For Protocol Amendment 14 of RTOG 0912, A Randomized Phase II Study of Concurrent Intensity Modulated Radiation Therapy (IMRT), Paclitaxel, and Pazopanib (NSC 737754)/Placebo for the Treatment of Anaplastic Thyroid Cancer

NCI/Local Protocol #: RTOG 0912

NCI Protocol Version Date: March 6, 2020

Section	Change
Cover page	Amendment 14 was added to the Document History Table.
5.3.1	Protocol Specific Requirements for RTOG 0912 Site Registration was updated per standard NCI language since the RT Facilities Inventory form is no longer used.
13.5.5	The statement, "*This change was done in a blinded fashion regarding the clinical outcomes"* was added for clarification to the final analysis.
Informed Consent	No changes to the text of the sample consent; the version date of the consent was changed to be consistent with the amended protocol.

NRG ONCOLOGY

RTOG 0912

A RANDOMIZED PHASE II STUDY OF CONCURRENT INTENSITY MODULATED RADIATION THERAPY (IMRT), PACLITAXEL AND PAZOPANIB (NSC 737754)/PLACEBO, FOR THE TREATMENT OF ANAPLASTIC THYROID CANCER

CTEP Drug: Pazopanib (NSC 737754)

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology; ECOG-ACRIN Medical Research Foundation, Inc.; and SWOG.

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A RANDOMIZED PHASE II STUDY OF CONCURRENT INTENSITY MODULATED RADIATION THERAPY (IMRT), PACLITAXEL AND PAZOPANIB (NSC 737754)/PLACEBO, FOR THE TREATMENT OF ANAPLASTIC THYROID CANCER

CTEP Drug: Pazopanib (NSC 737754)

Protocol Agents (6/5/14)

Agent	Supply	NSC #	IND #
Pazopanib	NCI	737754	75648
Paclitaxel	Commercial	673089	N/A

Participating Sites (6/5/14)

☐ US Only
☐ Canada Only
☒ US and Canada
Approved International Member Sites

Document History

	Version/Update Date	Broadcast Date
Amendment 14	**March 6, 2020**	**N/A**
Amendment 13	February 24, 2020	N/A
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Amendment 8	March 11, 2015	March 26, 2015
Amendment 7	February 10, 2015	March 2, 2015
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Update	July 31, 2013	July 31, 2013
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A RANDOMIZED PHASE II STUDY OF CONCURRENT INTENSITY MODULATED RADIATION THERAPY (IMRT), PACLITAXEL AND PAZOPANIB (NSC 737754)/PLACEBO, FOR THE TREATMENT OF ANAPLASTIC THYROID CANCER

CTEP Drug: Pazopanib (NSC 737754)

<table>
<tr><th colspan="3">CANCER TRIALS SUPPORT UNIT (CTSU) CONTACT INFORMATION (24-FEB-2020)</th></tr>
<tr><th>For regulatory requirements:</th><th>For patient enrollments:</th><th>For study data submission:</th></tr>
<tr><td>Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal.
(Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission.)

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support.

Contact the CTSU Regulatory Help Desk at 1-866-651-2r878 for regulatory assistance.</td><td>Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org

Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.</td><td>NRG Oncology
50 South 16th Street, Suite 2800
Philadelphia, PA 19102

Submit data electronically via the NRG Oncology/RTOG web site, www.rtog.org

Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.</td></tr>
<tr><td colspan="3">The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' web site is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.</td></tr>
<tr><td colspan="3">For clinical questions (i.e. patient eligibility or treatment-related)
For eligibility questions, contact the Study Data Manager For other clinical questions, contact the Study PI of the Lead Protocol Organization.</td></tr>
<tr><td colspan="3">For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)
Contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</td></tr>
<tr><td colspan="3">The CTSU web site is located at https://www.ctsu.org</td></tr>
</table>

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NRG ONCOLOGY
RTOG 0912

A Randomized Phase II Study of Concurrent Intensity Modulated Radiation Therapy (IMRT), Paclitaxel, and Pazopanib (NSC 737754)/Placebo for the Treatment of Anaplastic Thyroid Cancer

SCHEMA (6/5/14)

1st RUN-IN COMPONENT-Completed

REGISTER

Pre-IMRT: Paclitaxel weekly + Pazopanib daily for 2-3 weeks

Concurrent Therapy: IMRT, 66 Gy, in 33 fractions for 6.5 weeks
Paclitaxel weekly for 6 weeks (6 doses)
+ Pazopanib daily for 6 weeks or until the end of radiation

Post-Concurrent Therapy: (Begins 25-31 days after the completion of IMRT)
Paclitaxel weekly + Pazopanib daily

If measurable disease remains: Continue Paclitaxel + Pazopanib until disease progression or significant toxicity requires that treatment be stopped.

If no measurable disease: Paclitaxel + Pazopanib for 4 cycles (12 weeks) or until disease progression or significant toxicity, whichever is first.

Note: Accrual will be suspended after 11 patients have been accrued to the run-in component; the study will remain closed until these 11 patients complete radiation therapy and a safety analysis performed. See Section 13.2.1 for further details.

2nd RUN-IN COMPONENT-Completed

REGISTER

Pre-IMRT: Paclitaxel (80 mg/m2) weekly + Pazopanib (600 mg suspension) daily for 2-3 weeks

Concurrent Therapy: IMRT, 66 Gy, in 33 fractions for 6.5 weeks
+ Paclitaxel, 50 mg/m^2, weekly for 6-7 weeks
+ Pazopanib 300 mg suspension daily for 6-7 weeks or until the end of RT

Note: Accrual will be suspended after 11 patients have been accrued to this 2nd run-in component.

The study will remain closed until these 11 patients complete radiation therapy and a safety analysis performed. See Section 13.2.1 for further details.

IMRT is required for this study. See the pre-registration requirements for IMRT in Section 5.1.

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NRG ONCOLOGY

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A Randomized Phase II Study of Concurrent Intensity Modulated Radiation Therapy (IMRT), Paclitaxel, and Pazopanib (NSC 737754)/Placebo for the Treatment of Anaplastic Thyroid Cancer

SCHEMA (Continued) (6/5/14)

3rd RUN-IN COMPONENT-Completed

Pre-IMRT: Paclitaxel (80 mg/m^2) weekly + Pazopanib (400 mg suspension) daily for 2-3 weeks

REGISTER

Concurrent Therapy: IMRT, 66 Gy, in 33 fractions for 6.5 weeks
+ Paclitaxel, 50 mg/m^2, weekly for 6-7 weeks
+ Pazopanib 300 mg suspension daily for 6-7 weeks or until the end of RT

Note: Accrual will be suspended after 11 patients have been accrued to this 3rd run-in component. The study will remain closed until these 11 patients complete radiation therapy and a safety analysis performed. See Section 13.2.1 for further details.

RANDOMIZED PHASE II COMPONENT

STRATIFY

Presence of Metastatic Disease
1. M0
2. M1
3. Mx

RANDOMIZE

Pre-IMRT:
Paclitaxel, 80 mg/m^2, weekly
+ Pazopanib/placebo, 400 mg suspension, daily for 2-3 weeks

Concurrent Therapy
IMRT, 66 Gy, in 33 fractions for 6.5 weeks
+ Paclitaxel, 50 mg/m^2, weekly for 6-7 weeks
+ Pazopanib/placebo, 300 mg suspension, daily for 6-7 weeks or until the end of RT

IMRT is required for this study. See the pre-registration requirements for IMRT in Section 5.1.

Patient Population: (See Section 3.0 for Eligibility)
Pathologically (histologically or cytologically) proven diagnosis of anaplastic thyroid cancer (a diagnosis that is noted to be "consistent with anaplastic thyroid cancer" with the presence of a thyroid mass is acceptable)

Required Sample Size: Each Run-In Component: 11 patients; Phase II Component: 88 patients

ELIGIBILITY CHECKLIST (3/8/16)
(page 1 of 4)

NRG Oncology Institution #
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Case #

_____(Y) 1. Does the patient have pathologically (histologically or cytologically) proven diagnosis of anaplastic thyroid cancer? (A diagnosis that is noted to be "consistent with anaplastic thyroid cancer" with the presence of a thyroid mass is acceptable.)

_____(Y/NA) 2. If there was a total or partial thyroidectomy completed within 3 months of enrollment, is the surgical specimen showing anaplastic thyroid cancer at least 1 cm in greatest dimension?

_____(Y) 3. Was a history/physical examination done within 2 weeks prior to registration?

_____(Y) 4. Was imaging of the neck and brain (CT scan or MRI) and chest/abdominal imaging (chest x-ray, chest CT scan, or full body PET/CT are acceptable) done within 4 weeks prior to registration and as described in Section 3.1.3?

_____(Y) 5. Was an electrocardiogram done within 10 days prior to registration?

_____(Y) 6. Is the patient's Zubrod Performance Status 0-2?

_____(Y) 7. Is the patient at least 18 years of age?

_____(Y) 8. Does the patient have adequate bone marrow, hepatic, and renal function as specified in Section 3.1?

_____(Y) 9. Were the serum electrolytes done within 10 days prior to registration?

_____(Y) 10. Was the patient's history of QTc prolongation, family history of prolonged QTc, and relevant cardiac disease documented within 10 days of registration?

_____(Y) 11. Were the patient's medications evaluated within 10 days of registration, with attempt to change any medication that affects CYP3A4?

_____(Y) 12. Was the patient's blood pressure taken and recorded by a health care professional within 10 days of registration?

_____(Y) If yes, was the patient's blood pressure < 140/90?

_____(Y) If the patient's systolic blood pressure was > 140 and/or diastolic blood pressure was > 90, does the treating physician believe it is feasible to control the patient's blood pressure to < 140/90 prior to treatment?

_____(Y) 13. Did the patient have a PT/INR/PTT as specified in Section 3.1 within 10 days prior to registration?

_____(Y/NA) 14. For women of child bearing potential, was a serum or urine pregnancy test completed within 10 days of registration?

_____(Y) If yes, was the pregnancy test negative?

Continued on next page

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_____(Y/NA) 15. If a woman of child bearing potential or sexually active male, is the patient willing to use medically acceptable forms of contraception while on treatment and for 6 months post-treatment?

_____(N) 16. Does the patient have any other known active invasive malignancy? (except non-melanomatous skin cancer or differentiated thyroid cancer; the presence of prostate cancer confined to the prostate with a PSA < 1 for more than 6 months also is allowed)

_____(N) 17. Did the patient have prior systemic chemotherapy for anaplastic thyroid cancer?

_____(N) 18. Did the patient have chemotherapy or radiotherapy within 4 weeks of registration (6 weeks for nitrosoureas or mitomycin C) or has the patient not recovered from adverse events due to agents administered > 4 weeks previously?

_____(N) 19. Did the patient have prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields?

_____(N) 20. Does the patient have any of the cardiovascular conditions specified in Section 3.2.4?

_____(Y/N) 21. Is the patient taking medications associated with a risk or QTc prolongation and/or Torsades de Pointes (see Section 3.2.5)?

_____(Y) If yes, can these medications be avoided or replaced with medications that do not carry these risks?

_____(N) 22. Does the patient require heparin? (other than low-molecular weight heparin)

_____(N) 23. Does the patient have any condition that may impair the ability to absorb oral medications/investigational product, as specified in Section 3.2?

_____(N) 24. Does the patient have any condition that may increase the risk of gastrointestinal bleeding or gastrointestinal perforation, as specified in Section 3.2?

_____(N) 25. Did the patient have a history of hemoptysis within 30 days of registration? (patients who have minimal bleeding from the mouth, which is clearly not related to a source in the lungs, are eligible only after good hemostasis has been documented).

_____(N) 26. Does the patient have uncontrolled intercurrent illness or psychiatric illness/social situations that would limit compliance with study requirements?

_____(N) 27. Does the patient have a history of prior allergic reaction to the study drug(s) involved in this protocol?

Continued on next page

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_____(N) 28. Does the patient have QTc prolongation, defined as a QTc interval ≥ 480 msecs or other significant EKG abnormalities?

_____(N) 29. Does the patient have <u>known</u> brain metastasis?

_____(N) 30. Is the patient HIV-positive and on combination antiretroviral therapy?

_____(N/Y) 31. Is the patient receiving prohibited medications that act through the CYP450 system per Section 7.4.1?

_____(Y) If yes, has Dr. Sherman or Dr. Bible been contacted to discuss the patient's medications?

<u>The following questions will be asked at Study Registration</u>:
IMRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION.

_____ 1. Institutional person randomizing this case?

_____(Y) 2. Has the Eligibility Checklist been completed?

_____(Y) 3. In the opinion of the investigator, is the patient eligible?

_____ 4. Date informed consent signed

_____ 5. Patient's Initials (First Middle Last) [May 2003; If no middle initial, use hyphen]

_____ 6. Verifying Physician

_____ 7. Patient ID

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnicity

_____ 11. Gender

_____ 12. Country of Residence

_____ 13. Zip Code (U.S. Residents)

_____ 14. Method of Payment

_____ 15. Any care at VA or military hospital?

_____ 16. Calendar base date

Continued on next page

ELIGIBILITY CHECKLIST (3/25/14)
(page 4 of 4)

NRG Oncology Institution #
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_____ 17. Randomization date

_____ 18. Medical Oncologist's name

_____(Y/N) 19. Have you obtained the patient's consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 20. Have you obtained the patient's consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 21. Have you obtained the patient's consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

_____(Y/N) 22. Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

_____(Y/N) 23. Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?

_____(Y/N) 24. Does the site require expedited drug service for the patient?

If yes, select one of the following couriers and provide the account number.

_____United Parcel Service (UPS) Account number:_____

_____ Federal Express (FedEx) Account number:_____

_____ 25. Presence of Distant Metastatic Disease (M0, M1, MX)

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/NRG Oncology audit.

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Anaplastic Thyroid Cancer

There are approximately 37,000 new cases of thyroid cancer annually in the U.S. alone, resulting in 1600 deaths. Of the 37,000 cases, 1-2% are anaplastic thyroid cancer. While differentiated thyroid cancers are typically curable, anaplastic thyroid cancer (ATC) is one of the most aggressive and deadly solid tumors, with a 1-year survival rate of only approximately 10% and with very few long-term survivors (Goutsouliak 2005).

ATC often presents with a rapidly growing neck mass. Other common symptoms include hoarseness and neck pain. Because airway and esophageal compromise are of major concern, obtaining local control of this disease in the neck is crucial, as it is essential for patient quality of life, particularly in preventing asphyxiation and allowing maintenance of oral nutrition. Improving local control also is thought to improve overall survival (Haigh 2001). Historical methods to improve local control in ATC have included surgery and/or radiation therapy.

1.2 Anaplastic Thyroid Cancer and Surgery

The role of surgery is limited in ATC for the following reasons: 1) These tumors are rarely resectable at diagnosis due to their ill-defined borders, as well as their attachment to surrounding vital structures in the neck; and 2) Systemic disease is almost uniformly present, at least at the microscopic level, even upon initial diagnosis. However, there has been some evidence that surgery followed by post-operative radiation therapy and chemotherapy can result in better patient outcomes than radiotherapy alone (Haigh 2001).

1.3 Anaplastic Thyroid Cancer and Radiation Therapy/Chemotherapy

Non-surgical treatment approaches, such as the use of hyperfractionated radiation therapy with weekly doxorubicin, can improve median survival to 12 months. Eventually, most patients succumb to distant metastatic disease (Unpublished data, Memorial Sloan-Kettering). Data from Princess Margaret Hospital have suggested that patients who underwent radical radiotherapy had significantly higher local progression-free rate versus those who underwent palliative radiotherapy, with median survival greater in patients with radical (11.1 months), versus palliative (3.2 months) radiotherapy ($p<0.0001$). However, there has been no significant difference in the median overall survival in patients undergoing hyperfractionation versus once-daily radiotherapy (Wang 2006). A range of doses was used in this study, and 60 Gy given over 40 fractions in 1.5 Gy per fraction was typically used when patients underwent a hyperfractionated regimen.

