypertension	≤Grade 3

[1] These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.
Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
- Hospitalization, or other serious outcomes for signs and symptoms of progression of the cancer.

10.4 Expedited Reporting Requirements for IND/IDE Agents

10.41 Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥24 hrs	7 Calendar Days	24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

NOTE: Refer to Section 10.31 for exceptions to Expedited Reporting

10.42 General reporting instructions

The Mayo IND Coordinator will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.

Use Mayo Expedited Event Report form [redacted] for investigational agents or commercial/investigational agents on the same arm.

Submit to [redacted]

10.43 Reporting of re-occurring SAEs

ALL SERIOUS adverse events that meet the criteria outlined in table10.41 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes, but is not limited to SAEs that re-occur again after resolution.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS)

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

Mayo Clinic Cancer Center (MCCC) Institutions:

If the event meets the criteria for IRB submission as a Reportable Event/UPIRTSO, Use Mayo Expedited Event Report form [redacted] and appropriate documentation to [redacted] The Mayo Regulatory Affairs Office will review and process the submission to the Mayo Clinic IRB.

10.52 Death

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.53 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND/IDE will be reported. Three options are available to describe the event:
  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy

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

10.54 Second Malignancy

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

10.55 Pregnancy, Fetal Death, and Death Neonatal

If a female subject (or female partner of a male subject) taking investigational product becomes pregnant, the subject taking should notify the Investigator, and the pregnant female should be advised to call her healthcare provider immediately. The patient should have appropriate follow-up as deemed necessary by her physician. If the baby is born with a birth defect or anomaly, a second expedited report is required.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion, the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation. Include this form:

[redacted]

10.551 Pregnancy

Pregnancy should be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium and perinatal conditions SOC. Pregnancy should be followed until the outcome is known.

10.552 Fetal Death

Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

Any fetal death should be reported expeditiously, as **Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)"** under the Pregnancy, puerperium and perinatal conditions SOC.

10.553 Death Neonatal

Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration - Other (neonatal loss)"** under the General disorders and administration SOC.

10.6 Required Routine Reporting

10.61 **Baseline and Adverse Events Evaluations**

Pretreatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation.

Grading is per CTCAE v4.0 **unless** alternate grading is indicated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Blood and lymphatic system disorders	Anemia	X	X
Gastrointestinal disorders	No. of stools	X	
	Diarrhea		X
	Mucositis oral		X
	Nausea	X	X
	Oral dysesthesia		X
	Vomiting		X
	Weight loss		X
General disorders and administration site conditions	Fatigue	X	X
Renal and urinary disorders	Proteinuria	X	X
Respiratory, thoracic and mediastinal disorders	Cough	X	X
Skin and subcutaneous disorders	Rash maculo-papular	X	X
	Palmar-plantar erythrodysesthesia syndrome	X	X
Vascular disorders	Hypertension	X	X

10.62 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

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

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

10.623 Grade 5 AEs (Deaths)

10.6231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6232 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.

10.7 Late Occurring Adverse Events

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 Test Schedule in Section 4.0).

10.8 *[Insert industry partner name]* Additional Event Reporting Instructions

Insert any additional language requested by industry partners in this section.

11.0 TREATMENT EVALUATION

NOTE: This study uses protocol RECIST v1.1 template dated 2/16/2011. See the footnote for the table regarding measureable disease in Section 11.44, as it pertains to data collection and analysis.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1)(Eisenhauer, Therasse et al. 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule of Evaluations

For the purposes of this study, patients should be reevaluated every 8 weeks for the first year and then every 12 weeks after Year 1.

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

11.212 A malignant lymph node is considered measurable if its short axis is >1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

NOTE:
Tumor lesions in a previously irradiated area are considered measurable disease under the following conditions:

- If they have progressed at screening evaluation

11.22 Non-Measurable Disease

All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/ pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above.

However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non- pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 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 must 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 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.

11.32 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.
- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.
- FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A ‘positive’ FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered ‘negative.’ New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
    a. Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
    b. No FDG-PET at baseline and a positive FDG-PET at follow-up:
        i. If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

ii. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.

iii If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

11.33 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 8 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.)

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. <u>These lesions can be non-nodal or nodal (as defined in 11.21)</u>, where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

  Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.
- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.
- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.433.

11.43 Response Criteria

11.431 All target lesions and target lymph nodes followed by CT/MRI/PET-CT/ must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.432 Evaluation of Target Lesions

- Complete Response (CR):All of the following must be true:
  a. Disappearance of all target lesions.
  b. Each target lymph node must have reduction in short axis to <1.0 cm.
  c. Normalization of tumor biomarkers.
- Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 11.41).
- Progression (PD): At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up.
  b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD

must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.433 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- Complete Response (CR): All of the following must be true:
  a. Disappearance of all non-target lesions.
  b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.
  c. Normalization of tumor biomarkers
- Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes and/or maintenance of tumor marker level above the normal limits.
- Progression (PD): At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up.
  b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)
  c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

11.44 Overall Objective Status

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

11.441 For Patients with Measurable Disease

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

*See Section 11.431

** NOTE: This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the MCCC protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

11.45 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. A patient is classified as having PD due to "symptomatic deterioration" if any of the following occur that are not either related to study treatment or other medical conditions:

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

12.0 DESCRIPTIVE FACTORS

12.1 Diagnosis: Pheochromocytoma vs. Paraganglioma

12.2 Baseline MIBG statuses: Positive vs. Negative vs. Unknown

12.3 Prior history of TKI use: Yes for this cancer or other condition vs. no vs. unknown

12.4 Prior chemotherapy therapy for this cancer: Yes vs. no.

12.5 Bone disease: Yes vs. no.

12.6 Secretory functional: Yes vs. no.

12.7 Inherited associated genetic syndrome: Yes vs. no vs. unknown

12.8 Bone modulating therapy (e.g., zoledronic acid, denosumab, etc.): Yes vs. no.

13.0 TREATMENT/FOLLOW–UP DECISION AT EVALUATION OF PATIENT

13.1 Continuation of treatment

Patients who are CR, PR, or SD will continue treatment per protocol.

13.2 Progressive disease (PD)

Patients who develop PD while receiving therapy will go to the event-monitoring phase.

13.3 Off protocol treatment

Patients who go off protocol treatment for reasons other than PD will go to the event-monitoring phase per Section 4.

13.4 Complete response

If the patient has achieved CR then treatment will continue for a maximum of 5 years from time of registration.

13.5 Duration of therapy for PR or SD

Patients who are in PR or SD will continue on therapy until PD or for maximum 5 years from registration date and then they will go to event monitoring. Subsequent treatment is at the discretion of their attending physician

13.6 Progressive Disease (PD)

Patients who develop PD at any time should go to event monitoring.