Delivering high dose radiation to the tumor when treating anaplastic thyroid cancer is limited by the presence of the spinal cord and lung, which lie in close proximity to the tumor target. Intensity modulated radiation therapy (IMRT) improved tumor coverage when compared to conventional radiotherapy techniques while significantly reducing the dose to these surrounding normal tissues (Nutting 2001; Lee 2003). At the University of California-San Francisco Medical Center, IMRT has been used for the treatment of anaplastic thyroid cancer in combination with chemotherapy (Posner 2000). This treatment strategy has been shown to prolong survival with a median survival as high as 43 months in patients who also had complete surgical resection. Treatments are typically given in once a day rather than twice daily fractionation.

While doxorubicin often has been considered the “standard” agent for treating ATC patients with advanced disease, many preclinical studies have shown very limited activity (Ain 1996). Ain, et al. (2000) have shown significant activity with paclitaxel in 6 human ATC cell lines, and a subsequent, small multi-institutional phase II study using single agent paclitaxel in advanced ATC demonstrated a promising response rate of 53%.

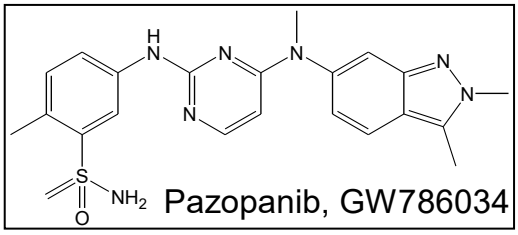
1.4 Anaplastic Thyroid Cancer and Angiogenesis inhibition

Vascular Endothelial Growth Factor (VEGF) receptor (r) inhibitors have shown promise in anaplastic and differentiated thyroid cancers. In nude mice, Bauer, et al. (2002) demonstrated significant response of ATC to monoclonal antibodies to VEGFr. In the treatment of differentiated thyroid cancers, phase II studies with multiple agents that act as angiogenesis inhibitors (e.g., xatinib, sorafinib, sutinib, pazopanib, lenalidomide) also have shown activity (Adjei 2008; Gupta-Abramson 2008).

Oxygen free radicals formed by radiation are essential for the induction of radiation-induced DNA-damage. One might predict that inhibition of angiogenesis would decrease oxygen delivery to the tumor, thereby attenuating the antitumor activity of radiation. However, both preclinical and clinical models have shown that antiangiogenic agents improve response to radiotherapy (Gorski 1998; Nieder 2007; Hess 2001). To explain these results, several researchers invoke the pathologic nature of tumor neovessels, which are dilated, tortuous, and highly permeable. These characteristics of tumor vasculature result in increased interstitial fluid pressure (IFP), a hallmark of solid tumors. In theory, pretreatment with antiangiogenic agents reduces the number of inefficient vessels and improves tumor perfusion. In support of this 'vascular normalization' hypothesis, antibody to VEGF-A reduces tumor vascular density and IFP. Another theoretical premise holds that antiangiogenic therapy sensitizes tumor cells to radiation-induced apoptosis by interfering with autocrine loops. Many solid tumor types, including head and neck squamous cell carcinoma (HNSCC), express VEGF receptors. VEGF-A produced by tumor cells may promote tumor cell survival by an autocrine loop. As such, VEGF-A blockade may sensitize tumor cells to the radiation-induced apoptosis. The 2 theoretical mechanisms of vascular normalization and tumor sensitization may coexist.

1.5 Pazopanib

Pazopanib is a second-generation, multi-targeted tyrosine kinase inhibitor against VEGFR-1, 2, and 3, platelet-derived growth factor receptor, c-kit, Ret and other kinases. Preclinical data suggests synergy with radiation therapy when started 1 week prior to the start of radiation therapy (Confidential Information, GlaxoSmithKline). Currently, pazopanib is undergoing a phase II study in differentiated, medullary, and anaplastic thyroid cancers at the Mayo Clinic, with evidence of activity in all 3 tumor types (Bible 2009). Phase I studies have shown that pazopanib also can be safely administered with paclitaxel (Tan 2008). Moreover, in non-small cell lung cancer, it has been shown to be safely given 1 week after surgery, making its use in the immediately post-operative period feasible.



Pazopanib, GW786034

1.5.1 *Nonclinical Pharmacokinetics and Drug Metabolism*

Mean bioavailability ranged from 47% in dogs to 72% in rats. There was a 4- to 5-fold decrease in exposure in fed compared to fasting dogs, but in monkeys the exposure did not change substantially on feeding. Pazopanib is highly (>98.8%) plasma protein bound in mouse, rat, dog, monkey, and human plasma. In vitro data indicate that pazopanib is highly permeable across membranes and is a substrate for the P-glycoprotein (P-gp) transporter and breast cancer resistant protein (BCRP). Following oral administration of radiolabeled pazopanib, excretion of drug-related material was rapid and essentially complete. Circulating metabolites observed in humans were minor and were also noted in the nonclinical species. Metabolism appeared to be predominantly mediated by CYP3A4 and to a lesser extent by CYP1A2 and CYP2C8. The majority of the dose was excreted via feces in humans, rats, and monkeys.

1.5.2 *Clinical Experience of Pazopanib*

Approximately 3000 subjects with cancer have been enrolled in clinical studies of pazopanib as of September 2009. In October 2009, the FDA approved pazopanib tablets for the treatment of subjects with advanced renal cell carcinoma (RCC). In addition, several clinical studies evaluating pazopanib in non-small cell lung cancer (NSCLC), ovarian cancer, breast cancer, soft tissue sarcoma (STS), cervical cancer, hepatocellular cancer (HCC), multiple myeloma (MM), and glioma are in progress or have been completed.

1.5.3 *Clinical Efficacy of Pazopanib*

In a randomized, double-blind, placebo-controlled phase 3 study evaluating the efficacy and safety of pazopanib monotherapy in treatment-naive and cytokine-pretreated subjects with advanced RCC, the median progression-free-survival (PFS) was significantly prolonged with pazopanib compared with placebo in the overall study population (9.2 vs. 4.2 months). The

objective response rate (RR) was 30% with pazopanib and only 3% with placebo (Sternberg, in press). In subjects with ovarian cancer, 31% of subjects experienced a CA-125 response to pazopanib, with a median time to response of 29 days and median duration of response of 113 days (Investigator's Brochure, 2010). Median PFS was 84 days and the overall RR was 18%. In advanced or metastatic STS, the rate of PFS at 12 weeks was 43.9% for leiomyosarcoma, 48.6% for synovial sarcoma, 26.3% for adipocytic sarcoma, and 39% for other types of sarcoma (Sleijfer, 2008). In a phase 2 trial of subjects with early-stage NSCLC, 86% of subjects experienced a reduction in tumor volume after short-term, preoperative use of pazopanib (~2-6 weeks) as assessed by high-resolution CT scanning (Altorki, 2008). Interim results from a phase 2 study of pazopanib in subjects with recurrent or metastatic breast invasive breast cancer showed that the clinical benefit rate was 26% (Taylor, 2009). The median TTP was 3.7 months, and 50% of subjects with measurable target lesions had some decrease in size. PFS at 3 and 6 months was 55% and 28%, respectively. Preliminary results from a randomized study in subjects with first-line advanced ErbB2-positive advanced or metastatic breast cancer showed that a higher response rate (36.2% vs. 22.2%) was observed in subjects on combination lapatinib 1000 mg once daily + pazopanib 400 mg once daily compared to monotherapy lapatinib 1500 mg once daily (Slamon, 2008). In a randomized phase 2 study of pazopanib vs. lapatinib vs. the combination of pazopanib/lapatinib in advanced and recurrent cervical cancer, there was a 34% reduction in risk for progression in subjects receiving pazopanib relative to lapatinib. The median PFS was 17.1 weeks in the lapatinib group and 18.1 weeks in the pazopanib group (Monk 2009). Interim analysis of data from 26 subjects showed that pazopanib has both a favorable toxicity profile and promising clinical activity in subjects with advanced and progressive differentiated thyroid cancers (Bible 2009). Five confirmed partial responses (PRs) [19%] were reported. Pazopanib has not shown efficacy in phase 2 studies conducted in MM or glioma (Investigator's Brochure, 2010)

1.5.4 *Safety of Pazopanib*

The randomized, phase 3 study in mRCC subjects provided a key comparison of safety with pazopanib compared to placebo (Sternberg, in press). The overall frequency of adverse events (AEs) reported during the study was higher in the pazopanib arm (92%) compared with placebo (74%). The most common AEs reported in >20% of subjects in the pazopanib arm were diarrhea (52%), hypertension (40%), hair color change (depigmentation; 38%), nausea (26%), anorexia (22%), and vomiting (21%). Most of the events were grade 1 or 2. A higher number of grade 3 AEs were reported in the pazopanib arm (33%) compared with the placebo arm (14%). The most frequent grade 3 AEs in the pazopanib arm were increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), hypertension, and diarrhea. The frequency of grade 4 and grade 5 AEs was similar between the pazopanib and placebo arms: grade 4 in 7% and 6%, respectively; grade 5 in 4% and 3%, respectively.

A comprehensive review of all completed and ongoing pazopanib clinical trials with a cut-off date of September 2009, lists 15 most commonly occurring serious AEs (SAEs) [Investigator's Brochure, 2010]. Vomiting and diarrhea are the most commonly reported SAEs across all the pazopanib studies. As a consequence of this, dehydration also is seen with pazopanib treatment. For most reports, the AEs resolved after supportive treatment such as antiemetics, antidiarrheal agents, and IV fluids. GI perforation is commonly associated with VEGF pathway inhibitors. This may manifest as abdominal pain which is not uncommon in cancer subjects for many reasons. Of the 42 subjects in pazopanib trials with SAEs of abdominal pain, only three had a documented underlying intestinal perforation. In July 2006, the DCTD, NCI, issued an Action Letter to investigators using pazopanib describing the occurrence of bowel perforations in subjects on pazopanib clinical trials.

Dyspnea also is frequently seen in pazopanib-treated subjects and may reflect the underlying disease under treatment. Anemia is commonly seen in cancer subjects in association with chemotherapy, hemorrhage, or infection. The SAEs of pyrexia were attributed to multiple causes: concurrent infections, the underlying malignancy, hepatic events, other concomitant medications, and unknown causes. Hepatic events are thought to be on-target tyrosine kinase inhibitor (TKI) class effects, as hepatic enzyme elevations have been seen with other agents of this class. Careful clinical evaluation is, therefore, warranted in subjects with hepatic abnormalities. Pneumonia can be a complication of chemotherapy or can result from debilitation and advanced disease. Review of the 33 SAEs showed the presence of an

underlying cause other than pazopanib in 19 of the 30 subjects. Fatigue and asthenia are commonly reported and have multiple causes.

Hypertension observed with pazopanib is a known class effect. There have been 30 SAEs of hypertension and 3 SAEs of hypertensive crisis in pazopanib clinical trials. There were 28 subjects who were effectively treated with antihypertensive medication initiation or dose adjustment, while 4 had no such treatment. Although there were 29 SAEs of pleural effusion, the body of data does not suggest that any of these cases were due to pazopanib. There have been 24 SAEs of pulmonary embolism (PE) reported in pazopanib trials. This is of particular relevance since other members of this class have been associated with PE and other venous thromboembolic events.

In addition, there have been reports of cardiac and cerebral ischemic events, GI perforation or hemorrhage, pulmonary hemorrhage, cerebrovascular hemorrhage, QT prolongation, and Torsades de Pointes in pazopanib clinical trials.

1.5.5 *Clinical Pharmacokinetics of Pazopanib* **(2/27/12)**

The oral bioavailability of pazopanib reflects absorption that is limited by solubility above doses of 800 mg once daily (Investigator's Brochure, 2010; Hurwitz, 2009). Increases in doses above 800 mg to 2000 mg, in the fasted state will not result in increased systemic exposure. Geometric mean pazopanib t½ values ranged from 18.1-52.3 hours. The mean t½ was 30.9 hours in the 800 mg once daily group (Hurwitz 2009). Oral absorption is significantly enhanced when dosed with food; therefore, it is recommended to administer pazopanib on an empty stomach, at least 1-2 hours after a meal.

A study evaluating the pharmacokinetics (PK) of pazopanib when crushed or delivered as an oral suspension demonstrated that administration of pazopanib as a suspension lead to increased systemic exposure to pazopanib compared to administration of the whole tablet. Administration of the oral suspension compared to whole-tablet pazopanib increased AUC (0-72) by 33% (Heath, 2011). A pediatric study of pazopanib oral suspension (ADVL0815, Children's Oncology Group Study) has recently been completed and the PK data is currently being analyzed.

Preliminary information on the PK of pazopanib administered in combination with lapatinib has been reported (Dejonge, 2006). Thirty-three subjects received doses of lapatinib ranging from 750-1500 mg once daily along with pazopanib at doses of 200-500 mg daily. Preliminary mean plasma concentrations 24 hours after administration (C24) on day 22 were ~19 mcg/mL and 23 mcg/mL after pazopanib doses of 250 mg and 500 mg, respectively. These values are similar to the mean C24 values observed after administration of 800 mg pazopanib alone (23.1 mcg/mL). Plasma lapatinib concentrations at 750-1500 mg daily were similar to those observed after monotherapy. Concurrent administration of pazopanib and lapatinib was generally well tolerated; coadministration of lapatinib may alter the PK of pazopanib (Dejonge, 2006).

Preliminary PK information on the combination of pazopanib and paclitaxel administered to subjects with advanced cancer has been reported (Suttle, 2007). Twelve subjects received paclitaxel (15-80 mg/m^2 on days 1, 8, and 15 every 28 days) and pazopanib at 400 or 800 mg/day starting on day 2 of the first cycle. Coadministration of pazopanib increased paclitaxel mean Cmax and AUC0-8 approximately 20-35% (Suttle, 2007).

Age, body weight, gender, and race had no significant influence on pazopanib PK.

1.5.6 *Effects of Pazopanib in Differentiated Thyroid Cancer Patients*

A three-outcome, one-stage Phase II clinical trial of pazopanib (800 mg orally daily until progression or intolerance) in patients with rapidly progressive radioiodine-refractory differentiated thyroid cancers is in progress. The median number of 4 week cycles administered thus far is 11 (range: 1-19+, total: 343+), with 14 of 37 patients still receiving protocol therapy. Fourteen of the 37 evaluable patients required dose reductions due to: elevated AST/ALT levels (4 patients), hypertension (2 patients), neurologic difficulties (1 patient), mucositis (1 patient), radiation recall tracheitis (1 patient), diarrhea with intermittent phlebitis (1 patient), nausea and colonic inflammation (1 patient), fatigue with weight loss (1 patient), cough (1 patient), and abdominal pain (1 patient). In addition, 2 patients discontinued treatment due to

adverse hemorrhagic events (one grade 3 GI hemorrhage and one grade 4 intracranial hemorrhage in the absence of brain metastases; both events were self limited with complete patient recovery upon discontinuation of study drug). Two patients (5.4%) died while on study: a 62 year old male presenting emergently with tachycardia, hypotension, and dehydration died during his first cycle of treatment due to an acute massive myocardial infarction; a 63 year old male hospitalized with acute cholecystitis after 2 cycles of treatment requiring surgery that was later complicated by a bowel volvulus with perforation at the site of a remote surgical anastomosis.

Ten of the 20 patients (50%) who were not taking hypertensive medications prior to the start of study treatment required antihypertensive medication. Modest levels of fatigue, altered taste perception, and skin/hair hypopigmentation also were commonly encountered.

There were no complete responses, but 18 confirmed RECIST partial responses (PR) [48.6%; 90% CI: 34.3-63.2%]. The duration of response (time from when PR first documented to disease progression) ranged from 3.5+ months to 15+ months, with responses continuing over a year in 4 patients. In terms of cell type, there were 8 PRs among the 11 patients with follicular (72.7%), 5 PRs among the 11 patients with Hürthle cell (45.4%), and 5 PRs among the 15 patients with papillary (33.3%) histologies.

Twenty-five of 37 patients (67.6%; 9 with follicular, 6 with Hürthle cell, and 10 with papillary) remained on study treatment for at least 6 months. The percentage decrease in tumor size from pre-treatment levels ranged from 30 to 59% in 19 of 37 patients (Figure 1 below) while the percentage decrease in thyroidglobulin from pre-treatment levels was at least 30% in 29 of the 33 patient who were anti-thyroidglobulin antibody negative. Examination of the effects of pazopanib on the rates of RECIST tumor measurement progression among responders (shown for 9 representative DTC patients in figure 1a) suggests that pazopanib therapy may be modifying disease natural history in a sizable fraction of patients.

Figure 1: Maximum Percentage Change in Tumor Size, DTC Patients

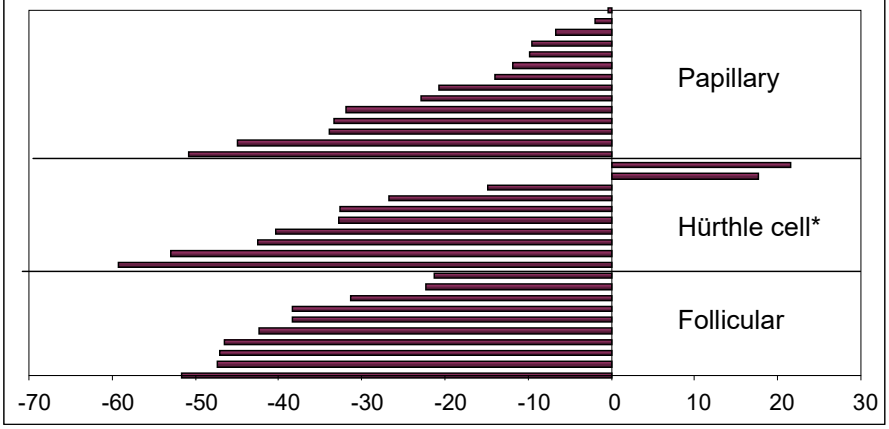
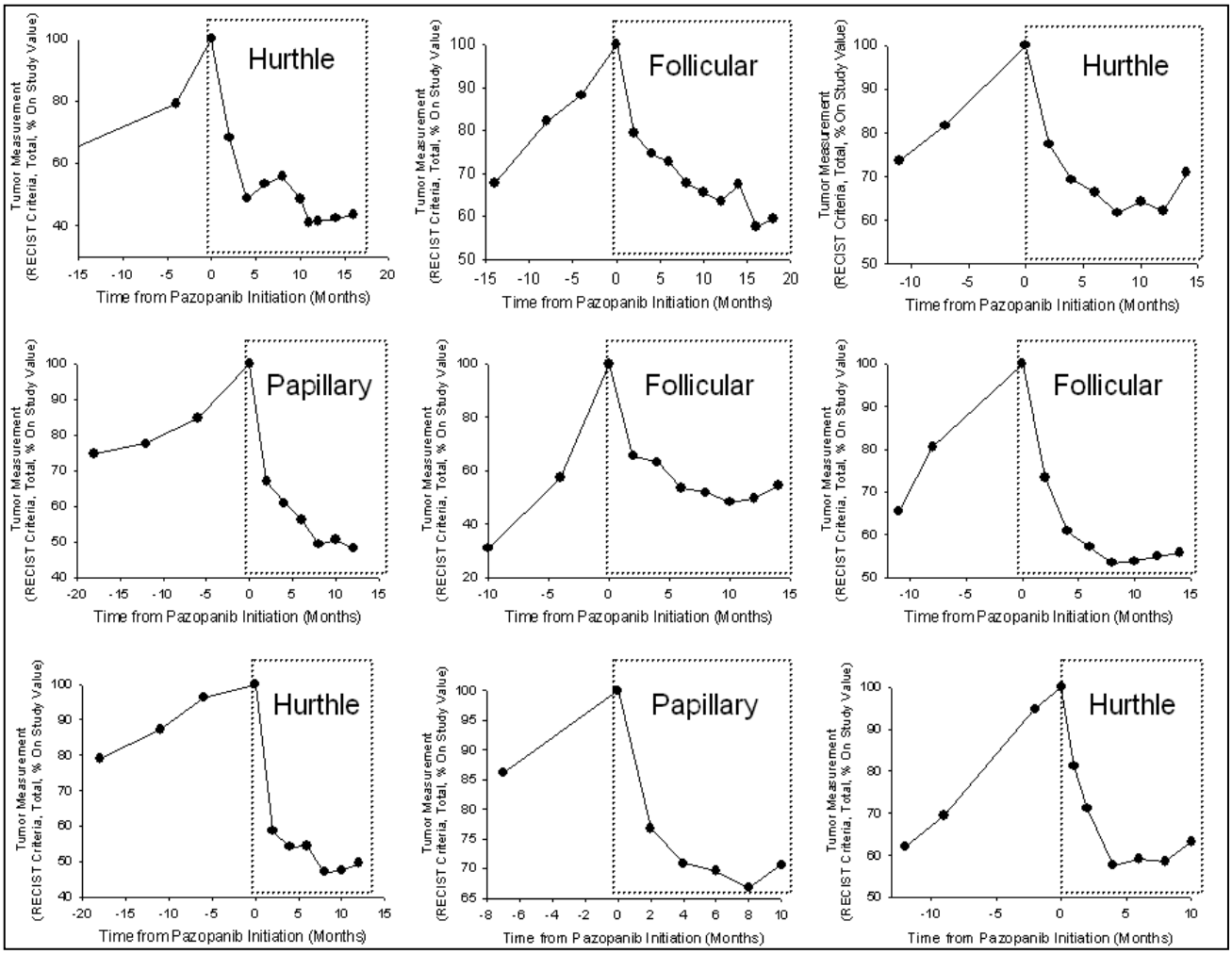


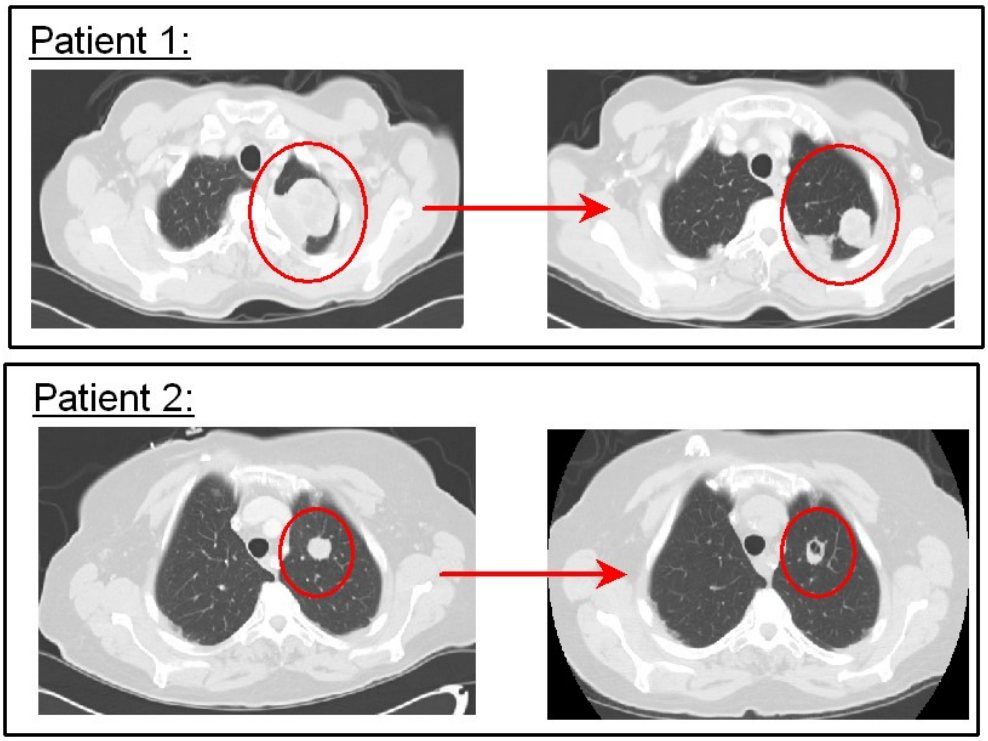
Figure 1a: RECIST Changes In 9 Sample Patients



1.5.7 *Effects of Pazopanib in Anaplastic Thyroid Cancer Patients*

A cohort of ATC patients are being treated with pazopanib in parallel with the trial of pazopanib in DTC discussed above. Although this trial has not yet reached interim analysis, there has been evidence of antitumor effect in several patients, with tumor shrinkage and cavitation of pulmonary nodules observed in several patients as illustrated in Figure 2 below. However, to date, antitumor effects have not been durable in ATC patients attaining a response to pazopanib in the ongoing trial.

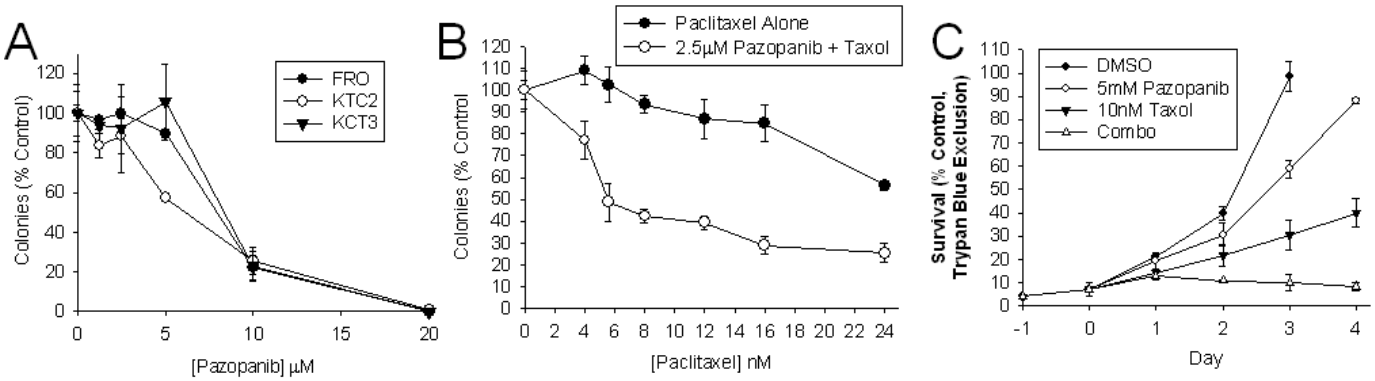
Figure 2: Films Of 2 ATC Patients On Pazopanib



1.5.8 *In Vitro effects of Pazopanib Combined with Paclitaxel in Anaplastic Thyroid Cancer Cell Lines*

There are no data available at present related to the combined effects of paclitaxel and pazopanib in ATC in patients. Pilot studies in ATC cell lines, however, indicate that pazopanib has single agent effects at clinically achievable concentrations (Figure 3 below). Moreover, pazopanib can enhance the *in vitro* anti-tumor effects of paclitaxel in ATC cell lines, as shown in KTC2 ATC cells in panels B and C below (Figure 3).

Figure 3: Pazopanib And Paclitaxel In ATC Cell Lines



1.6 Rationale to Use Paclitaxel, Pazopanib, and Radiation Therapy To Treat Anaplastic Thyroid Cancer

Given the dismal prognosis of ATC patients (<10% 1-year survival), the fact that these tumors are highly vascular, the potential utility of VEGF inhibitors as radiosensitizers, and the preliminary evidence of activity in thyroid cancers of small molecule VEGF inhibitors including sorafenib, sunitinib, and pazopanib, it is logical to add a VEGF inhibitor to the current standard approach to ATC. In particular, bevacizumab,

a monoclonal antibody that potently inhibits VEGF, when added to a platin/paclitaxel combination in a phase III study in lung cancer has produced an improvement in survival (Sandler 2006). In HNSCC, NRG Oncology has shown that the combination of cisplatin/paclitaxel/radiation therapy also can be given together safely with good efficacy (Garden 2004). Data has shown that doses of paclitaxel can be given as high as 50 mg/m^2 weekly with radiation therapy (Hainsworth 2002).

Paclitaxel and pazopanib have been evaluated in a phase I study (Tan 2008). This study showed that without radiation therapy, paclitaxel 80 mg/m^2 weekly with pazopanib 800 mg daily could be given safely. Only 1 dose limiting toxicity was seen at this dose (grade 3 groin abscess). However, pazopanib did increase the mean paclitaxel AUC by 45% and Cmax by 40%. Due to this increase in mean exposure, it was felt by representatives at GSK and CTEP that it would be more reasonable to decrease the pazopanib dose during radiation therapy by 50% (i.e., 400 mg daily) and that the paclitaxel should be reduced by 25% after radiation therapy (Personal Communication with CTEP, 2009).

Due to logistical reasons as well as patient ease considerations, it was decided by the investigators that standard fractionation using 2 Gy per fraction to a total dose of 66 Gy will be the radiotherapy regimen. This is biologically equivalent in terms of cell kill to the hyperfractionated regimen (Wang 2006).

1.7 Current Experience of the Use of Paclitaxel, Pazopanib, and Radiation Therapy to Treat Anaplastic Thyroid Cancer (6/5/14)

Three run-in components for RTOG 0912 have been completed.

- After the first run-in, there was concern about patients' difficulty in swallowing pazopanib pills. It was decided to do a second run-in with a pazopanib slurry, and due to the lack of data in adults, pharmacokinetic data was collected during the 2nd run-in.
- After the 2nd run-in, it was noted there was an increase in elevated liver enzymes requiring pazopanib to be held during the first few weeks of radiation therapy correlating to elevated serum levels of pazopanib on day 15 of treatment (prior to the start of radiation therapy). Therefore, a 3rd run-in component was completed with a lower dose of pazopanib during the pre-radiation therapy period.
- After the 3rd run-in, it was felt that toxicities were consistent with what is seen with concurrent chemotherapy and radiation therapy for the treatment of anaplastic thyroid cancer as defined in the protocol. Patients at this dose level received pazopanib slurry at 400 mg daily with paclitaxel 80 mg/m^2 weekly for 2-3 weeks followed by radiation therapy with paclitaxel at 50 mg/m^2 weekly and pazopanib slurry at 300 mg daily.

2.0 OBJECTIVES (6/5/14)

2.1 Primary Objective for Run-In Components

To evaluate the safety of IMRT, paclitaxel, and pazopanib suspension

2.2 Primary Objective for Phase II Component

To evaluate and compare overall survival at 1 year from study registration

2.3 Secondary Objectives for Phase II Component

2.3.1 To evaluate local-regional control at 6 and 12 months;

2.3.2 To evaluate the rate of grade 4 (CTCAE, v. 4.0) hemorrhage, grade 4 febrile neutropenia, or any Grade 5 adverse event assessed to be definitely, probably, or possibly related to the induction or concurrent treatment components of the protocol regimen;

2.3.3 To evaluate the rates of other adverse events (CTCAE, v. 4.0) assessed to be definitely, probably, or possibly related to the induction or concurrent treatment components of the protocol regimen;

2.3.4 To evaluate the rate of treatment discontinuation due to toxicity during the induction or concurrent treatment components of the protocol regimen;

2.3.5 To evaluate response (as per RECIST) of the primary site following the treatment component in subjects with measurable disease prior to chemoradiation.

3.0 PATIENT SELECTION (6/5/14)

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED. For questions concerning eligibility, please contact the study data manager.

3.1 Conditions for Patient Eligibility (3/8/16)

3.1.1 Pathologically (histologically or cytologically) proven diagnosis of anaplastic thyroid cancer (a diagnosis that is noted to be "consistent with anaplastic thyroid cancer" with the presence of a thyroid mass is acceptable);

Note: Tissue collection for central review is mandatory (see Section 10.2), but central review is not required for eligibility. Due to the aggressiveness of this disease, treatment will be started prior to central review.

3.1.2 If there was a total or partial thyroidectomy completed within 3 months of enrollment, the surgical specimen must show the area of anaplastic thyroid cancer to be at least 1 cm in greatest dimension.

3.1.3 The following minimum diagnostic workup is required:

- History/physical examination within 2 weeks prior to registration;
- Imaging of neck and brain (CT scan or MRI) and chest/abdominal imaging (chest x-ray or chest CT scan, or full body PET/CT are acceptable) within 4 weeks prior to registration;

Note: The CT scan of the neck must be done with contrast or if an MRI is done, with gadolinium; therefore, the CT portion of a full body PET/CT has to be a high resolution CT to be acceptable for eligibility.

Abdominal imaging must cover the liver and adrenal glands; therefore, separate imaging is not required if these areas are covered by a chest CT scan.