13.7 Inevaluable patients

If a patient fails to complete the first cycle of treatment for reasons other than toxicity, the patient will be regarded as inevaluable and will be replaced.

13.8 Ineligible

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- 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 18.0 of the protocol.
- If the patient never received treatment, on-study material must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

13.9a Major violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.9b Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 BODY FLUID BIOSPECIMENS

Optional blood and urine specimen for correlative studies will be collected from Mayo Clinic patients at baseline for Mayo Clinic biomarker study (IRB 13-005838) . Patient will be consented separately for the study and provided with study card for blood and urine collection. Collection, transport and processing should follow IRB 13-005838 instructions.

15.0 DRUG INFORMATION

15.1 Lenvatinib (E7080, Lenvima®)

15.11 **Background**: Lenvatinib is an oral, multiple receptor tyrosine kinase (RTK) inhibitor that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; the platelet derived growth factor (PDGF) receptor PDGFRα; KIT; and RET.

15.12 **Formulation**: Lenvatinib is available as 4 mg and 10 mg capsules. The following are capsule inactive ingredients: Calcium Carbonate, USP; Mannitol, USP; Microcrystalline Cellulose, NF; Hydroxypropyl Cellulose, NF; Hydroxypropyl Cellulose (type H), NF; and Talc, USP. The hypromellose capsule shell contains titanium dioxide, ferric oxide yellow, and ferric oxide red. The printing ink contains shellac, black iron oxide, potassium hydroxide, and propylene glycol.

15.13 **Preparation and storage**: Store at controlled room temperature, 25 degrees C (77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F)

15.14 **Administration:** Take lenvatinib at the same time each day with or without food. The capsules should be swallowed whole with water. Alternatively, add the lenvatinib capsules to a tablespoon of water or apple juice in a small glass to produce a suspension. Leave the capsules in the liquid for at least 10 minutes. Stir for at least 3 minutes. Drink the mixture. After drinking, add the same amount of water or apple juice (one tablespoon) to the glass. Swirl the contents of the glass a few times and swallow the additional liquid. If a patient misses a dose, and it cannot be taken within 12 hours, then that dose should be skipped and the next dose should be taken at the usual time of administration.

15.15 **Pharmacokinetic information**:

Absorption: Lenvatinib is rapidly absorbed after oral administration with tmax typically observed from 1 to 4 hours postdose. Food does not affect the extent of absorption, but slows the rate of absorption. When administered to healthy subjects with food, peak plasma concentrations are delayed by 2 hours.

Distribution: In vitro binding of lenvatinib to human plasma proteins is high and ranged from 98% to 99% (0.3 – 30 μg/mL, mesilate). This binding was mainly to albumin with minor binding to α1-acid glycoprotein and γ-globulin. In vitro blood to plasma ratios of lenvatinib (0.1 - 10 μg/mL) remained constant in humans (0.589 – 0.608).

Metabolism: Lenvatinib is extensively metabolized in humans. The main metabolic pathways in humans were identified as oxidation by AO, demethylation via CYP3A4, glutathione conjugation with elimination of the O-aryl group (chlorbenzyl moiety), and combinations of these pathways followed by further biotransformations (eg, glucuronidation, hydrolysis of the glutathione moiety, degradation of the cysteine moiety, and intramolecular rearrangement of the cysteinylglycine and cysteine conjugates with subsequent dimerization).

Half-life elimination: Plasma concentrations decline bi-exponentially following Cmax. The terminal exponential half-life of lenvatinib is about 28 hours.

Excretion: Following administration of radiolabeled lenvatinib to 6 subjects with solid tumors, approximately two-thirds and one-fourth of the radiolabel were eliminated in the feces and urine, respectively.

Special populations: No dose adjustments are required on the basis of hepatic function in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. In patients with severe

(Child Pugh C) hepatic impairment, the starting dose should be lowered. No dose adjustments are required on the basis of renal function in patients with mild or moderate renal impairment. In patients with severe renal impairment, the starting dose should be lowered. Further dose adjustments may be necessary on the basis of individual tolerability.

15.16 **Potential Drug Interactions**: In vitro, cytochrome P450 3A4 was the predominant (>80%) cytochrome isoform involved in the P450-mediated metabolism of lenvatinib. In vivo, inducers and inhibitors of CYP3A4 had a minimal effect on lenvatinib exposure. Lenvatinib is not considered a strong inducer or inhibitor of cytochrome P450 or uridine 5′-diphospho-glucuronosyl transferase (UGT) enzymes. Lenvatinib may be co-administered without dose adjustment with CYP3A, P-glycoprotein (P-gp), and BCRP inhibitors or CYP3A and P-gp inducers.

15.17 **Known potential adverse events**:
Common known potential toxicities, >10%:
Gastrointestinal disorders: Abdominal pain, diarrhea, nausea, vomiting
General disorders and administrative site conditions: Asthenia
Metabolism and nutrition disorders: Decreased appetite, dehydration
Renal and urinary disorders: Acute kidney injury
Vascular disorders: Hypertension

Less common known potential toxicities, 1%-10%:
Metabolism and nutrition disorders: dehydration
Respiratory, thoracic, and mediastinal disorders: pulmonary embolism
Vascular disorders: hypotension

Rare known potential adverse events, <1% (Limited to important or life-threatening):

Blood and lymphatic disorders: Thrombocytopenia

Cardiac disorders: Acute myocardial infarction, myocardial infarction, cardiac failure, congestive cardiac failure, coronary artery occlusion, left ventricular dysfunctioion

Endocrine disorders: hypothyroidism

Gastrointestinal disorders: abdominal pain lower, abdominal pain upper, anal fistula, constipation, diverticular perforation, intestinal perforation, pancreatitis, acute pancreatitis, rectal hemorrhage, rectal perforation, stomatitis, upper gastrointestinal hemorrhage

Hepatobiliary disorders: Cholecystitis, cholecystitis acute, hepatic failure, hepatic function abnormal, hepatitis acute, hyperbilirubinemia, liver injury

Infections and infestations: Colonic abscess, perineal abscess, urinary tract infection, urosepsis

Investigations: Alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, ejection fraction increased, lipase increased, weight decreased

Metabolism and nutrition disorders: Hypocalcemia, hypokalemia, hypomagnesemia

Musculoskeletal and connective tissue disorders:

Neoplasms benign, malignant and unspecified: Intracranial tumor hemorrhage, tumor hemorrhage

Nervous system disorders: Cerebral hemorrhage, cerebral infarction, cerebrovascular accident, dizziness, hemorrhage intracranial, headache, ischemic stroke, monoparesis,, reversible posterior leukoencephalopathy syndrome, subarachnoid hemorrhage, transient ischemic attack

Renal and urinary disorders: Hematuria, proteinuria, renal failure, renal impairment, renal tubular necrosis

Reproductive system and breast disorders: Female genital tract fistula, vaginal hemorrhage

Respiratory, thoracic, and mediastinal disorders: Epistaxis, hemoptysis, pulmonary hemorrhage

Vascular disorders: Hypertensive crisis

15.18 **Drug procurement**

Each participating site will order/monitor drug supply through Eisai Inc.