- Electrocardiogram within 10 days prior to registration;

3.1.4 Zubrod Performance Status 0-2;

3.1.5 Age ≥ 18 years of age;

3.1.6 CBC/differential within 10 days prior to registration on study, with adequate bone marrow and organ function defined as follows:

- Absolute neutrophil count (ANC) ≥ 1500 cells/mm^3;
- Platelets ≥ 100,000 cells/mm^3;
- Hemoglobin ≥ 9.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 9.0 g/dl is acceptable);

3.1.7 Adequate hepatic function within 10 days prior to registration, defined as follows:

- Total bilirubin < 1.5 x institutional ULN (except for patients with Gilbert's syndrome and elevations of indirect bilirubin);
- AST or ALT < 2.5 x institutional ULN; **Note**: patients who have both bilirubin > ULN and AST/ALT > ULN are not eligible (unless they have Gilbert syndrome and elevations of indirect bilirubin).

3.1.8 Adequate renal function, defined as follows:

- Spot urine protein to creatinine ratio (UPCR) < 1 or a 24-hour urine protein collection < 1 gm within 10 days prior to registration;
- Creatinine <1.5 mg/dl or within normal institutional limits within 10 days prior to registration; **Note**: if neither criteria is met, the creatinine clearance must be > 50 ml/min/1.73m^2 per either 1) the Cockcroft-Gault equation; 2) Jeliffe method; or 3) 12- or 24-hour urine collection.

3.1.9 **(10/28/10)** Serum electrolytes including sodium, potassium, BUN, creatinine, glucose, magnesium, phosphate, and calcium within 10 days prior to registration;

3.1.10 Documentation of the patient's history of QTc prolongation, family history of prolonged QTc, and relevant cardiac disease within 10 days prior to registration;

3.1.11 **(7/15/13)** Evaluation of the patient's medications within 10 days prior to registration with attempt to change any medication that affects CYP3A4 (see Sections 7.4.1, 9.2, and Appendix VII).

3.1.12 **(4/18/12)** Blood pressure ≤ 140/90 within 10 days of registration (must be taken and recorded by a health care professional); **Note**: if the systolic blood pressure is > 140 and/or diastolic blood pressure is > 90 at the time of registration, the patient's blood pressure must be controlled. Systolic blood pressure must be < 140 and diastolic blood pressure must be < 90 on

at least 2 separate measurements prior to the start of treatment (see Section 4.1.1), and the treating physician must believe that this is feasible in order to enroll the patient.

3.1.13 PT/INR/PTT within 1.2 x the upper limit of normal within 10 days prior to registration **unless** the patient is receiving Coumadin and has a stable INR that is in range for the desired level of anticoagulation;

3.1.14 Negative pregnancy test (serum or urine) within 10 days of registration in women of child-bearing potential;

3.1.15 Women of childbearing potential and male participants who are sexually active must agree to practice adequate contraception during treatment and for 6 months post-treatment;

3.1.16 The patient must provide study specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility (3/8/16)

3.2.1 Known active invasive malignancy (except non-melanomatous skin cancer or anaplastic thyroid cancer; the presence of prostate cancer confined to the prostate with a PSA ≤ 1 for more than 6 months also is allowed);

3.2.2 Prior systemic chemotherapy for anaplastic thyroid cancer;

- Patients who have had chemotherapy or radiotherapy within 4 weeks of registration (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered > 4 weeks previously;
- Patients receiving other investigational agents.

3.2.3 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;

3.2.4 Patients with any of the following cardiovascular conditions within the past 6 months:

- Cerebrovascular accident (CVA) or transient ischemic attack (TIA);
- Admission for unstable angina;
- 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 for less than 6 weeks
- arterial thrombosis;
- Symptomatic peripheral vascular disease;
- Class III or IV heart failure as defined by the NYHA functional classification system (see Appendix III); **Note**: a patient who has a history of Class III heart failure and is asymptomatic on treatment may be considered eligible for the study.

3.2.5 Certain medications that are associated with a risk for QTc prolongation and/or Torsades de Pointes, although not prohibited, should be avoided or replaced with medications that do not carry these risks, if possible. Comprehensive lists of agents that that are associated with a risk for QTc prolongation and/or Torsades de Pointes can be found in Appendix VI.

3.2.6 Patients who require heparin (other than low-molecular weight heparin);

3.2.7 Patients with any condition that may impair the ability to absorb oral medications/investigational product including:

- prior surgical procedures affecting absorption including, but not limited to major resection of stomach or small bowel;
- active peptic ulcer disease;
- malabsorption syndrome.

3.2.8 Patients with any condition that may increase the risk of gastrointestinal bleeding or gastrointestinal perforation, including:

- active peptic ulcer disease;
- known intraluminal metastatic lesions;
- inflammatory bowel disease (e.g., ulcerative colitis, Crohn's disease) or other gastrointestinal conditions which increase the risk of perforation;
- history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 28 days prior to beginning study treatment.

3.2.9 History of hemoptysis within 30 days of registration. **Note**: patients who have minimal bleeding from the mouth, which is clearly not related to a source in the lungs, i.e. surgery such as a non-lung biopsy, are eligible only after good hemostasis has been documented;

3.2.10 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection or psychiatric illness/social situations that would limit compliance with study requirements;

3.2.11 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

3.2.12 Prior allergic reaction to the study drug(s) involved in this protocol;

3.2.13 QTc prolongation defined as a QTc interval ≥ 480 msecs or other significant EKG abnormalities are ineligible; Note: if unsure about EKG abnormality, the treating physician should discuss this with Drs. Sherman or Bible.

3.2.14 Known brain metastasis;

3.2.15 HIV-positive patients on combination antiretroviral therapy because of the potential for pharmacokinetic interactions with pazopanib; in addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.2.16 **(7/15/13)** Certain medications that act through the CYP450 system are specifically prohibited in patients receiving pazopanib and others should be avoided or administered with extreme caution.

- Strong inhibitors of CYP3A4 such as ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinivir, retonavir, saquinavir, telithromycin, voriconazole may increase pazopanib concentrations and are prohibited; although, in exceptional circumstances, they may be administered in conjunction with lowering the dose of pazopanib by 50% of what would otherwise be administered. Grapefruit juice is also an inhibitor of CYP450 and should not be taken with pazopanib (see Section 7.4.1).
- Strong inducers of CYP3A4, such as rifampin, may decrease pazopanib concentrations, are strictly prohibited (see Section 7.4.1).
- Medications that have narrow therapeutic windows and are substrates of CYP3A4, CYP2D6, or CYP2C8 should be avoided and, if necessary, administered with caution (see Section 7.4.1).
- A list of medications that are specifically prohibited or those that should be used with caution during this trial of pazopanib can be found in Section 9.0. Comprehensive lists of agents that could affect pazopanib through the cytochrome P450 system can be found in Appendix VII.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management (2/10/15)

4.1.1 Systolic blood pressure must be ≤ 140 and diastolic blood pressure must be ≤ 90 on at least 2 separate measurements within 2 weeks prior to treatment, if > 140/90 at baseline (see Section 3.1.12);

4.1.2 All wounds, whether surgical or other, must be completely healed prior to the initiation of treatment.

4.2 Highly Recommended Evaluations/Management

The following pre-treatment evaluations/interventions are not required but are highly recommended:

4.2.1 PET/CT scan within 2 weeks prior to registration;

4.2.2 Dental evaluation and, if applicable, prophylaxis within 12 weeks prior to treatment (see Appendix IV);

4.2.3 Nutritional evaluation for a prophylactic gastrostomy (PEG) tube placement anytime prior to treatment;

4.2.4 Serum Thyroid Stimulating Hormone (TSH) suppression (i.e. lowering TSH below the lower limits of normal) through the use of thyroid hormone replacement (e.g. levothyroxine) should be considered at the start of and throughout the treatment course. However, the decision to suppress TSH is up to the treating physician after weighing the risks and benefits for an individual patient. If the treating physician is unsure or uncomfortable with this, it is strongly recommended that an endocrinologist be consulted.

5.0 REGISTRATION PROCEDURES (24-FEB-2020)

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave,);
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and

In addition, all investigators act as the Site-Protocol PI or as, consenting/treating/drug shipment must be rostered at the enrolling site with a participating organization (i.e., Alliance). Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

Note: This trial is not utilizing the services of the ITC for dosimetry digital treatment data submission. See below for information on installing TRIAD for submission of digital RT data prior to enrolling patients.

IMRT is required for this study.

5.1 Pre-Registration Requirements for IMRT Treatment Approach (6/5/14)

5.1.1 In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements or determining if they already have been met are available on the Imaging and Radiation Oncology Core (IROC) Houston (former Radiological Physics Center [RPC]) web site. Visit http://irochouston.mdanderson.org and select "Credentialing" and "Credentialing Status Inquiry".

An IMRT phantom study with the IROC Houston must be successfully completed (if the institution has not previously met this IMRT credentialing requirement). Instructions for requesting and irradiating the phantom are available on the IROC Houston web site at http://irochouston.mdanderson.org; select "Credentialing" and "NRG Oncology". Upon review and successful completion of the phantom irradiation, the IROC Houston will notify both the registering institution and NRG Oncology that the institution has completed this requirement. Subsequently, NRG Oncology will update the RSS web site.

5.1.2 The institution or investigator must update a current or complete a new Facility Questionnaire (available on the IROC Houston web site at http://irochouston.mdanderson.org) and then complete a credentialing status inquiry form also found on the IROC Houston web site, to determine if the site has met all of the requirements. This will be completed in place of updating the previous Facility Questionnaire. When the requirements are met, (prior to enrolling patients), the site and NRG Oncology will be notified. NRG Oncology then will update the RSS database.

5.2 Digital RT Data Submission to NRG Using TRIAD (24-FEB-2020)

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:
Site staff that will be submitting images via TRIAD will need to register with CTEP and have a valid and active CTEP-IAM account.

- Must be registered as an Associate, Associate Plus, Non-Physician Investigator, or Investigator registration type. Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in Registration and Credential Repository (RCR).

To submit images, site staff must hold the TRIAD Site User role on an NCTN or ETCTN roster. Individuals requiring a TRIAD Site User role should contact the person holding a primary role at the site for their affiliated NCTN or ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD, and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installation:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account username and password and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

5.3 Regulatory Pre-Registration Requirements (06-MAR-2020)

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

5.3.1 IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRB Manager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of your screen
    - Enter the protocol number in the search field at the top of the protocol tree, or

- Click on the By Lead Organization folder to expand, then select *RTOG* and protocol number *RTOG-0912*;
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log on to the CTSU members' website → Regulatory → Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status
You can verify your site's registration status on the members' side of the CTSU website.

- Log on to the CTSU members' website;
- Click on *Regulatory* at the top of your screen;
- Click on *Site Registration;*
- Enter your 5-character CTEP Institution Code and click on Go.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

5.3.2 *Pre-Registration Requirements FOR CANADIAN INSTITUTIONS*
In addition to the requirements above, Canadian institutions must also complete and submit additional regulatory documents to the CTSU Regulatory Office (as noted in section 5.3.1):

- Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form,
- Qualified Investigator Undertaking Form, and
- Research Ethics Board Attestation Form.

5.4 Registration (24-FEB-2020)

5.4.1 The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

6.0 RADIATION THERAPY (3/25/14)

Note: This trial is not utilizing the services of the ITC for dosimetry digital treatment data submission. See Section 5.2 for information on installing TRIAD for submission of digital RT data prior to enrolling patients.

IMRT is required for this study. See the pre-registration requirements for IMRT in Section 5.1.

IMRT must begin within 3 weeks from the start of Drug Therapy and at least 5 days (120 hours) after the last dose of pre-IMRT paclitaxel (see Section 7.0).

6.1 Dose Specifications (6/5/14)

Prescription dose shall be according to the following (also see Section 6.4):

6.1.1 PTV_{66} (CTV_{66} + margin) will receive 66 Gy in 33 fractions at 2 Gy per fraction. $PTV_{59.4}$ ($CTV_{59.4}$ + margin) will receive 59.4 Gy in 33 fractions at 1.8 Gy per fraction. All targets will be delivered simultaneously. Treatment will be delivered once daily, 5 fractions per week, over 6.5 weeks

6.1.2 The reported doses for PTV_{66} shall include the prescription dose as well as the maximum point dose (maximum dose encompassing 0.03 cc volume) for that PTV, % PTV receiving ≥ 93%, ≥ 110% and ≥ 115% of the prescription dose of that PTV, and the mean dose for that PTV (see plan scoring table in Section 6.6.2).

All plans shall be normalized such that 95% of the volume of PTV_{66} is covered by the 66 Gy isodose surface while more than 95% of the volume of $PTV_{59.4}$ being covered by the 59.4 Gy isodose surface (see plan scoring table in Section 6.6.2)

6.2 Technical Factors (3/25/14)

6.2.1 *External Beam Equipment and Beam Delivery Methods*

Megavoltage equipment capable of delivering static intensity modulation with a multileaf collimator or dynamic intensity modulation (using a multileaf collimator or tomotherapy) is required. Volume arc delivery techniques can be used, but re-credentialing might be necessary (see Section 5.1.1). Institutions should contact the IROC Houston if they intend to use volume arc delivery.

6.3 Treatment Planning, Imaging and Localization Requirements

6.3.1 The immobilization device should at least include the head and neck. It is strongly encouraged that the participating centers also include the shoulders in the immobilization. This is to further ensure accurate patient set-up on a daily basis.

6.3.2 Treatment planning CT scans will be required to define gross target volume(s), and clinical target volume(s). The treatment planning CT scan should be acquired with the patient in the same position and using the same immobilization device as for treatment.

All tissues, including entire lung volumes (both lungs), to be irradiated must be included in the CT scan. CT scan thickness should be ≤ 0.3 cm slices through the region that contains the primary target volumes. The regions above and below the target volume may be scanned with 0.5 cm slice thickness.

6.3.3 The GTV and CTV (see Section 6.4), and normal tissues must be outlined on all CT slices in which the structures exist.

6.4 Treatment Planning/Target Volumes (7/15/13)

The definition of volumes will be in accordance with the 1993 ICRU Report #50, but the dose reporting and prescription are specified in Sections 6.1 and 6.6.2.

6.4.1 *The Gross Tumor Volume (GTV)* is defined as all known gross disease determined from CT, clinical information, and endoscopic findings. Grossly positive lymph nodes are defined as any lymph nodes > 1 cm or nodes with a necrotic center. It is strongly encouraged that the radiation oncologist outline the radiologic extent of the primary tumor and neck nodes along with a radiologist. Whenever possible, it is recommended that the diagnostic images be fused to the planning CT scan image dataset to more accurately define the GTV. To further subdivide the GTV, gross disease at the primary site is designated as GTV-P and clinically involved gross lymph nodes are designated GTV-N. In situations where the patient underwent surgery prior to IMRT, the GTV is defined as the preoperative gross disease plus the post-operative surgical bed.

6.4.2 *The Clinical Target Volume (CTV)*: See the bulleted list below for delineation details.

For patients without complete surgical resection: In terms of the GTV (GTV-P and GTV-N), a margin of ≥ 5 mm should be given circumferentially around the GTV (GTV-P and GTV-N) and this volume will be called the CTV_{66} (CTV_{66}-P and CTV_{66}-N).* This margin can be reduced to as low as 1 mm for tumors in close proximity to critical structures, e.g., tumors next to the spinal cord. For regions deemed to be at high risk for microscopic disease, all potential routes of spread for primary and nodal GTVs should be delineated by the treating radiation oncologist. This is known as CTV for subclinical disease or $CTV_{59.4}$*

- For patients who have undergone a complete surgical resection: CTV_{66} should include the preoperative gross disease at the primary disease site or any grossly involved lymph nodes as well as the post-operative bed. A $CTV_{59.4}$ also can be delineated if the region is at risk for microscopic spread and the region has not had surgery.
- To further define the subclinical region at risk for microscopic spread at the primary disease site, $CTV_{59.4}$-P includes CTV_{66}-P +5 mm margin and ensuring that the following is generously covered: tracheal-esophageal groove, levels II-VI, upper mediastinum to the level of the carina. At the discretion of the treating physician, level I and the retropharyngeal nodes can be covered when indicated.

Note: The outer most boundary of $CTV_{59.4}$-P should be at least 10 mm from the GTV-P. Typically, it is larger as coverage of the regions defined above is necessary. In regions near the spinal cord, the margin can be as low as 1 mm.

- **(4/19/11)** Regarding the lymph nodal subclinical regions, $CTV_{59.4}$-N includes, as stated above, levels II-VI bilaterally and the upper mediastinum down to the level of the carina. At the discretion of the treating physician, level I and the retropharyngeal nodes can be covered when indicated.