NOTE: Outdated or remaining drug is to be destroyed on-site per procedures in place at each institution.

15.19 **Nursing guidelines**

15.191 Hypertension is very common with agent. Monitor BP as per protocol and report BP elevations to the study team.

15.192 Diarrhea is common. This may be increased in patients who are undergoing simultaneous treatment with immunotherapy agents. Instruct patients to report any diarrhea immediately and treat symptomatically per protocol instructions.

15.193 Other GI side effects can occur, including decreased appetite, weight loss, and nausea/vomiting. Manage patient symptomatically and monitor for effectiveness.

15.194 Patients may experience fatigue. Instruct patients in energy conserving lifestyle.

15.195 Dermatologic related side effects have been seen, including: hand-foot syndrome, rash, and alopecia. Instruct patients to report these signs and symptoms to the study team immediately.

15.196 Patients may experience increased risk of bleeding. Instruct patients to report any unusual bruising or bleeding to the study team. Patients should not undergo invasive procedures without first discussing with the study team.

15.197 Monitor for proteinuria per protocol.

15.198 Rarely agent may cause decreased LVEF. Instruct patients to report any peripheral edema, DOE, chest pain or significant fatigue to the study team.

15.199 Monitor LFTs and renal function. Report any elevations to the provider.

16.0 STATISTICAL CONSIDERATIONS AND METHODOLOGY

16.1 Statistical Design:

A Simon two-stage, phase II optimal clinical trial design was chosen to examine anti-tumor activity and safety profile of lenvatinib as a treatment for patients with progressive malignant pheochromocytoma or paraganglioma.

16.11 Primary endpoint

The primary endpoint is the confirmed tumor response rate defined as 100% times the number of eligible patients who has started lenvatinib and whose objective tumor status was a CR or PR on 2 consecutive evaluations at least 4 weeks apart (using RECIST v1.1 criteria) divided by the number of eligible patients who has started lenvatinib.

16.12 Operating Characteristics

The largest tumor response rate for which there would be little interest in pursuing further studies of this lenvatinib regimen in patients with progressive malignant pheochromocytoma or paraganglioma is 10%. The smallest tumor response rate for which there would be interest in pursuing further studies of this lenvatinib regimen in patients with progressive malignant pheochromocytoma or paraganglioma is 30%. The study design proposed below yields a 85% chance of detecting that the true tumor response rate is at least 30% at a 0.15 significance level when the true tumor response rate is at least 10%

16.121 Stage 1: Enter 6 eligible patients. If no tumor responses are documented among these 6 patients within the first 6 cycle of treatment, we will consider the regimen lacking in sufficient antitumor activity to recommend further testing in this patient population and terminate further enrollment. If at least one response is observed among these 6 patients within the first 6 cycles of treatment, we will proceed to Stage 2.

16.122 Stage 2: Enter an additional 17 eligible patients. If three or fewer tumor responses are documented among all 23 eligible patients within the first 6 cycle of treatment, we will consider the regimen lacking in sufficient antitumor activity to recommend further testing in this patient population. If four or more tumor responses are documented among all 23 eligible patients within the first 6 cycle of treatment, this will be considered of the regimen to have promising antitumor activity in this patient population.

We anticipate enrolling a minimum of 6 and a maximum 23 eligible. At the close of stage 1 or stage 2 enrollment, if more patients than planned have been enrolled only the first 6 eligible patients or the first 23 eligible patients enrolled, respectively, will be used to evaluate the decision rule. We anticipate accruing 2 additional patients (25 total) to account for patients found to be ineligible after signing a consent or who refused to start study treatment after signing a consent form.

16.13 Power and Significance Level

Assuming that the number of tumor responses is binomially distributed, the probability of declaring that this regimen warrants further studies (i.e. statistical power) under various tumor response rates and the probability of stopping

accrual after the first stage can be tabulated as a function of the true tumor response rates as shown in the following table.

If the true tumor response rate is	10%	15%	20%	25%	30%
Then the probability of declaring that the regimen warrants further study is…	0.15	0.37	0.59	0.75	0.85
And the probability of stopping at the completion of stage 1	0.53	0.38	0.26	0.18	0.12

16.14 Accrual Time and Study Duration:

No similar studies have been conducted for comparison. Based on our anecdotal experience from referrals of patients from outside institutions who would otherwise fit eligibility criteria we believe we will be able to enroll 4 to 8 patients per year at our institution (Mayo clinic). We believe we can complete accrual within the proposed 3-year period.

16.2 Analysis Plan:

16.21 Primary Endpoint:

Ninety-five percent confidence intervals for the true response proportion will be calculated according to the approach of Duffy and Santner (Duffy and Santner 1987).

16.22 Definitions and analyses of secondary clinical endpoints

- Safety profile of lenvatinib
- Duration of tumor response
- Progression-free survival time
- Overall survival time
- Patient reported quality of life (QOL) using EQ-5D, and FACT-G

16.221 Safety profile of lenvatinib

All adverse events will be graded using the NCI CTCAE Version 4.0. For each type of adverse event classified as either possibly, probably, or definitely related to study treatment, the proportion of patients experiencing a severe (grade 3 or higher) adverse event will be noted per cycle. The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine adverse event patterns.

16.222 Time to event distributions

Time to event distributions will be estimated using the Kaplan-Meier method

16.2221 Duration of response

Duration of response is defined for all patients whose tumor met the criteria of CR or PR (using the RECIST criteria) as the date at which the patient's objective status is first noted

to be either a CR or PR to the date progression is documented.

16.2223 Progression-free survival
Progression-free survival is defined as the time from registration to documentation of disease progression. If a patient dies without a documentation of disease progression, the patient will be considered to have had tumor progression at the time of their death unless there is sufficient documented evidence to conclude no progression occurred prior to death.

If the patient is declared to be a major treatment violation, the patient will be censored on the date the treatment violation was declared to have occurred. In the case of a patient starting treatment and then never returning for any evaluations, the patient will be censored for progression on Day 1 post treatment.

16.2224 Overall survival time
Overall survival time is defined as the time from registration to death due to any cause.

16.2225 Patient reported quality of life (QOL) using EQ-5D, and/or FACT-G
Descriptive statistics, and scatter plots will form the basis of presentation of these data both overall and by other outcomes (toxicity, response and survival measures). Correlations between the QOL outcomes and other outcome measures will be carried out by standard parametric and non-parametric tests (e.g. Pearson's and Spearman's rho). Comparison between continuous variables will be made with Wilcoxon rank sum tests, Fisher's exact tests will be used to determine differences between categorical variables, and Log-rank test will be used to test differences between time-to-event outcomes.

16.23 Correlative aims:

16.231 For patients with secretory tumors

To examine changes in urinary catecholamine and metanephrine levels during treatment, time series plots of urinary catecholamines and metanephrines levels will be constructed (with patient whose tumor responded to treatment in red and patients whose tumor remained stable or progressed in blue) to visually assess trends prior to treatment discontinuation within and between chemistries as well as difference in trends between those whose tumor responded to treatment and those whose tumor did not.

To examine whether lenvatinib-induced changes in urinary catecholamine and/or metanephrine levels during the first cycle of treatment may be associated with objective tumor response, the fold change from baseline levels for each biomarker will be determined. For each biomarker, a plot of the fold change versus response status will be constructed to visually assess differences between those whose tumor

responded to treatment and those whose tumor did not. If feasible, Wilcoxon rank sum tests will be used to examine whether fold changes in a given biomarker during the first cycle of treatment differs between whose tumor responded to treatment and those whose tumor did not.

16.232 To examine associations between tumor response and somatic mutational status in archived tumors, or germline mutational status in patient's peripheral blood mononuclear cells, (presence of SDHD, SDHB, RET, VHL, neurofibromatosis type-1).

For SDHD, SDHB, RET, VHL, neurofibromatosis type-1, a 95% confidence interval for the difference in proportion of patients who have a documented tumor response among those with that particular biomarker present and proportion of patients who have a documented tumor response among those without that particular biomarker present.

16.3 Reporting and Exclusions

16.31 Evaluation of adverse events.

All subjects will be evaluable for adverse events from the time of their first treatment with lenvatinib.

16.32 Evaluation of response.

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

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

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

16.4 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.

16.41 Adverse Event Stopping Rules

NOTE: NCI CTCAE v4.0 will be used to determine grading for adverse event stopping rules.

If 2 or more of the first 5 patients enrolled or 30% or more of the patients enrolled thereafter develop a grade 4 or severer non-hematologic toxicity (except for hypertension) or grade 4 or severer hematologic toxicity that are considered possibly, probably, or definitely related to treatment, enrollment to the study will be suspended. The study team will review all adverse event data. A trial recommendation will be formulated and presented to the MCCC DSMB – the study may permanently close or may re-open to accrual after CTEP and IRB approvals of protocol/consent form modifications.

16.5 Results Reporting on ClinicalTrials.gov

At study activation, this study will have been registered within the "ClincialTrails.gov" website. The Primary and Secondary Endpoints along with other required information for this study will be reported on www.ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 3 years after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time the last patient registered has been followed for at least 6 months.

16.6 Subset Analyses for Minorities:

16.61 Study availability

This study will be available to all eligible patients, regardless of gender, race or ethnic origin.

16.62 Statistical analysis by subset

There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analyses will look for differences in treatment effect based on racial groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.63 Regional population

The geographical region served by MCCC has a population which includes approximately 3% minorities. Based on prior MCCC studies involving similar disease sites, we expect about 3-5% of patients will be classified as minorities by race and about 33% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	1	1
Not Hispanic or Latino	12	12	24
Ethnic Category: Total of all subjects	**12**	**13**	**25**
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	1	1	2
Black or African American	0	1	1
Native Hawaiian or other Pacific Islander	0	0	0
White	11	11	22
Racial Category: Total of all subjects	**12**	**13**	**25**

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, 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.

17.0 PATHOLOGY CONSIDERATIONS/TISSUE BIOSPECIMENS

17.1 Summary Table of Research Tissue Specimens to be collected for this Protocol

Collection (Section for more information)	Mandatory or Optional	Type of Tissue to Collect	Block, Slides, Core, etc. (# of each to submit)	≤42 days after Registration	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
Tumor tissue for correlative studies (Section 17.3)	Optional	Formalin Fixed Paraffin embedded	FFPE Block or 10 unstained FFPE slides (5 micron) and 1 FFPE slide stained with hematoxylin and eosin (H&E)	X	Yes	Ambient

17.2 Correlative Tissue Collection (Optional)

17.21 Tissue Kits will not be provided for this protocol.

17.22 Paraffin Embedded Tissue

17.221 Submit one formalin fixed paraffin-embedded (FFPE) tumor tissue block (if available) with largest amount of invasive tumor (at least 1 cm of tumor for cases of surgical resection) from metastatic tumor biopsy.

Or 10 unstained FFPE slides (5 micron), and 1 FFPE slide stained with hematoxylin and eosin. Do not coverslip unstained slides.

17.222 Send to attention of:

[redacted]

17.223 Store at room temperature

17.23 Frozen Tissue: Not applicable

17.3 Background and Methodology

17.31 Background

The genetics of pheochromocytomas and paragangliomas are very complex (Dahia 2006). Adrenal pheochromocytoma is strongly associated with multiple endocrine neoplasia 2A and 2B, von Hippel-Lindau disease (VHL), and familial paraganglioma syndrome (Neumann, Bausch et al. 2002; Boedeker, Ridder et al. 2005), and is less commonly seen with neurofibromatosis type 1 (NF 1) or MEN 1. However, malignant adrenal pheochromocytoma is infrequently seen in association with these genetic syndromes. On the contrary, extra-adrenal malignant paragangliomas are most frequently seen in association with familial paraganglioma syndrome (PGL), an autosomal dominant disorder presenting with paragangliomas in the head and neck, but also in the thorax, abdomen, and urinary bladder (Neumann, Bausch et al. 2002; Boedeker, Ridder et al. 2005). Most cases are caused by mutations in the succinate dehydrogenase gene (SDH) subunits B, C and D even in apparent "sporadic" cases. Extra-adrenal malignant

paraganglioma is strongly associated with mutations of the B subunit of the gene (SDHB).

Global expression profiles of large series of sporadic pheochromocytomas and paragangliomas have generated 2 unique transcription signatures (Eisenhofer, Bornstein et al. 2004; Dahia, Ross et al. 2005). In the first cluster belong mutations of the VHL, SDHB and SDHD genes known to be associated to VHL and PGL syndromes, while in the second cluster belong mutations in the RET and NF1 genes associated with the MEN syndromes. Both VHL and SDH mutations are known to dysregulate the hypoxia response (Dahia, Ross et al. 2005). Mutations in the SDH gene, an enzyme of the Krebs cycle, also lead to activation of HIF mediated hypoxia signals likely through accumulation of Krebs cycle intermediates, mitochondrial complex II inhibition, and HIF1a over-expression (Gimenez-Roqueplo, Favier et al. 2001; Gimenez-Roqueplo, Favier et al. 2002; Gottlieb and Tomlinson 2005; Pollard, Briere et al. 2005; Selak, Armour et al. 2005; Pollard, El-Bahrawy et al. 2006).