Note: The outer most boundary of the $CTV_{59.4}$-N should be at least 10 mm away from the GTV-N. In regions near the spinal cord, the margin can be as small as 1 mm.

Note: The consensus guideline, available on the NRG Oncology/RTOG web site, http://www.rtog.org/CoreLab/ContouringAtlases/HN.aspx for head and neck cancer is for **NODE NEGATIVE** patients only. One can use this guideline to treat the appropriate nodal levels only for **NODE NEGATIVE** patients for whom surgery was not done.

6.4.3 A separate planning Target Volume (PTV) will provide a margin around the CTV's to compensate for the variabilities of treatment set up and internal organ motion. A minimum of 5 mm around the CTV's is required in all directions to define each respective PTV (PTV_{66}, $PTV_{59.4}$). Careful consideration should be made when defining the superior and inferior margins in three dimensions. **Note that at any given point, the margin from the GTV at the primary site to the $PTV_{59.4}$ should be at least 15 mm. This also applies to post-operative cases. The only exception is when the tumor is close to the spinal cord where CTV margin may be reduced to 1 mm with the intent of protecting the spinal cord.**

6.4.4 *Planning*

The treatment plan used for each patient will be based on an analysis of the volumetric dose, including dose-volume histogram (DVH) analyses of the PTVs and critical normal structures. An

"inverse" planning using computerized optimization should be used. The treatment aim will be the delivery of radiation to the PTVs and the exclusion of non-involved tissue.

6.5 Critical Structures (6/5/14)

6.5.1 **Note:** Structures marked "required" in the table below **must** be contoured and submitted for review. **Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name as listed.**

The following table outlines the naming of the various normal and critical structures for submission to TRIAD:

New Standard Name	Description
GTV	**Required**
CTV_6600	Primary Tumor Bed plus involved nodes **Required**
CTV_5940	At risk regions **Required**
PTV_6600	CTV-PTV 5 mm margin **Required**
PTV_5940	CTV-PTV 5 mm margin **Required**
SpinalCord	Spinal Cord **Required**
SpinalCord_05	Planning risk Volume of 5 mm margin **Required**
Parotid_L	Left Parotid **Required**
Parotid_R	Right Parotid **Required**
OralCavity	Oral Cavity **Required**
BrachialPlexus	Brachial Plexus **Required**
Mandible	Mandible **Required**
Submandibula_L	Left Submandibular gland **Contouring Optional**
Submandibula_R	Right Submandibular gland **Contouring Optional**
Esophagus_Up	Cervical Esophagus **Required**
LarynxGSL	Glottic/Supraglottic Larynx **Required**
External	External border of patient used to define Unspecified Tissue **Required**
Lungs	Total lung **Required**
NonPTV	Unspecified tissues outside PTV **Contouring Optional**

6.5.2 *Critical Normal Structures*

Surrounding critical normal structures, including spinal cord, parotid glands, skin (in the region of the target volumes), oral cavity, mandible, brachial plexus, esophagus and glottic larynx **must** be outlined.

Physicians should assist the planner in identifying the critical normal structures. A planning risk volume (PRV) is applied only to the true spinal cord. The spinal cord. PRV will be defined as a three-dimensional margin of 5 mm. The normal tissues will be contoured and considered as solid organs. The tissue within the skin surface and outside all other critical normal structures and PTVs is designated as unspecified tissue.

DVH's must be generated for all critical normal structures, any corresponding PRVs, and the unspecified tissues. Dose constraints for critical normal structures are listed in Sections 6.6.3 and 6.6.4.

The treating physician is encouraged to call Dr. Lee, the Co-Principal Investigator, at 212-639-3341 should questions arise.

6.5.3 The method used for tissue heterogeneity calculations shall be reported. The dose prescription is to be based on a dose distribution corrected for heterogeneities.

6.5.4 *Planning Priorities*

Critical normal structure constraints followed by the prescription goals are the most important planning priorities. The priorities in addressing the protocol aims and constraints will be in the following order:

1) Spinal Cord Dose Constraints (Section 6.6);
2) Dose coverage to tumor volumes (Section 6.6.2);
3) Normal structure dose constraints for plan scoring (Section 6.6.3);
4) Other normal structures not used for plan score (Section 6.6.4).

6.6 Compliance Criteria (9/30/15)

6.6.1 Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Holidays and weekends are not considered treatment breaks. Treatment breaks, if necessary, should ideally not exceed five treatment days at a time and ten treatment days total. Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and not for social or logistical reasons. Any treatment break(s) exceeding two treatment days for reasons other than toxicity/illness will be considered a protocol deviation.

6.6.2 Treatment plans will be scored as Per Protocol, Variation Acceptable, or Deviation Unacceptable. Institutions are encouraged to generate treatment that fall within the dose limits defining the per protocol category (see tables below). For those target to critical structures geometries that are more challenging, some variation from the per protocol dose limits is acceptable. The variation acceptable dose limits are given in the table below. Plans that fall outside of the variation acceptable dose limits are scored as deviation unacceptable.

	Per Protocol	**Variation Acceptable**	**Variation Unacceptable**
PTV_6600			
Total RT dose to 95% of the PTV_6600	66 Gy	66 Gy - 62.7 Gy	< 62.7 Gy
Percentage of PTV_6600 receiving 61.4 Gy (93% of 66 Gy)	≥ 99%	≥ 97%	≤ 97%
Percentage of PTV_6600 receiving 72.6 Gy (110% of 66Gy)	≤ 20%	≤ 40%	≥ 40%
Percentage of	≤ 5%	<20%	≥ 20%

PTV_6600 receiving 75.9 Gy (115% of 66 Gy)			
Mean dose of PTV_6600	≤ 70.4 Gy	70.4 -72.6 Gy	≥ 72.6 Gy
PTV_5940			
Total RT dose to 95% of PTV_5940	59.4 Gy	59.4 -56.4 Gy	< 56.4 Gy
Percentage PTV_5940 receiving 55.2 Gy (93% of 59.4 Gy)	≥ 99% Gy	≥ 97%	≤ 97%

6.6.3 Acceptable Dose Limits On Critical Structures for Plan Scoring

	Critical Normal Tissue		
Maximum dose to 0.03 cc of SpinalCord	≤ 45 Gy	45 - 48 Gy	≥ 48 Gy
Maximum dose to 0.03 cc of SpinalCord_05	≤ 50 Gy	50-54 Gy	≥ 54 Gy
Mean dose to one of Parotid glands	≤ 26 Gy		
50% of one of the Parotid glands		≤ 30 Gy	≥ 30 Gy
20 cc of both parotids		≤ 20 Gy	≥ 20 Gy
Percentage of Lungs receiving 20 Gy	≤ 20%	≤ 25%	≥ 25%

6.6.4 Suggested Dose Limits Not for Plan Scoring (Should Not Compromise Tumor Volume Coverage)

Oral cavity (excluding PTV's)	Mean dose ≤ 35 Gy
Submandibular glands	Mean Dose ≤ 39 Gy
LarynxGSL	Mean dose ≤ 60 Gy
Maximum dose to 1cc of un-specified Tissue	≤ 69.3 Gy
Maximum dose to 0.03cc of BrachialPlexus Maximum dose to 0.03cc of BrachialPlexus when Tumor Volume is overlapped with BrachialPlexus	≤ 60 Gy ≤ 66 Gy

6.7 R.T. Quality Assurance Reviews (6/5/14)

The Co-Principal Investigator, Nancy Lee, MD, will remotely perform RT Quality Assurance Reviews. These reviews will be ongoing and will be facilitated by IROC Philadelphia RT .

6.8 Radiation Therapy Adverse Event Reporting (7/15/13)

See Section 7.9 for adverse event reporting.

7.0 DRUG THERAPY (10/21/16)

The drug therapy prior to IMRT must begin within 1 week of receiving pazopanib/placebo; however, it is recommended that treatment begin as soon as possible after sites receive the pazopanib/placebo.

For Emergency Unblinding/Code Breaks, see Section 7.4.1 (2nd paragraph from the bottom of the section)**.**

7.1 Treatment (7/15/13)

Note: Patients who must take medications with a risk or possible risk of Torsades de Pointes should be watched carefully for symptoms of QTc prolongation, such as syncope. Performing additional EKGs on patients who must take one or more of these medications is not required; however, additional investigations, including EKGs, may be performed as per the treating physician's judgment; see Section 7.6.1, under "Management of QTc Prolongation".

(3/8/12) Patient Education: Institutions must provide patient education regarding the pazopanib/placebo suspension. Patients should be educated regarding swirling the suspension for 30 seconds prior to withdrawing the dose from the bottle, drawing up the prescribed dose, and storage of the suspension. Patients should demonstrate that they can draw up the appropriate daily dose and should be reminded to take the suspension on an empty stomach either 1 hour before or 2 hours after meals. Instructions to the patient for disposal of leftover pazopanib suspension and cleanup of pazopanib suspension spills have been included on the medication diary form (DP).

7.1.1 Run-In Components (Completed 6/5/14)

Prior to Radiation Treatment: Patients will receive weekly paclitaxel and daily (7 days/week) pazopanib for 2-3 weeks.

During Radiation Treatment: Patients will receive weekly paclitaxel and daily (7 days/week) pazopanib for 6-7 weeks with radiation treatment (or until radiation treatment is completed).

Accrual will be suspended after 11 patients have been accrued to the run-in component; the study will remain closed until these 11 patients complete radiation therapy and a safety analysis is performed. See Section 13.2.1 for details.

7.1.2 Phase II Component (6/5/14)

Prior to Radiation Treatment: Patients will receive weekly paclitaxel and either daily (7 days/week) pazopanib or placebo for 2-3 weeks.

During Radiation Treatment: Patients will receive weekly paclitaxel and either daily (7 days/week) pazopanib or placebo for 6-7 weeks with radiation treatment (or until the end of radiation therapy).

7.2 Prior to Radiation Therapy: Treatment Details (2/10/15)

7.2.1 Patients will receive paclitaxel 80 mg/m^2, administered intravenously weekly for 2 weeks. Radiation therapy should not begin until at least 5 days (or about 120 hours) after the last dose of paclitaxel during the pre-chemotherapy phase. For logistics reasons, a third dose of paclitaxel may be given at the investigator's discretion.

The body surface area (BSA) should be calculated using actual body weight. Note: It is not necessary to recalculate the BSA for each treatment if the patient's weight has not changed by more than 10%.

In addition, patients will take pazopanib/placebo 400 mg suspension orally daily for 2 weeks (or until the day before the start of radiation therapy), starting either on the same day as the first dose of paclitaxel or the day after the first dose of paclitaxel. However, as noted above in Section 7.0, pazopanib/placebo may be started up to a week later than the first dose of paclitaxel due to unforeseen circumstances such as a delay receiving the pazopanib/placebo. Please contact the Co-Principal Investigators, Drs. Sherman and Lee, or the Medical Oncology Co-Chair, Dr. Bible, with any questions.

Due to holidays or patients' personal reasons, paclitaxel can be given within a 48 hour window each week without protocol violation, although it is highly recommended that this be avoided if possible.

Patients will be asked to document daily pazopanib/placebo on a medication diary during pre-radiation treatment, concurrent treatment, and post-concurrent treatment, which will be collected by the institution as source documentation. Institutions will submit the **(DP)** form to NRG Oncology at the end of treatment (see Sections 11.3, 11.4, 11.6, and 12.1).

To calculate BSA, please use the Dubois formula (the use of other formulas will not be a deviation if the results are within 10% of the results obtained by the Dubois formula):

$$\text{BSA (m2)} = 0.007184 \times \text{weight (kg)}^{0.425} \times \text{height (cm)}^{0.725}$$

BSA does not need to be recalculated on a weekly basis unless the patient's weight has changed > 10% from the last time it was calculated.

Note: If there is an unforeseen delay to start the radiation therapy after 2 weeks, a third week of treatment may be given after contacting and getting the consent of either Co-Principal Investigator, Drs. Sherman, Bible, or Lee.

Prior to starting pazopanib/placebo, an evaluation of the medications currently taken by the patient must be done; see Section 7.4.1. **If a patient must continue to take a medication that strongly inhibits CYP3A4, Drs. Sherman or Bible must be contacted to discuss the reason(s) the patient must be on the drug.** If Drs. Sherman or Bible approve the patient's medication, the dose of pazopanib must be decreased by 50% of what otherwise would have been administered while the patient is on the drug.

Pazopanib/placebo may be taken orally or through a feeding tube.
Patients receive pazopanib/placebo on an outpatient basis. *If taken orally*, patients are instructed to swallow the suspension once a day (preferably in the morning) 7 days/week on an empty stomach, either 1 hour before or 2 hours after proximal food intake with about 1 cup (240 mL) of water.

If administered via a feeding tube, the suspension should be given with subsequent administration of sufficient water via the feeding tube to assure that the suspension is flushed through the tube. These instructions should be followed throughout the study at any point the suspension cannot be taken orally and needs to be taken through a feeding tube.

It is preferable that pazopanib/placebo be taken prior to the start of radiation therapy and paclitaxel throughout the treatment course.

Paclitaxel may be given intravenously according to institutional guidelines although it is recommended that it be given intravenously over 1 hour while diluted in 500 ml of 0.9% sodium chloride or 5% dextrose solution. The recommended premedications include the following (other regimens are permitted per institutional guidelines):

1. Dexamethasone 10 mg intravenously approximately 30 minutes prior to the paclitaxel.
2. Diphenhydramine 25 mg intravenously approximately 30 minutes prior to the paclitaxel.
3. Ranitidine 50 mg or cimetidine 300 mg intravenously approximately 30 minutes prior to the paclitaxel

7.2.2 Pazopanib/placebo should be taken as described in section 7.2.1 until the day before radiation therapy is scheduled to begin. Radiation therapy should not begin until at least 5 days (or about 120 hours) after the last dose of paclitaxel as noted in section 7.2.1.

7.3 During Radiation Therapy: Treatment Details (7/15/13)

7.3.1 Patients will receive paclitaxel 50 mg/m², administered intravenously weekly, starting within 72 hours of the start of radiation therapy, although the strong preference is that it starts on the first

day of radiation therapy. The body surface area (BSA) should be calculated using actual body weight (see Section 7.2.1).

In addition, patients will take pazopanib/placebo 300 mg suspension orally daily, starting on the same day as the first fraction of radiation therapy is scheduled.

Due to holiday or personal reasons, paclitaxel can be given within a 48 hour window each week without protocol violation, although it is highly recommended that this be avoided if possible.

7.3.2 Technique of administration — See Section 7.2.1

7.3.3 Paclitaxel will be given for approximately 6-7 weeks (or until the end of radiation therapy). The pazopanib/placebo will be given as outlined in Section 7.3.1 until radiation therapy is completed. Patients will be asked to document daily pazopanib/placebo on the medication diary **(DP)**, which will be collected by the institution and submitted to NRG Oncology (see Section 12.1).

7.3.4 If within the timeframe that drug (i.e. paclitaxel and pazopanib/placebo) should begin concurrently with radiation therapy the parameters for drug delivery (as stated in Section 7.6, "Dose Modifications") are not met, radiation therapy should not be delayed. Radiation treatment should begin either with the drug dose being modified or delayed, as specified in Section 7.6.

7.4 Study Agents (9/13/16)

7.4.1 Pazopanib HCl (GW786034B) [NSC 737754]

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

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

Classification: VEGFR tyrosine kinase inhibitor

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

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

Mechanism of Action: Pazopanib is a highly potent inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinases (VEGFR1, VEGFR2, and VEGFR3), platelet derived growth factor receptor (PDGFR alpha and beta) and C-Kit. Vascular endothelial growth factor receptor inhibition may block VEGF driven angiogenesis and, as a consequence, constrain tumor growth.

How Supplied: The Powder for Oral Suspension is supplied in 200 mL amber type III glass multi-dose bottles containing 5 g or 0 g of pazopanib. When reconstituted with 90 mL of purified or Sterile Water the suspension will contain 50 mg/mL or 0 mg/mL as free base/placebo. Powder for Oral Suspension excipients include Mannitol Pearlitol 100SD,Sucralose, Guar Gum 5000, Hypromellose, Citric Acid Monohydrate, Sodium Phosphate, Dibasic, Anhydrous, Colloidal Silicon Dioxide, Methylparaben and Lemon Flavor. The placebo suspension contains the same excipients as the pazopanib suspension with the addition of microcrystalline cellulose and Opadry White YS-1-7003 to aid in visual blinding. **Note**: **The suspension must be prepared by the institution's pharmacy prior to dispensing it to the patient.**

Storage: The Powder for Oral Suspension must be stored at Room Temperature. The reconstituted suspension must be refrigerated (2–8°C) and should be used within 35 days.