17.32 Methodology

We will investigate if the somatic mutations and germline mutations in paragangliomas and pheochromocytomas correlated with outcome data. FFPE collected at registration will be subjected to DNA extraction and analyzed for mutations in select genes using DNA sequencing.

Ten 5-micron unstained slides and 1 hematoxylin and eosin (H&E) stained slide will be cut from fresh frozen paraffin embedded (FFPE) tissue block. Pathologist will review slides and circle areas with adequate tumor tissue (>20%-40%). Circled H&E slide will serve as template for microdissection (using razor blade or scalpel) of unstained slides for DNA extraction. DNA extraction will be performed using Qiagen FFPE kit as per manufacturer's protocol. Approximately 30 ng of input DNA will be placed into a polymerase chain reaction. The Ion Ampliseq Cancer Hotspot Panel v2 primers (Life technologies) and Illumina MiSeq instrument will be used for gene sequencing. The mutations and genetic alterations identified will be correlated with reference to clinical data obtained during the conduct of the trial.

Germline mutation data will be collected from consenting patients and correlated with outcome data. If it is already performed we will obtain the report. If not performed, consulatation will be perfoemed with genetic counelsor and germline testing obtained if conseted and recommended.

Both of the above components, somatic mutational profile and germline testing are optional correlatives.

18.0 RECORDS AND DATA COLLECTION PROCEDURES

18.1 Submission Timetable

Data submission instructions for this study can be found in the Data Submission Schedule (in Medidata Rave®).

18.2 Event monitoring

See Section 4.0 and Data Submission Schedule for the event monitoring schedule.

18.3 CRF completion

This study will use Medidata Rave® for remote data capture (rdc) of all study data.

18.4 Site responsibilities

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Supporting documentation

This study requires supporting documentation for evidence of response to study therapy and progression after study therapy (CR, PR, PD).

18.6 Labelling of materials

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.7 Incomplete materials

Any materials deemed incomplete by the MCCC Operations Office will be considered "not received" and will not be edited or otherwise processed until the missing information is received. A list of the missing documents will be made available to the appropriate co-sponsor/participant.

18.8 Overdue lists

A list of overdue materials and forms for study patients will be generated monthly. The listings will be sorted by location and will include the patient study registration number. The appropriate co-sponsor/participant will be responsible to obtain the overdue material.

18.9 Corrections forms

If a correction is necessary the QAS will query the site. The query will be sent to the appropriate site to make the correction and return the query and documentation of correction back to the QAS.

19.0 BUDGET

19.1 Costs charged to patient: routine clinical care

19.2 Tests to be research funded:

19.3 Other budget concerns:

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Appendix I ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

*As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

From http://www.ecog.org/general/perf_stat.html

Appendix II Patient Medication Diary

Name _____ **Study ID Number** _____

Please complete this diary on a daily basis. Write in the amount of the dose of lenvatinib that you took in the appropriate "Day" box (for example: 20 mg).

On the days that you do not take any study drug, please write in "0". If you forget to take your daily dose, please write in "0", but remember to take your prescribed dose at the next regularly scheduled time.

If you experience any health/medical complaints or take any medication other than lenvatinib, please record this information.

Week of: _____

Study Drug	***Day 1***	***Day 2***	***Day 3***	***Day 4***	***Day 5***	***Day 6***	***Day 7***
Lenvatinib							

Week of: _____

Study Drug	***Day 8***	***Day 9***	***Day 10***	***Day 11***	***Day 12***	***Day 13***	***Day 14***
Lenvatinib							

Week of: _____

Study Drug	***Day 15***	***Day 16***	***Day 17***	***Day 18***	***Day 19***	***Day 20***	***Day 21***
Lenvatinib							

Week of: _____

Study Drug	***Day 22***	***Day 23***	***Day 24***	***Day 25***	***Day 26***	***Day 27***	***Day 28***
Lenvatinib							

Patient signature: _____

Health or medical complaints during this time:

Other medications or supplements taken during this time:

Name of medication or supplement	How much did you take? (example: Two 500mg pills)	When did you take it (examples: Every day Or Day 19 and Day 20)

Use a separate sheet of paper if more space is needed.

My next scheduled visit is: _____
If you have any questions, please call: _____

Study Coordinator Use Only

Number of pills returned _____ Number of vials returned: _____
Discrepancy Yes____/No____ Verified by _____ Date_____

Appendix III Potential drugs that could interact with lenvatinib (via CYP 3A4)

Inhibitors and inducers of CYP3A are shown below. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx . The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below.

Inhibitors of CYP3A	Inducers of CYP3A
Strong inhibitors: INDINAVIR NELFINAVIR RITONAVIR CLARITHROMYCIN ITRACONAZOLE KETOCONAZOLE NEFAZODONE Posaconazole SAQUINAVIR SUBOXONE TELITHROMYCIN Voriconazole **Moderate inhibitors:** Aprepitant Erythromycin Diltiazem Fluconazole grapefruit juice Seville orange juice Verapamil **Weak inhibitors:** Cimetidine **All other inhibitors:** Amiodarone NOT azithromycin Chloramphenicol Boceprevir Ciprofloxacin Delaviridine diethyl-dithiocarbamate Fluvoxamine Gestodene Imatinib Mibefradil Mifepristone Norfloxacin Norfluoxetine star fruit Telaprevir Troleandomycin	Carbamazepine Efavirenz Nevirapine Barbiturates Glucocorticoids Modafinil Oxcarbarzepine Phenobarbital Phenytoin Pioglitazone Rifabutin Rifampin St. John's Wort Troglitazone

Appendix IV Hypertension Management Guidelines

D.1. Guidelines for the management of lenvatinib-Induced Hypertension: Non-secretory tumors

(For secretory tumors please see Section D.2.)

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 lenvatinib is well documented in clinical trials. With secretory paraganglioma and pheochromocytoma this could be a major toxicity.

NOTE: that hypertension management of secretory tumors is more complex due to the additional risk of hypertension issues in these patients and management is discussed separately below. For example consultation with HTN specialist is required in patients with secretory tumors prior to study initiation.

- While subjects are receiving treatment with lenvatinib, 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 AE.
- Decisions to hold or decrease the lenvatinib dose during treatment must be based on BP readings taken in the clinic by a medical professional.

Recommended Hypertension Monitoring and Management for non-secretory tumors (BP in mmHg)

Grade (CTCAE v4)	Antihypertensive Therapy	Blood Pressure Monitoring	Lenvatinib Dose Modification
Persistent* Grade 1 Pre-hypertension Systolic 120-139 Diastolic 80-90		Standard	No Change
Persistent Grade 2-Moderate Systolic 140-159 Diastolic 90-99 Protocol-specific guidance supersedes any other management guidelines, including CTCAE v4.	Step 1) Initiate anti-hypertensive treatment (calcium channel blocking agents, e.g. amlodipine, are generally the preferred agents) and if needed, after 24-48 hr Rx, increase dose in stepwise fashion every 24-48 hours until BP is controlled or at max dose of Rx Step 2) If BP still not controlled, add another anti-hypertensive Rx, a LA DHP CCB, ACE1, ARB, or ABB; increase dose of this drug as described in Step 1 Step 3) If BP still not controlled, add 3rd drug from the list of anti-	BP should be monitored as recommended by the treating physician	No change except as described in Step 4

Recommended Hypertension Monitoring and Management for <u>non-secretory</u> tumors (BP in mmHg)

Grade (CTCAE v4)	Antihypertensive Therapy	Blood Pressure Monitoring	Lenvatinib Dose Modification
	hypertensives in Step 2; increase dose of this drug as described in Step 1 Step 4) If BP still not controlled, discontinue lenvatinib until BP controlled, then resume <u>NOTE</u>: Stopping or reducing the dose of lenvatinib is expected to cause a decrease in BP. <u>The treating physician should monitor the subject for hypotension and adjust the number and dose of anti-hypertensive medic-ation(s) accordingly</u>		
Persistent Grade 3 Severe Systolic ≥160 Diastolic ≥100 Protocol-specific guidance supersedes any other management guidelines, including CTCAE v4	HOLD lenvatinib until systolic BP ≤159 <u>and</u> diastolic BP ≤99 BP management is identical to that for Grade 2 (see Steps 1-4 above) **<u>with 2 major exceptions:</u>** **<u>1) If systolic BP >180 or diastolic BP >110 and the subject is symptomatic:</u> optimal management with intensive IV support in ICU; STOP lenvatinib and notify hospital staff that stopping drug may result in a decrease in BP** **and** **<u>2) If systolic BP >180 or diastolic BP >110 and the subject is asymptomatic, consideration to initiation of</u> 2 new antihypertensives together should be given in step 1 (and dose escalated appropriately as in step 1).**	BP should be monitored as recommended by the treating physician **<u>unless the subject is symptomatic with systolic BP >180 or diastolic BP >110 in which case, monitoring should be intensive</u>**	HOLD lenvatinib until systolic BP ≤159 <u>and</u> diastolic BP ≤99. After this, lenvatinib may be re-administered. If BP is still Grade 2, manage as described above for Grade 2 hypertension. In most circumstances, if BP cannot be controlled after an optimal trial of antihypertensive medications, consider either 1 dose reduction of lenvatinib when systolic BP ≤159 <u>and</u> diastolic BP ≤99 <u>or</u> stopping lenvatinib. **HOWEVER,** **<u>If the subject requires hospitalization for management of symptomatic systolic BP >180 or diastolic BP >110,</u>**

Recommended Hypertension Monitoring and Management for non-secretory tumors (BP in mmHg)

Grade (CTCAE v4)	Antihypertensive Therapy	Blood Pressure Monitoring	Lenvatinib Dose Modification
	NOTE: Stopping or reducing the dose of lenvatinib is expected to cause a decrease in BP. The treating physician should monitor the subject for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly		permanently discontinue lenvatinib or if BP is controlled to systolic BP ≤159 and diastolic BP ≤99, consider re-starting lenvatinib at 1 lower dose level after consultation with the Principal Investigator
Grade 4 Life-threatening consequences of hypertension	**Optimal management with intensive IV support in ICU; STOP lenvatinib and notify hospital staff that stopping lenvatinib may result in a decrease in BP**	Intensive	Permanently discontinue lenvatinib or if systolic BP ≤159 and diastolic BP ≤99, consider restarting lenvatinib at 1 lower dose level after consultation with the Principal Investigator

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

- See table below for suggested antihypertensive medications by class
- If subjects require a delay of >2 weeks for management of hypertension, discontinue protocol therapy
- 24-48 hours should elapse between modifications of antihypertensive therapy
- Hypertension should be graded using CTCAE v4

*NOTE: **For the purposes of dosage reductions related to hypertension, persistent hypertension is defined as blood pressure elevations that meet the grading criteria on at least 2 separate measurements 7 days or more apart. (For the purpose of AE grading standard CTCAE will be utilized.)**

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 AEs 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 lenvatinib. If such a medication is discontinued and replaced, the transition period should occur no less than 7 days prior to the first dose of lenvatinib. Based on prior clinical experience with lenvatinib, the use of calcium channel blockers (dihydropyridine category) and ACE inhibitors as first-line and second-line therapy is recommended.

Oral Antihypertensive Medications for patients with non-secretory tumors

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

D2. Management of Lenvatinib-Induced Hypertension: Secretory Tumors

All patients with secretory pheochromocytomas or paragangliomas are required to: 1) be evaluated in consultation, and followed by, a hypertension specialization with experience in the management of hypertension in the setting of catecholamine-secreting tumors (usually an endocrinologist, nephrologist, or a cardiologist), and 2) receive α- and β-adrenergic blockade for at least 7-14 days prior to initiation of lenvatinib (see below for guidelines regarding proper α- and β-blockade). The hypertension specialist of record for each patient should be committed to following the patient during the clinical study on an as needed basis.

Recommended Hypertension Monitoring and Management for Patients with Catecholamine-Secreting Tumors (BP in mmHg)
(CTCAE SOC Vascular Disorders/Hypertension)

Grade (CTCAE v4)	Antihypertensive Therapy	Blood Pressure Monitoring	Lenvatinib Dose Modification
Persistent* Grade 1 Pre-hypertension Systolic 120-139 Diastolic 80-90	Standard α- and β-adrenergic blockade	Standard	No Change
Persistent*Grade 2- Moderate Systolic 140-159 Diastolic 90-99 Protocol-specific guidance supersedes any other management guidelines.	Step 1) Advance dose of α-adrenergic blocker until BP is controlled or at max dose of Rx. The β-adrenergic blocker dosage should be advanced for a target heart rate of less than 80 bpm. Step 2) If BP still not controlled, add another anti-hypertensive Rx (usually best a calcium channel blocker such as amlodipine), in conjunction with the patient's identified hypertension specialist, increasing dosage of this drug as described in step 1 or as suggested by patient's identified hypertension specialist. Step 3) If BP is still not controlled, consider either 1 dose reduction of lenvatinib or withholding lenvatinib until BP is better controlled. NOTE: Stopping or reducing the dose of lenvatinib is expected to cause a decrease in BP. The treating physician must therefore monitor the subject for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly	BP should be monitored as recommended by the treating physician and patient's identified hypertension specialist	No change except as described in Step 4