Stability: Stability studies are ongoing.

Potential Drug Interactions: *In vitro* data indicate that pazopanib is primarily metabolized by CYP3A4 isoenzyme. Potent CYP3A4 inducers and inhibitors are prohibited on pazopanib

trials. Pazopanib also is a substrate for p-glycoprotein and breast cancer resistance protein (BCRP) transporters and concomitant administration of inhibitors such as lapatinib will result in increased plasma pazopanib concentrations.

Clinical studies indicate that pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6. Use caution when combining pazopanib with CYP3A4, CYP2C8, and CYP2D6 substrates known to have a narrow therapeutic window.

In vitro studies also showed that pazopanib is a potent inhibitor of UGT1A1 and OATP1B1. Pazopanib may increase concentrations of drugs primarily eliminated through these systems.

Avoid co-administration of pazopanib with medicines that increase gastric pH. If the concomitant use of a proton pump inhibitor (PPI) is medically necessary, pazopanib/placebo should be taken without food once daily in the evening with the PPI. If the concomitant administration of an H_2-receptor antagonist is medically necessary, pazopanib/placebo should be taken without food at least 2 hours before or at least 10 hours after a dose of an H_2-receptor antagonist. Administer pazopanib/placebo at least 1 hour before or 2 hours after administration of short-acting antacids.

Avoid co-administration of pazopanib/placebo with simvastatin. Concomitant use of pazopanib and simvastatin increases the risk of ALT elevation. Data are not sufficient to assess the risk of concomitant administration of other statins and pazopanib.

Precautions: Pazopanib/placebo should be used with caution in patients with a history of QT interval prolongation, in patients taking antiarrhythmics or other medications that may prolong QT interval, and those with relevant pre-existing cardiac disease. Monitor ECGs and serum electrolytes (e.g., calcium, magnesium, potassium) at baseline and periodically and maintain within the normal range.

For patients who develop hepatic impairment, refer to the protocol document for appropriate dose modification or dose delay.

Adverse Events **(3/11/15)**

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

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2383 patients.* Below is the CAEPR for Pazopanib (GW786034)

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

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 4.0 Term) [n= 2383]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Hemolytic uremic syndrome[2]	
		Thrombotic thrombocytopenic purpura[2]	
CARDIAC DISORDERS			
		Left ventricular systolic dysfunction	
		Myocardial infarction	
	Sinus bradycardia		
ENDOCRINE DISORDERS			
	Hypothyroidism		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dyspepsia		
		Gastrointestinal fistula[3]	***Gastrointestinal fistula[3] (Gr 2)***
		Gastrointestinal hemorrhage[4]	
		Gastrointestinal perforation[5]	***Gastrointestinal perforation[5] (Gr 2)***
	Mucositis oral		
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
	Fever		
HEPATOBILIARY DISORDERS			
		Hepatic failure	
INVESTIGATIONS			
	Activated partial thromboplastin time prolonged		
Alanine aminotransferase increased			***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
Aspartate aminotransferase increased			***Aspartate aminotransferase increased (Gr 3)***
Blood bilirubin increased			***Blood bilirubin increased (Gr 3)***
	Creatinine increased		***Creatinine increased (Gr 2)***
		Electrocardiogram QT corrected interval prolonged	
Lymphocyte count decreased			***Lymphocyte count decreased (Gr 3)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 3)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 2)***
White blood cell decreased			***White blood cell decreased (Gr 2)***

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 4.0 Term) [n= 2383]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 2)***
	Hypercalcemia		
Hyperglycemia			***Hyperglycemia (Gr 2)***
	Hyperkalemia		***Hyperkalemia (Gr 2)***
	Hypermagnesemia		
	Hypernatremia		
	Hypoalbuminemia		***Hypoalbuminemia (Gr 2)***
	Hypocalcemia		***Hypocalcemia (Gr 2)***
	Hypoglycemia		***Hypoglycemia (Gr 2)***
	Hypokalemia		
	Hypomagnesemia		
Hyponatremia			***Hyponatremia (Gr 2)***
	Hypophosphatemia		***Hypophosphatemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Tumor pain		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 3)***
	Headache		***Headache (Gr 2)***
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
	Proteinuria		***Proteinuria (Gr 2)***
		Urinary fistula	***Urinary fistula (Gr 2)***
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
		Female genital tract fistula	***Female genital tract fistula (Gr 2)***
		Uterine fistula	***Uterine fistula (Gr 2)***
		Vaginal fistula	***Vaginal fistula (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
	Respiratory hemorrhage[6]		***Respiratory hemorrhage[6] (Gr 2)***
		Respiratory, thoracic and mediastinal disorders – Other (interstitial lung disease)[7]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Palmar-plantar erythrodysesthesia syndrome		

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 4.0 Term) [n= 2383]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
Skin and subcutaneous tissue disorders - Other (hair color change/hair depigmentation)			***Skin and subcutaneous tissue disorders - Other (hair color change/hair depigmentation) (Gr 2)***
	Skin hypopigmentation		***Skin hypopigmentation (Gr 2)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr 3)***
		Thromboembolic event[8]	
		Vascular disorders - Other (arterial thromboembolic event)[8]	

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

[2]Thrombotic microangiopathy (TMA) which includes both Hemolytic uremic syndrome (HUS) and Thrombotic thrombocytopenic purpura (TTP) has been reported in clinical trials of GW786034.

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

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

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

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

[7]Interstitial lung disease may include, Adult respiratory distress syndrome, Pneumonitis, Pulmonary fibrosis, Respiratory, thoracic and mediastinal disorders - Other (Acute respiratory distress syndrome), Respiratory, thoracic and mediastinal disorders - Other (Aveolitis), Respiratory, thoracic and mediastinal disorders - Other (Bronchiolitis obliterans), Respiratory, thoracic and mediastinal disorders - Other (Interstitial fibrosis), Respiratory, thoracic and mediastinal disorders - Other (Interstitial pneumonia), Respiratory, thoracic and mediastinal disorders - Other (Interstitial pneumonitis), Respiratory, thoracic and mediastinal disorders - Other (Organizing pneumonia), Respiratory, thoracic and mediastinal disorders - Other (Pulmonary infiltrates), Respiratory, thoracic and mediastinal disorders - Other (Toxic pneumonitis).

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

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

Adverse events also reported on Pazopanib (GW786034) trials but with the relationship to Pazopanib (GW786034) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia; Hemolysis
CARDIAC DISORDERS - Acute coronary syndrome; Atrial fibrillation; Cardiac disorders - Other (sinus arrest); Cardiac disorders - Other (supraventricular extrasystoles); Cardiac disorders - Other (Takotsubo [Broken Heart Syndrome]); Cardiac disorders - Other (Torsades de Pointes); Chest pain - cardiac; Pericardial effusion; Supraventricular tachycardia
ENDOCRINE DISORDERS - Adrenal insufficiency
EYE DISORDERS - Blurred vision; Dry eye; Eye disorders - Other (asthenopia); Eye disorders – Other (eye/retinal hemorrhage); Eye disorders - Other (foreign body sensation in eyes); Eye pain; Floaters; Glaucoma; Photophobia; Retinal tear
GASTROINTESTINAL DISORDERS - Abdominal distension; Dry mouth; Duodenal obstruction; Dysphagia; Esophagitis; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (hyperactive bowel); Gastrointestinal disorders - Other (oropharyngeal pain); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gastrointestinal pain; Oral pain; Pancreatitis; Periodontal disease; Proctitis; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Malaise; Non-cardiac chest pain; Pain
INFECTIONS AND INFESTATIONS - Infection[9]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
INVESTIGATIONS - Cardiac troponin T increased; Cholesterol high; Ejection fraction decreased; GGT increased; INR increased; Investigations - Other (blood lactate dehydrogenase increased); Investigations - Other (blood TSH increased); Lipase increased; Serum amylase increased; Weight gain
METABOLISM AND NUTRITION DISORDERS - Hypertriglyceridemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Chest wall pain; Generalized muscle weakness; Head soft tissue necrosis; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Neck pain
NERVOUS SYSTEM DISORDERS - Extrapyramidal disorder; Intracranial hemorrhage; Ischemia cerebrovascular; Memory impairment; Paresthesia; Peripheral sensory neuropathy; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Suicide attempt
RENAL AND URINARY DISORDERS - Hematuria; Urinary frequency
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation; Reproductive system and breast disorders - Other (vaginal necrosis); Vaginal discharge; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Laryngeal edema; Pharyngolaryngeal pain; Pleural effusion; Pleuritic pain; Pneumothorax; Postnasal drip; Sore throat; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Hyperhidrosis; Pruritus; Purpura; Skin hyperpigmentation; Skin ulceration
VASCULAR DISORDERS - Flushing; Hot flashes; Hypotension; Vasculitis

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

Clinical Supplies **(6/5/14)**
Pazopanib (NSC 737754/IND 75648) and matching placebo will be provided free of charge by GlaxoSmithKline and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI). Drug provided free of charge as part of a research protocol must be used only for the intended study. It is the responsibility of the Investigator to ensure the provided/investigational product is only dispensed to eligible study patients.

Pazopanib powder for oral suspension and matching placebo for pazopanib will be supplied in a 200 ml amber type III glass bottle.

Each blinded, patient-specific bottle will be labeled with the following:
- the protocol number (i.e., “RTOG-0912”);
- the bottle number (i.e., “Bottle 1 of 2” and “Bottle 2 of 2”);

- the patient ID number (e.g.,"0912-YYY", where “0912-YYY” represents the protocol number and sequence number which represents the unique patient ID number assigned by NRG Oncology at the time of patient registration)
- the patient initials (i.e., First initial, Middle initial, Last initial [e.g., “FML”]);
- the agent identification (i.e. “Pazopanib or Placebo suspension”);
- a blank line for the pharmacist to enter the patient’s name;
- administration instructions (i.e., “Take __ mL once a day for [cycle length] days.”);
- storage instructions (i.e., “Store at controlled room temperature [20ºC-25 ºC]).”;
- emergency contact instructions;
- a Julian date.

The Julian date indicates the day the bottle was labeled and shipped and is composed of the last 2 digits of the calendar year (e.g., 2009 = 09, 2010 = 10) and a day count (e.g. January 1 = 001, December 31 = 365). For example, a bottle labeled and shipped on January 1, 2009 would have a Julian date of ‘09001’, and a bottle labeled and shipped on December 31, 2009 would have a Julian date of ‘09365’. The Julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will recall all bottles (i.e. both Pazopanib and Placebo) shipped on or before that date thus eliminating any chance of breaking the blind.

Drug Ordering **(9/13/16)**
BLINDED (pazopanib or placebo) THERAPY

Note: This section reflects ordering instructions for the open label 2nd run-in component and the blinded (randomized phase II) component of the study.

No blinded starter supplies will be available for this study. Blinded, patient-specific clinical supplies will be sent to the registering investigator at the time of randomization. This randomization will be performed by NRG Oncology. The patient ID number assigned by NRG Oncology must be recorded by the registering institution for proper study medication dispersion. Once a patient has been registered, NRG Oncology will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by NRG Oncology the day the patient is registered, will be processed by the PMB the next business day, and shipped the following business day.

Note: Open label run-in supplies will be provided on a patient-specific basis, and no starter supplies will be available. Shipments within the United States will be sent by US Priority Mail (generally 2 to 3 day delivery). Thus, if a patient is registered on Monday, NRG Oncology would enter a clinical drug request for that patient on Monday, and PMB would process that request on Tuesday and ship the drug on Wednesday. Sites could expect to receive their order approximately Friday or Monday. Shipments to United States sites can be expedited (i.e. receipt on Thursday in example above) by the provision of an express courier account name and number to NRG Oncology at the time the patient is registered/randomized.

The initial shipment will be 5 x 5000 mg bottles of pazopanib/placebo suspension 50 mg/mL, a sufficient supply to complete the two to three week Pre-IMRT portion (400 mg/day) and 6 to 7 weeks of concurrent therapy (300 mg/day). This supply should be sufficient to complete all of the protocol assigned treatment with pazopanib/placebo. If a bottle gets wasted or destroyed, sites may reorder bottles by using On-line Agent Ordering Processing (OAOP). Please include a note stating that the request is for replacement bottles. The assigned patient ID number (e.g., "0912-YYY") and the patient initials (e.g. "FML") should be entered in the "Patient or Special Code" field. The agent name for the pazopanib must be written on the order form as “Pazopanib or Placebo”. All drug orders should be shipped directly to the physician responsible for treating the patient.

Drug Transfers **(6/5/14)**

Bottles **MAY NOT** be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g. a patient moves from one participating clinical site to another participating clinical site, the principal investigator at a given clinical site changes) must be approved in advance by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number 240-276-7893) a Transfer Investigational Agent Form available on the CTEP home page (http://ctep.cancer.gov). The patient ID number (e.g., "0912-YYY") and the patient initials (e.g., "FML") should be entered in the "Received on NCI Protocol No." and the "Transferred to NCI Protocol No." fields in addition to the protocol number (i.e., "RTOG-0912").

Drug Returns **(2/10/15)**

Only undispensed clinical supplies should be returned to the PMB. When it is necessary to return study drug (e.g. sealed bottles remaining when a patient permanently discontinues protocol treatment, expired bottles recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Drug List available on the CTEP home page (http://ctep.cancer.gov). The patient ID number (e.g., "0912-YYY") and the patient initials (e.g., "FML") should be entered in the "Lot Number" field.

Emergency Unblinding/Code Breaks

The decision to break the code must be based on a life-threatening event or extraordinary clinical circumstance for which knowledge of drug assignment will affect clinical judgment.

During business hours (8:30 AM to 4 PM ET), call NRG Oncology at 215-574-3150 and ask to speak to the Study Statistician. For after hours, weekends, and holidays, call 215-459-3576. NRG Oncology/Study Statistician will require the protocol number (i.e., "RTOG-0912"), the patient ID number (e.g., "0912-YYY"), and the patient initials (e.g. "FML") to unblind the patient. **Note: If a patient is emergently unblinded, he/she is considered to be off-therapy and must discontinue protocol treatment.**

Drug Accountability **(6/5/14)**

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the CTEP home page (http://ctep.cancer.gov). A separate NCI Investigational Agent Accountability Record must be maintained for each patient ID number (e.g., "0912-YYY") on this protocol.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 240-276-6575 Monday through Friday between 8:30 am and 4:30 pm Eastern Time. You may also contact PMB via e-mail at PMBAfterHours@mail.nih.gov.

The Investigator Brochure (IB), if available, for this drug will be supplied by the PMB/NCI. All requests for IBs should be e-mailed to ibcoordinator@mail.nih.gov or the IB Coordinator may be contacted at 240-276-6575.

The Julian Date – Order number (e.g., 2014352-0003) from the patient-specific label must be used as the Lot number on the NCI DARF.

7.4.2 Paclitaxel **(7/15/13)**

Refer to the package insert for complete prescribing and toxicity information.

Description

Paclitaxel (Taxol®) is a poorly soluble plant product from the western yew, Taxus brevifolia.

Preparation
Paclitaxel is a sterile solution concentrate, 6 mg/ml in 5 ml vials (30 mg/vial); 100 mg/16.7ml vial; or 300 mg/50 ml vial, in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water. The contents of the vial must be diluted just prior to clinical use. Paclitaxel, at the appropriate dose, will be diluted in 1000 ml of D5W, USP, in 5% polyolefin containers due to leaching of diethylhexphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized. Each bag/bottle should be prepared immediately before administration. **Note**: Formation of a small number of fibers in solution (acceptable limits established by the USP Particular Matter Test for LVP's) have been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: Millex-GV Millipore Products) into the *i.v.* fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

Administration
Paclitaxel, at the appropriate dose and dilution, will be given as a 1-hour infusion. See Section 7.1. The paclitaxel is mixed in 500 or 1000 cc of D5W in non-PVC containers and infused via polyolefin-lined nitroglycerin tubing or low absorption AVI‰ with 0.22 m in-line filter.