Recommended Hypertension Monitoring and Management for Patients with Catecholamine-Secreting Tumors (BP in mmHg)
(CTCAE SOC Vascular Disorders/Hypertension)

Grade (CTCAE v4)	Antihypertensive Therapy	Blood Pressure Monitoring	Lenvatinib Dose Modification
Persistent* Grade 3 Severe Systolic ≥160 Diastolic ≥100 Protocol-specific guidance supersedes any other management guidelines.	HOLD lenvatinib until systolic BP ≤159 and diastolic BP ≤99 BP management is identical to that for Grade 2 (see steps 1-3 above) **with 2 major exceptions: 1) If systolic BP >180 or diastolic BP >110 and the subject is symptomatic: optimal management is with intensive IV support in ICU; STOP lenvatinib and notify hospital staff that stopping lenvatinib may result in a decrease in BP and 2) If systolic BP >180 or diastolic BP >110 and the subject is asymptomatic, Consultation with patient's identified hypertension specialist is required as to the proper medical therapy, addition of additional anti-hypertensive medications and monitoring.** NOTE: Stopping or reducing the dose of lenvatinib is expected to cause a decrease in BP. The treating physician should monitor the subject for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly	BP should be monitored as recommended by the treating physician and patient's identified hypertension specialist **unless the subject is symptomatic with systolic BP >180 or diastolic BP >110 in which case, monitoring should be intensive.**	HOLD lenvatinib until systolic BP ≤159 and diastolic BP ≤99. After this, lenvatinib may be re-administered. If BP is still grade 2, manage as described above for grade 2 hypertension. In most circumstances, if BP cannot be controlled after an optimal trial of antihypertensive medications, consider either 1 dose reduction of lenvatinib when systolic BP ≤159 and diastolic BP ≤99 or stopping lenvatinib. **HOWEVER, If the subject requires hospitalization for management of symptomatic systolic BP >180 or diastolic BP >110,** permanently discontinue lenvatinib or if BP is controlled to systolic BP ≤159 and diastolic BP ≤99, consider re-starting lenvatinib at 1 lower dose level after consultation with the study Principal Investigator
Grade 4 Life-threatening consequences of hypertension	**Optimal management with intensive IV support in ICU; Contact of patient's identified hypertension specialist. STOP lenvatinib and notify hospital staff that stopping lenvatinib may result in a decrease in BP**	Intensive	Permanently discontinue lenvatinib or if systolic BP ≤159 and diastolic BP ≤99, consider re-starting lenvatinib at 1 lower dose level after consultation with the study Principal Investigator
Abbreviations: Dihydropyridine calcium-channel blockers (DHP-CCB), selective beta blockers (BB), Angiotensin Converting Enzyme Inhibitors (ACEI), Angiotensin II Receptor Blockers (ARB), alpha beta blocker (ABB)			

Recommended Hypertension Monitoring and Management for Patients with Catecholamine-Secreting Tumors (BP in mmHg)
(CTCAE SOC Vascular Disorders/Hypertension)

Grade (CTCAE v4)	Antihypertensive Therapy	Blood Pressure Monitoring	Lenvatinib Dose Modification
• See table below for suggested antihypertensive medications by class • If subjects require a delay of >2 weeks for management of hypertension, discontinue protocol therapy • 24-48 hours should elapse between modifications of antihypertensive therapy • Hypertension should be graded using CTCAE v4 * **NOTE: For the purposes of dosage reductions related to hypertension, persistent hypertension is defined as blood pressure elevations that meet the grading criteria on at least 2 separate measurements 7 days or more apart. (For the purpose of AE grading standard CTCAE will be utilized.)**			

Oral Antihypertensive Medications for patients with secretory tumors

(Decisions about changes in antihypertensive medications in this group of patients are best made with communication between patient's primary oncologists and identified hypertension specialist).

Agent class	Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Dihydro-pyridine Calcium-Channel Blockers (DHP CCB)	nifedipine XL	30 mg daily	60 mg daily	90 mg daily	CYP 3A4 substrate
	amlodipine	2.5 mg daily	5 mg daily	10 mg daily	CYP 3A4 substrate
	felodipine	2.5 mg daily	5 mg daily	10 mg daily	CYP 3A4 substrate and inhibitor
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	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

Agent class	Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Blockers (ARBs)	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

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 AEs 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 lenvatinib. If such a medication is discontinued and replaced, the transition period should occur no less than 7 days prior to the first dose of lenvatinib. Based on prior clinical experience with lenvatinib, the use of calcium channel blockers (dihydropyridine category) and ACE inhibitors as first-line and second-line therapy is recommended.

D.3. Guidelines Regarding Proper α- and β-Adrenergic Blockade

α-Adrenergic blockade should be started first, under the care of a hypertension specialist, to normalize blood pressure and expand the contracted blood volume. On the second or third day of α-adrenergic blockade, patients are encouraged to start a diet high in sodium content (≥5,000 mg daily) because of the catecholamine-induced volume contraction and the orthostasis associated with α-adrenergic blockade. This degree of volume expansion may be contraindicated in patients with congestive heart failure or renal insufficiency. After adequate α-adrenergic blockade has been achieved (typically 5 to 7 days), β-adrenergic blockade is initiated. The whole process should take place at least 1-2 week prior to initiation of lenvatinib.

For α-adrenergic blockade phenoxybenzamine is the preferred drug. The initial dosage is 10 mg once or twice daily, and the dose is increased by 10 to 20 mg in divided doses every 2 to 3 days as needed to control blood pressure. The final dosage of phenoxybenzamine is typically between 20 and 100 mg daily. The patient should be warned about the orthostasis, nasal stuffiness, and fatigue that occur in almost all patients. With their more favorable side-effect profiles and cost-effectiveness, selective α_1-adrenergic blocking agents (e.g., prazosin, terazosin, or doxazosin) may be used for those patients who are intolerant of the side effects of phenoxybenzamine or cannot afford phenoxybenzamine. Ultimately, the choice of the agents is at the discretion of the hypertension specialist.

The β-adrenergic antagonist should be administered only after α-adrenergic blockade is effective (with near-normal BP) because with β -adrenergic blockade alone hypertension may be more severe from the unopposed α-adrenergic stimulation. β-adrenergic blockade is indicated to control the tachycardia associated with both the high concentrations of circulating catecholamines and the α-adrenergic blockade. The clinician should exercise caution if the patient is asthmatic or has congestive heart failure. Chronic catecholamine excess can produce a myocardiopathy that may become evident with the initiation of β -adrenergic blockade, resulting in acute pulmonary edema. Therefore, when the β -adrenergic blocker is administered, it should be used cautiously and at a low dose. For example, a patient is usually given 10 mg of propranolol every 6 hours to start. On the second day of treatment, the β-adrenergic blockade (assuming the patient tolerates the drug) is converted to a single long-acting dose of a

cardioselective β-blocker. The dose is then increased as necessary to control the tachycardia (goal heart rate is 60-80 beats per minute).

Metyrosine, a catecholamine synthesis inhibitor, may be used in patients with particularly high metanephrines/normetanephrines and/or for difficult to control hypertension prior to initiation of lenvatinib. Typical doses may be up to 1-2 grams per day, but dose escalation is often limited by sedation.

Metyrosine may also be used if there is significant concern for lenvatinib-induced catecholamine release following initiation of therapy.

Orally Administered Drugs for Initial α- and β-Adrenergic Blockade

Drug	Dosage, mg/day* Initial (maximum)	Side effects
α-Adrenergic Blocking Agents		
Phenoxybenzamine	10† (100)†	Postural hypotension, tachycardia, miosis, nasal congestion, diarrhea, inhibition of ejaculation, fatigue
Prazosin	1 (20)‡	First-dose effect, dizziness, drowsiness, headache, fatigue, palpitations, nausea
Terazosin	1 (20)†	First-dose effect, asthenia, blurred vision, dizziness, nasal congestion, nausea, peripheral edema, palpitations, somnolence
Doxazosin	1 (20)	First-dose effect, orthostasis, peripheral edema, fatigue, somnolence
Combined α- and β-Adrenergic Blocking Agent		
Labetalol	200† (1,200)†	Dizziness, fatigue, nausea, nasal congestion, impotence
Calcium channel blocker		
Nicardipine sustained release	30† (120)†	Edema, dizziness, headache, flushing, nausea, dyspepsia
Catecholamine synthesis inhibitor		
α-Methyl-ρ-L-tyrosine (Metyrosine)	1,000‡ (4,000)‡	Sedation, diarrhea, anxiety, nightmares, crystalluria, galactorrhea, extrapyramidal symptoms

*Given once daily unless otherwise indicated
†Given in two doses daily
‡Given in three or four doses daily

Appendix V Drugs with Risk of Torsades De Pointes

The following list contains medications that are generally accepted as having an increased risk of QT prolongation and/or torsades de pointes. **Concomitant administration of lenvatinib and a medication on this list is prohibited.**

Generic Name	Brand Name	Comments
Amiodarone	Cordarone®, Pacerone®	Low risk torsades de pointes
Arsenic trioxide	Trisenox®	Torsades de pointes
Bepridil	Vasocor®	
Chloroquine	Aralen®	
Chlorpromazine	Thorazine®	
Cisapride	Propulsid®	Restricted availability in U.S.
Clarithromycin	Biaxin®	
Disopyramide	Norpace®	Torsades de pointes
Dofetilide	Tikosyn®	Torsades de pointes
Dolasetron	Anzemet®	
Droperidol	Inapsine®	Torsades de pointes
Erythromycin	Erythrocin®, E.E.S. ®	IV > PO
Halofantrine	Halfan®	
Haloperidol	Haldol®	IV > PO, high doses increase QT prolongation and torsades de pointes
Ibutilide	Corvert®	Torsades de pointes, female > male, non-Caucasian > Caucasian
Levomethadyl	Orlaam®	
Mesoridazine	Serentil®	
Methadone	Dolophine®, Methadose®	
Pentamidine	Pentam®, Nebupent®	
Pimozide	Orap®	
Procainamide	Pronestyl®, Procan®, Procanbid®	N-acetylprocainamide causes torsade de pointes, not parent compound
Quinidine	Cardioquin®, Quinaglute®	Torsades de pointes
Sotalol	Betapace®	Torsade de pointes female > male
Sparfloxacin	Zagam®	
Thioridazine	Mellaril®	

Note: The above list is not all-inclusive. Consult your local pharmacist for any questions.

Appendix VI Patient Blood Pressure Diary

Today's date _____

Patient Initials _____
Patient Study ID _____

INSTRUCTIONS TO THE PATIENT:

1. Your blood pressure readings have two numbers. The first number is the pressure in your blood vessels during a heartbeat (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 once daily:
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. Repeat your blood pressure within 1-4 hours. If your blood pressure is still elevated please contact your doctor's office at [redacted] for instructions. Also, you should contact your doctor's office at any time your blood pressure exceeds 180 mmHg (systolic) or 105 mmHg (diastolic), or at any time you have symptoms that you think may be related to hi blood pressure (examples include headache, nausea, vomiting, confusion, anxiety, restlessness). If you need to call after business hours or during holidays or weekends, please call [redacted] and ask for the Medical Oncologist on call.
5. Please bring this form to your visit at the end of Cycle 1, 2 and 3.

Date	Blood Pressure readings	Other readings (include time of day)	Date	Blood Pressure readings	Other readings (include time of day)
	/			/	
	/			/	
	/			/	
	/			/	
	/			/	
	/			/	
	/			/	

Date	Blood Pressure readings	Other readings (include time of day)	Date	Blood Pressure 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/Coordinator's Signature

Appendix VII FACT-G (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

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

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

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

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

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

Appendix VIII EQ-5D-5L Questionnaire

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems walking ❑
- I have slight problems walking ❑
- I have moderate problems walking ❑
- I have severe problems walking ❑
- I am unable to walk ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

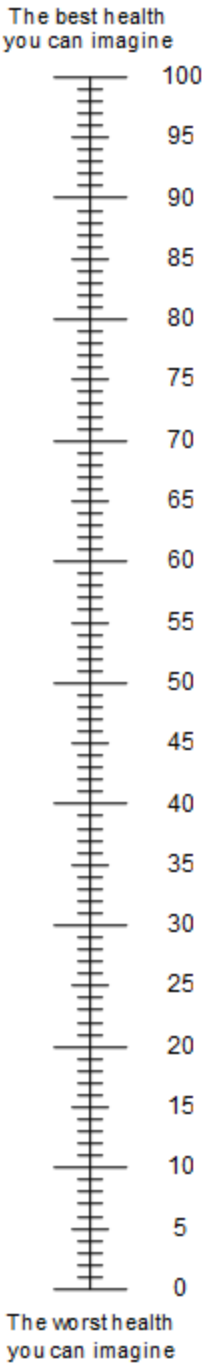
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix IX Patient Information Sheet

You have been given a booklet to complete for this study. The booklet contains some questions about your health as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. The booklet contains two sets of questions:
   EQ-5D-5L questionnaire (6 questions)
   FACT-G questionnaire (27 questions)

2. Please select one answer for each question.

3. Please complete the booklet during your scheduled clinical visit and return it to your nurse or your physician

Thank you for taking the time to help us!