Adverse Events
- Hematologic: neutropenia, leukopenia, thrombocytopenia, anemia
- Gastrointestinal: nausea/vomiting, diarrhea, mucositis
- Hepatic: elevated liver function tests
- Cardiac: heart block, bradycardia
- Neurologic: peripheral neuropathy, arthralgia/myalgia
- Dermatologic: alopecia, onycholysis
- Reproductive: Infertility; may be teratogen
- Miscellaneous: moderate–severe hypersensitivity reactions, flushing, rash, dyspnea, fatigue

Stability and Storage
All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours. Paclitaxel vials should be stored between 2°-25°C (36°-77°F).

Supply
Paclitaxel is commercially available in the United States.

7.5 Clinical Trials Agreement

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

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

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

2. For a clinical protocol where there is an investigational Agent used in combination with another investigational Agents, each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data".
   a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator, the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to the Collaborator for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to the Collaborator for advisory review and comment prior to submission for publication. The Collaborator will have 30 days from the date of receipt for review. The Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to the Collaborator's intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to the Collaborator for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

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

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

7.6 Dose Modifications (9/30/15)

7.6.1 Pazopanib/Placebo

Appropriate dose modifications for pazopanib-related adverse events are outlined in the following subsections. If treatment has been held for more than 21 days to allow for resolution of an adverse event, the treating physician should contact Drs. Sherman or Bible to review the

subject's condition prior to resuming the patient's treatment, except for delays due to hypertension (see "Hypertension" below). As a patient progresses from one treatment to another (i.e., pre-radiation therapy, radiation therapy), the patient should remain at the SAME DOSE LEVEL. Dose level reductions follow:

Pre-Radiation Therapy

Dose level	Pazopanib/Placebo suspension
DL 1	400 mg (8 mL) daily
DL-1	300 mg (6mL) daily
DL-2	200 mg (4 mL) daily
DL-3	100 mg (2 mL) daily

During Radiation Therapy

Dose level	Pazopanib/Placebo suspension
DL 1	300 mg (6 mL) daily
DL-1	150 mg (3 mL)daily
DL-2	100 mg (2 mL) daily
DL-3	50 mg (1 mL)daily

Hypertension **(4/19/11)**

Increases in blood pressure 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 pazopanib treatment has been seen in animal studies as well as clinical trials.

- While patients are receiving treatment with pazopanib/placebo, the early initiation of antihypertensive treatment for grade 1 or 2 hypertension to minimize more severe or persistent hypertension is not considered a grade 3 adverse event.
- Decisions to hold or decrease the pazopanib/placebo dose during treatment must be based on BP readings taken in the clinic by a medical professional.
- In case of new-onset or worsening (grade ≥ 2) hypertension, refer to the chart on the following page.
- Ultimately, antihypertensive treatment must be individualized based on the presence of comorbidity such as diabetes, cardiovascular, or renal disease, additionally taking into account the safety and efficacy of any prior antihypertensive therapy received. In addition, oral and/or intravenous sodium intake should be carefully monitored in these patients. Blood pressure should be performed at least once weekly until stable blood pressure control is achieved. Early consultation with a cardiologist is strongly encouraged in case of uncontrolled hypertension.

Dose Modifications for Pazopanib/Placebo Due to Hypertension (7/15/13)

Grade (CTCAE, v. 4.0)	Antihypertensive Therapy	Blood Pressure Monitoring	Pazopanib/Placebo 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	Step 1) Initiate BP treatment 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. BP treatment is unnecessary if BP drops to grade < 1 within 1 hour without	BP should be monitored as recommended by the treating physician	No change except as described in Step 4.

guidelines, including CTCAE, v. 4.0.	any intervention. It also does not need to be initiated if other causes are strongly suspected (severe anxiety), although this would require permission from a co-chair (Keith Bible, Eric Sherman, or Nancy Lee). 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 antihypertensives in Step 2; increase dose of this drug as described in Step 1. Step 4) If BP still not controlled, consider either 1 dose reduction of pazopanib/placebo or stopping pazopanib/placebo. *NOTE: Stopping or reducing the dose of pazopanib/placebo is expected to cause a decrease in BP The treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly*		

Persistent Grade 3 Severe Systolic ≥160 Diastolic ≥100 Protocol-specific guidance supersedes any other management guidelines, including CTCAE, v. 4.0.	HOLD pazopanib/placebo until systolic BP ≤159 and diastolic BP ≤99. BP management is identical to that for Grade 2 (see Steps 1-4 above) **with 2 major exceptions:** **1) If systolic BP >180 or diastolic BP >110 and the patient is symptomatic: optimal management with intensive IV support in ICU; STOP pazopanib/placebo and notify hospital staff that stopping pazopanib/placebo may result in a decrease in BP and** **2) If systolic BP >180 or diastolic BP >110 and the patient is asymptomatic, 2 new antihypertensives must be given together in Step 1 (and dose escalated appropriately as in Step 1).** *NOTE: Stopping or reducing the dose of pazopanib/placebo is expected to cause a decrease in BP. The treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly*	BP should be monitored as recommended by the treating physician **unless the patient is symptomatic with systolic BP >180 or diastolic BP >110 in which case, monitoring should be intensive.**	HOLD pazopanib/placebo until systolic BP ≤159 and diastolic BP ≤99. In most circumstances, if BP cannot be controlled after an optimal trial of antihypertensive medications, consider either 1 dose reduction of pazopanib/placebo or stopping pazopanib/placebo. **HOWEVER, If the patient requires hospitalization for management of symptomatic systolic BP >180 or diastolic BP >110,** permanently discontinue pazopanib/placebo or if BP is controlled, re-start pazopanib/placebo at 1 lower dose level after consultation with Drs. Sherman or Bible.
Grade 4 Life-threatening consequences of hypertension	**Optimal management with intensive IV support in ICU; STOP pazopanib/placebo and notify hospital staff that stopping pazopanib/placebo may result in a decrease in BP**	Intensive	Permanently discontinue pazopanib/placebo or if BP is controlled, re-start pazopanib/placebo at 1 lower dose level after consultation with Drs. Sherman or Bible.

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 Appendix V for suggested antihypertensive medications by class
- If patients require a delay of > 2 weeks for management of hypertension, discontinue protocol therapy.
- If patients require > 2 dose reductions, discontinue protocol therapy.
- Patients may have up to 2 drugs for management of hypertension prior to any dose reduction in pazopanib/placebo.
- 24-48 hours should elapse between modifications of antihypertensive therapy.

Oral Antihypertensive Medications

Agents in bold characters in the table below are suggested as optimal choices to use with pazopanib in order to avoid or minimize potential drug interactions through CYP450:

Agent Class	Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Dihydro-pyridine Calcium-Channel Blockers (DHP CCB)	**nifedipine XL**	**30 mg daily**	**60 mg daily**	**90 mg daily**	**CYP 3A4 substrate**
	amlodipine	**2.5 mg daily**	**5 mg daily**	**10 mg daily**	**CYP 3A4 substrate**
	Felodipine	2.5 mg daily	5 mg daily	10 mg daily	CYP 3A4 substrate and inhibitor
Selective β Blockers (BB)	Metoprolol	25 mg twice daily	50 mg twice daily	100 mg twice daily	CYP 2D6 substrate
	Atenolol	**25 mg daily**	**50 mg daily**	**100 mg daily**	**No**
	Acebutolol	100 mg twice daily	200-300 mg twice daily	400 mg twice daily	Yes (CYP450 unknown)
	Bisoprolol	2.5 mg daily	5-10 mg daily	20 mg daily	Yes (CYP450 unknown)
Angiotensin Converting Enzyme Inhibitors (ACEIs)	Captopril	12.5 mg 3x daily	25 mg 3x daily	50 mg 3x daily	CYP 2D6 substrate
	Enalapril	5 mg daily	10-20 mg daily	40 mg daily	CYP 3A4 substrate
	Ramipril	2.5 mg daily	5 mg daily	10 mg daily	Yes (CYP450 unknown)
	Lisinopril	**5 mg daily**	**10-20 mg daily**	**40 mg daily**	**No**
	Fosinopril	10 mg daily	20 mg daily	40 mg daily	Yes (CYP450 unknown)
	Rarely used: **perindopril**	**4 mg daily**	**none**	**8 mg daily**	**Yes, but not CYP450**
	Rarely used: **Quinapril**	**10 mg daily**	**20 mg daily**	**40 mg daily**	**No**
Angiotensin II Receptor Blockers (ARBs)	Losartan	25 mg daily	50 mg daily	100 mg daily	CYP 3A4 substrate
	candesartan	4 mg daily	8-16 mg daily	32 mg daily	CYP 2C9 substrate
	Irbesartan	75 mg daily	150 mg daily	300 mg daily	CYP 2C9 substrate
	Telmisartan	**40 mg daily**	**none**	**80 mg daily**	**Yes, but not CYP450**
	Valsartan	**80 mg daily**	**none**	**160 mg daily**	**Yes, but not CYP450**

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

Proteinuria **(2/27/12)**
A 24-hour urine collection for quantitative protein determination must be obtained for a urine protein: creatinine ratio (UPCR) >1. If the UPCR had previously been greater than 1 in the past and the 24-hour urine for protein was found to be under 1 gram, a 24-hour urine collection for protein does not need to be repeated unless the UPCR is 20% higher. Pazopanib/placebo should be held while awaiting the results of the 24 hour urine collection for protein. Instructions for dose modifications due to proteinuria are summarized below.

Dose Modifications for Pazopanib/Placebo Due to Proteinuria

Proteinuria	Action to be Taken
UPC >1and <3	Obtain 24-hr urine protein and if <3 g, continue at current dose and monitor as clinically indicated
UPC ≥3 or 24-h urine protein ≥3 g	1. Interrupt pazopanib/placebo suspension. 2. Weekly UPC or 24-hr urine protein monitoring until UPC is <3 or 24-hr urine protein is <3 grams. Then restart pazopanib dose-reduced by 1 level. 3. If UPC >3 or 24-h urine protein ≥3g recurs, repeat steps 1 and 2. 4. If UPC ≥3 or 24-hr urine protein ≥3 recurs and the pazopanib dose can no longer be reduced, discontinue pazopanib and follow patient as specified in protocol.
Nephrotic syndrome	Permanently discontinue pazopanib and remove subject from study

Management of Metabolic Adverse Events **(2/27/12)**

Adverse Event/ CTCAE, v. 4.0 Category	**Grade**	**Treatment Modification**	**Follow Up**
Hypokalemia or hyper-kalemia	Grade ≥ 2	Hold pazopanib/placebo. Perform an EKG. Correct as soon as possible as treating physician determines. Resume treatment when resolved to grade 1 or less;	Monitor as clinically indicated.
Hypocalcemia/hypercalcemia; Hypophosphatemia/hyper-phosphatemia; Hypomagnesium/hypermag-nesimia	Grade ≥ 3	Hold pazopanib/placebo. Perform an EKG. Correct as soon as possible as treating physician determines. Resume treatment when resolved to grade 2 or less;	Correct remaining abnormal lab values to normal, if possible. Monitor as clinically indicated.

Management of QTc Prolongation
A repeat EKG must be performed on day 1 of concurrent and post-concurrent treatment (see Appendix I). If the QTc interval at 4 weeks is > 500 msec, the EKG should be repeated within 7 days and, if the QTc interval remains ≥500 msec, protocol treatment should be discontinued and the patient should be followed as specified in the protocol. Additionally, if the QTc interval is increased by 60 msec or more from baseline but the QTc interval remains at < 500 msec, an EKG should be repeated within 7 days. If the

repeat EKG again shows a ≥ 60 msec increase in the QTc interval from baseline, consideration should be given to discontinuing pazopanib/placebo or increasing monitoring, after discussion with Drs. Sherman or Bible.

Management of QTc prolongation of 500 msec *and* management of QTc prolongation of 60 msec or more from baseline:

If EKG reveals an increase in the QTc to >500 msec or an increase in the QTc by at least 60 msec from baseline	Repeat EKG before re-administration of pazopanib.
If repeat EKG shows QTc interval is ≥500 msec	Stop protocol treatment and follow patient as specified in protocol.
If on repeat ECG, QTc remains at least 60 msec longer than baseline but is less than 500 msec	Consider stopping protocol treatment and following patient as specified in protocol..

Management of Other Adverse Events for Pazopanib/Placebo **(2/10/15)**			
Adverse Event/ CTCAE, v. 4.0 Category	**Grade**	**Treatment Modifications**	**Follow Up**
Gastrointestinal Perforation, GI	Grade ≥ 1	Discontinue treatment and go to event monitoring	Monitor and treat as clinically indicated.
Diverticulitis/typhilitis	Grade ≥ 1	Hold pazopanib/placebo therapy until resolved, then resume pazopanib/placebo at the discretion of treating physician after complete resolution; no dose reduction.	Hold pazopanib/placebo until resolved, treat aggressively, then resume pazopanib/placebo; no dose reduction.
Hemorrhage/bleeding	Grade 1	No interruption in treatment unless hemoptysis. If hemoptysis, contact PI to determine if it is appropriate to continue pazopanib/placebo. Maintain current dose.	Monitor as clinically indicated.
Hemorrhage/bleeding	Grade 2	For non-pulmonary bleeding, hold pazopanib/placebo unless resolved to ≤grade 1; reduce dose to next lower dose level, and continue treatment. For pulmonary bleeding, permanently discontinue pazopanib/placebo and follow patient as specified in protocol. If grade 2 or greater hemorrhage/ bleeding recurs following dose reduction, stop pazopanib/placebo and follow patient as specified in protocol.	Monitor as clinically indicated.

Management of Other Adverse Events for Pazopanib/Placebo (Cont'd)			
Adverse Event/ CTCAE, v. 4.0 Category	**Grade**	**Treatment Modifications**	**Follow Up**
Hemorrhage/bleeding	Grade 3-4	Discontinue treatment.	Monitor as clinically indicated.
Vascular/Thrombosis	Grade 1	No interruption in treatment; maintain current dose.	Monitor as clinically indicated.
Vascular/Thrombosis	Grade 2, 3	• Hold pazopanib until patient is on stable dose of low molecular weight heparin (LMWH). Treatment may resume during the period of full-dose anticoagulation if all of the following criteria are met: • The patient must have been treated with an anticoagulant at the desired level for at least one week. • The patient must not have had a grade 3 or 4 or significant grade 2 hemorrhagic event while on anticoagulant.	Patient should be monitored as clinically indicated during anticoagulation treatment and after resuming study treatment. When treating with warfarin, international normalized ratio (INR) should be monitored within three to five days after any change in pazopanib/placebo dosing (e.g. re-initiating, escalating/de-escalating, or discontinuing pazopanib/placebo), and then at least weekly until the INR is stable. The dose of warfarin (or its derivatives) may need to be adjusted to maintain the desired level of anticoagulation.
Vascular/Thrombosis	Grade 4 or pulmonary embolus	Discontinue treatment, and follow patient as specified in protocol.	Monitor as clinically indicated.
Arterial Thrombosis/ ischemia	All grades	Discontinue pazopanib and follow patient as specified in protocol.	

Management of Other Adverse Events for Pazopanib/Placebo (Cont'd)			
Adverse Event/ CTCAE, v. 4.0 Category	**Grade**	**Treatment Modifications**	**Follow Up**
Anemia[1]	Grades 1 or 2	No interruption in treatment; maintain current dose.	Monitor as clinically indicated.
Anemia[1]	Grade 3 or 4	Interrupt treatment until toxicity is ≤grade 2; reduce one dose level. If no recovery to ≤grade 2 or recurrent grade 3 or 4, discontinue pazopanib/placebo and follow patient as specified in protocol. However, if the patient is benefiting from therapy, contact Drs. Sherman or Bible to discuss course of action.	Monitor as clinically indicated.
[1] The dose delays and modifications for anemia apply only to anemia which is due to hemorrhage or bleeding. No specific dose delays or dose reductions are required for anemia due to other causes, but the investigator should dose delay and dose-decrease, if he/she feels it is necessary, in a manner consistent with good medical practice.			

Management of Elevations in AST, ALT and/or Bilirubin			
Adverse Event/ CTCAE, v. 4.0 Category	**Grade**	**Treatment Modifications**	**Follow Up**
Elevations in AST, ALT, and/or bilirubin[c]	ALT ≤ 3.0 x ULN	Continue at current dose. Discontinue simvastatin if patient has been receiving simvastatin and has ALT >ULN.	Monitor as clinically indicated.
Elevations in AST, ALT, and/or bilirubin[c]	ALT > 3.0 x ULN to ≤ 8.0 x ULN **without** bilirubin elevation (defined as total bilirubin < 2.0 x ULN or direct bilirubin ≤ 35%)[a] and **without** hypersensitivity symptoms (e.g., fever, rash)	1) Continue pazopanib at current dose levels. Discontinue simvastatin if patient has been receiving simvastatin. 2) Monitor patient closely for clinical signs and symptoms; perform full panel LFTs[b] at least weekly until ALT/AST is reduced to Grade 1.	Monitor as clinically indicated.
Elevations in AST, ALT, and/or bilirubin[c]	ALT > 8.0 x ULN **without** bilirubin elevation (defined as total bilirubin < 2.0 x ULN or direct bilirubin ≤ 35%)[a] and **without** hypersensitivity symptoms (e.g., fever, rash)	**1st occurrence** 1) Interrupt pazopanib until toxicity resolves to ≤Grade 1 or baseline. Discontinue simvastatin if patient has been receiving simvastatin. Repeat full panel LFTs and clinical liver assessment within 24-72 hours, then full panel LFTs at least weekly until ALT/AST is reduced to Grade 1. Follow patient clinically as appropriate.	Monitor as clinically indicated

Management of Elevations in AST, ALT and/or Bilirubin (Cont'd)			
Adverse Event/ CTCAE, v. 4.0 Category	**Grade**	**Treatment Modifications**	**Follow Up**
Elevations in AST, ALT, and/or bilirubin[c]	ALT > 8.0 x ULN **without** bilirubin elevation (defined as total bilirubin < 2.0 x ULN or direct bilirubin ≤ 35%)[a] and **without** hypersensitivity symptoms (e.g., fever, rash)	**1st occurrence (cont'd)** 2) If the potential benefit for reinitiating pazopanib treatment is considered to outweigh the risk for hepatotoxicity, then consult Dr. Sherman or Dr. Bible before reintroducing pazopanib at a reduced dose (usually a decrease of 1 dose level.) Re-challenge may be considered if ALL following criteria are met: - ALT/AST reduced to Grade 1 - Total bilirubin < 1.5 x ULN or direct bilirubin ≤ 35% - No hypersensitivity signs or symptoms - Patient is benefiting from therapy. If approval for re-treatment is granted, the patient must be re-consented (ensuring documentation that patient is aware of all associated hepatotoxicity risks). Measure full panel LFTs at least weekly for 8 weeks at the reduced dose. **Recurrence** Discontinue pazopanib permanently and monitor patient closely for clinical signs and symptoms; perform full panel LFTs at least weekly until ALT/AST is reduced to Grade 1.	

Management of Elevations in AST, ALT and/or Bilirubin (Cont'd)			
Adverse Event/ CTCAE, v. 4.0 Category	**Grade**	**Treatment Modifications**	**Follow Up**
Elevations in AST, ALT, and/or bilirubin[c]	ALT >3.0 x ULN **with** concomitant elevation in bilirubin (defined as total bilirubin ≥ 2.0 x ULN; with direct bilirubin >35%)[a] or **with** hypersensitivity symptoms (e.g., fever, rash).	1) Permanently discontinue pazopanib (and simvastatin, if patient is receiving simvastatin) and report the event to Dr. Sherman within 24 hours**.** Have patients return to the clinic within 24 hours, if possible, for repeat full panel LFTs and liver event follow up assessments. 2) Consult a gastroenterologist / hepatologist to identify potential co-factors. 3) Monitor patient closely for clinical signs and symptoms. Perform full panel LFTs at least weekly until LFTs are reduced to Grade 1.	Monitor as clinically indicated.
Elevations in AST, ALT, and/or bilirubin[c]	For isolated total bilirubin elevation **without** concurrent ALT increases (defined as ALT < 3 X ULN).	Continue at current dose. Discontinue simvastatin if patient has been receiving simvastatin and has ALT > ULN.	Monitor as clinically indicated.

a. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable and a patient meets the criterion of total bilirubin > 1.5 x ULN, then the event should be promptly reported as an SAE.
b. Full panel LFTs include: AST, ALT, alkaline phosphatase, GGT, and total bilirubin. Coagulation tests should be performed as clinically indicated.
c. If a patient receiving concomitant simvastatin develops ALT elevations, follow guidelines for pazopanib dose modification and discontinue simvastatin.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; LFT, liver function test; SAE, serious adverse event; ULN, upper limit of normal

(2/27/12) *Management of Other Clinical Specific Non-Hematologic Toxicities Not Otherwise Addressed, That Are Possibly, Probably, or Definitely Related to* ***Pazopanib/Placebo***
If not addressed in protocol, but treating physician feels continuation of treatment a current dose level will be unsafe, the treating physician must discuss with a co-chair of the study first before making any dose adjustments or treatment delays.

Observation	Action
AE resolves promptly with supportive care	Maintain dose level
Grade 3-4 AE (possibly, probably, or definitely related) to pazopanib/placebo.	Reduce one dose level*
AE does not resolve to grade 2 or below after treating subject at the lowest reduced dose level.	In general, remove subject from study treatment**
*Alternatively and if medically appropriate, investigators may choose to hold dose for up to 14 days or withdraw patient from study treatment. If it is felt the toxicity is more likely related to another factor (e.g. radiation therapy or disease), the investigator may consult with a study chair (Drs. Sherman, Bible, or Lee) about continuing at the current dose level without delaying treatment. **After consultation with a study chair (Drs. Sherman, Bible, or Lee), the investigator may consider treating the patient at the lowest dose level, if the investigator feels the patient is benefitting from the agent.	

Management of Hematologic Adverse Events **(2/27/12)**
(3/8/12) With the exception of Neutropenic fever, changes in dose levels will only occur if the abnormal blood counts are within 24 hours of when paclitaxel is scheduled. This pertains to changes in dose levels for paclitaxel and pazopanib.

Adverse Event/ CTCAE, v. 4.0 Category	**Grade/Counts**	**Paclitaxel Modification**	**Pazopanib/Placebo Modification**
Neutropenia*	3 (500-999/m^3)	Hold therapy. Maintain dose level if recovered to grade 2 (≥ 1000/m^3) in 1 week. If not, decrease by one dose level and restart when absolute neutrophil count is ≥ 1000/m^3.	Hold therapy. Maintain dose level if recovered to grade 2 (≥ 1000/m^3) in 1 week. If not, decrease by one dose level and restart when absolute neutrophil count is ≥ 1000/m^3.
Neutropenic Fever		Hold therapy and decrease by one dose level. Restart when absolute neutrophil count is > 1000/m^3.	Hold therapy. Reduce by one dose level. Restart when recovered (≥ 1000/m^3).
Thrombo-cytopenia*	3 or 4 (< 50,000 m^3)	Hold therapy. Maintain dose level if recovered in 1 week (≥ 50,000/m^3). If not, decrease by one dose level and restart when platelet count is ≥ 50,000/m^3.	Hold therapy. Maintain dose level if recovered in 2 weeks (≥ 50,000/m^3). If not recovered in 2 weeks, decrease by one dose level and restart when platelet count is ≥ 50,000/m^3.

***Recurrent grade 3 or 4 neutropenia and/or thrombocytopenia will result in permanent discontinuation of pazopanib, unless Drs. Sherman or Bible approves continuing treatment.**

7.6.2 Paclitaxel **(9/13/16)**

Appropriate dose modifications for paclitaxel-related adverse events are outlined in the following subsections. If treatment has been held for more than 21 days to allow for resolution of an adverse event, the investigator should contact the sponsor (NRG Oncology) to review the subject's condition prior to resuming the patient's treatment except for delays due to hypertension (see Section 7.6, "Dose Modifications"). As a patient progresses from one treatment group to another (i.e., pre-radiation therapy (7.1), radiation therapy (7.2), the patient should remain at the SAME DOSE LEVEL unless otherwise noted. Dose level reductions follow:

Pre-Radiation Therapy

Dose level	Paclitaxel
DL 1	80 mg/ m^2 intravenously weekly
DL -1	60 mg/ m^2 intravenously weekly
DL -2	45 mg/ m^2 intravenously weekly

During Radiation Therapy

Dose level	Paclitaxel
DL 1	50 mg/ m^2 intravenously weekly
DL -1	38 mg/ m^2 intravenously weekly
DL -2	30 mg/ m^2 intravenously weekly

Management of Non-Hematologic Adverse Events That Are Possibly, Probably, or Definitely Related To ***Paclitaxel*** **(9/13/16)**

Adverse Event/ CTCAE, v. 4.0 Category	**Grade**	**Treatment Modifications**
Neuropathy	Grade 3	Hold therapy until grade <=2. Then reduce by one dose level.
	Grade 4	Discontinue paclitaxel.
Allergic Reaction	Grade 3-4	Discontinue paclitaxel. If it occurs before the start of radiation therapy, patient should be taken off protocol treatment (refer to Section 11.8 for follow up and data collection).
Elevations in AST, ALT, and/or bilirubin	AST/ALT 2 to <10 X ULN and total bilirubin elevations ≤ 1.5 X ULN	Decrease paclitaxel 1 dose level until AST/ALT < 2 x ULN, at which time, may return to original dose. If liver metastasis is present, do not decrease unless > 3 x ULN.
	AST/ALT >2 X ULN and < 10 X ULN and concurrent bilirubin elevations >1.5 X ULN	If elevation in bilirubin is predominantly direct (> 35%), decrease dose level by 2. Once bilirubin is < 1.5 x ULN, paclitaxel can be increased 1 dose level. Once AST/ALT < 2 x ULN and bilirubin < 1.5 x ULN, paclitaxel can be returned to normal dose. Contact study chairs (Drs. Sherman or Bible) if any questions.
	If AST/ALT ≥ 10 X ULN	Hold paclitaxel until AST/ALT < 10 X ULN and bilirubin ≤ 1.5 X ULN, and then restart at a reduction of 1 dose level. Once AST/ALT < 2 x ULN, paclitaxel can be increased to original dose level.
	Bilirubin > 5x ULN	Discontinue Paclitaxel

Dysphagia during radiation therapy	Grade 3-4	• If disease related (not related to treatment), no change. • If related to radiation therapy or paclitaxel before the fifth dose of paclitaxel, permanently decrease paclitaxel by 1 dose level during radiation therapy • If related to radiation therapy or paclitaxel before the third dose of paclitaxel, permanently decrease paclitaxel to dose level 2 during radiation therapy, but increase paclitaxel by 1 dose level once post radiation therapy starts.
Other non-hematologic toxicities	Grade 3-4	Hold paclitaxel until $\leq$ grade 2. Maintain dose level. Treating physician may decrease by one dose level with approval from study co-chair (Keith Bible, Nancy Lee, or Eric Sherman). If the treating physician feels that the continuation of treatment benefit outweighs the risk, the physician may discuss with a study co-chair and continue treatment with approval (grade 3 toxicity only).

Management Of Hematologic Adverse Events **(7/15/13)**
See Section 7.6, "Dose Modifications".

7.7 Modality Review (2/27/12)

The Co-Principal Investigator, Eric Sherman, MD, and the Medical Oncology Co-Chair, Keith Bible, MD, PhD will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: **Per Protocol/Acceptable Variation, Unacceptable Deviation, and Not Evaluable**. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

The Principal Investigator, Eric Sherman, MD, and the Medical Oncology Co-Chair, Keith Bible, MD, PhD will perform a Quality Assurance Review after complete data for the first 20 cases enrolled has been received at NRG Oncology. Drs. Sherman and Bible will perform the next review after complete data for the next 20 cases enrolled has been received at NRG Oncology. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at NRG Oncology, whichever occurs first.

7.8 Adverse Events (3/25/14)

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse event (AE) reporting. The CTCAE version 4.0 is located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

Adverse events (AEs) that meet expedited reporting criteria defined in the table(s) below will be reported via the CTEP-AERS (CTEP Adverse Event Reporting System) application accessed via the CTEP web site (https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613).

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS

7.8.1 Adverse Events (AEs) (3/25/14)

Definition of an AE: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease

temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. February 29, 2012;] http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm]

7.8.2 Serious Adverse Events (SAEs) (3/25/14)

Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in Section 7.9 will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in Section 7.9. **Contact the CTEP-AERS Help Desk if assistance is required.**

Definition of an SAE: Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.8.3 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) (3/25/14)

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS system **within 30 days of AML/MDS diagnosis.**

Secondary Malignancy:

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

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

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

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

Second Malignancy:

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

7.9 CTEP-AERS Adverse Event Reporting Requirements (6/5/14)

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the CTEP Adverse Event Reporting System, accessed via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613.

Submitting a report via CTEP-AERS serves as notification to NRG Oncology and satisfies NRG Oncology requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

- CTEP-AERS-24 Hour Notification requires that a CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by an CTEP-AERS 5 Calendar Day Report. Serious adverse events that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below.
- Supporting source document is not mandatory. However, if the CTEP-AERS report indicates in the *Additional Information* section that source documentation will be provided, then it is expected. If supporting source documentation accompanies an CTEP-AERS report, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation **to both the NCI at 301-230-0159 and the NRG Oncology dedicated SAE FAX, 215-717-0990.**
- A serious adverse event that meets expedited reporting criteria outlined in the following table but is assessed by the CTEP-AERS System as "expedited reporting NOT required" must still be reported to fulfill NRG Oncology safety reporting obligations. Sites must bypass the "NOT Required" assessment; the CTEP-AERS System allows submission of all reports regardless of the results of the assessment.

CTEP defines expedited AE reporting requirements for phase 2 and 3 trials as described in the table below. **Important:** All AEs reported via CTEP-AERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

Late Phase 2 and Phase 3 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 (panitumumab) and the commercially available agents in this study[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **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 NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days

Not resulting in Hospitalization ≥ 24 hrs	Not required	10 Calendar Days	

NOTE[1]: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 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 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[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.

NOTE: Deaths clearly due to progressive disease should **NOT** be reported via CTEP-AERS but rather should be reported via routine reporting methods (e.g., CDUS and/or CTMS).

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP-IND: None

8.0 SURGERY

Any salvage surgery (i.e. surgery to remove any part of the tumor) after the patient is registered for the study would require the patient to be removed from protocol treatment. (The patient would be followed as specified in the protocol.)

The exception would be if it is felt that the surgery would not affect any of the objectives/outcomes for the study—a very special circumstance. If the treating physician believes this circumstance exists, the physician must obtain approval from one of the Co-Principal Investigators (Drs. Sherman or Lee) in order for the patient to continue to receive protocol treatment.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

9.2 Non-permitted Supportive Therapy (9/30/15)

9.2.1 The patient's medications will be evaluated within 4 weeks prior to treatment (see Section 3.2.16) with attempt to change any medication that affects CYP3A4 (see Appendix VI).

Certain medications that act through the CYP450 system are specifically prohibited in patients receiving pazopanib. Strong inhibitors of CYP3A4 such as ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole may increase pazopanib concentrations and are prohibited although, if absolutely necessary, they may be administered in conjunction with lowering the dose of pazopanib to 400 mg daily. Grapefruit juice is also an inhibitor of CYP450 and should not be taken with

pazopanib. CYP3A4 inducers such as rifampin may decrease pazopanib concentrations and therefore are strictly prohibited. Caution should be used when strong inhibitors and/or inducers of CYP2D6 are co-administered with pazopanib. Concomitant use of pazopanib with agent with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6 or CYP2C8 should be avoided. In addition, the use of St. John's Wart is not permitted.

Pazopanib, 800 mg once daily, has no effect on CYP2C9, CYP1A2 or CYP2C19 in vivo although it does in vitro. Therefore, therapeutic doses of warfarin, a substrate of CYP2C9, and omeprazole, a substrate of CYP2C19 are permitted. Caffeine, a substrate of CYP1A2, is also permitted. A list of medications that are specifically prohibited or that should be used with caution during this trial of pazopanib can be found in Section 7.4.1. Comprehensive lists of agents that could affect pazopanib through the cytochrome P450 system can be found in Appendix VII.

9.2.2 Certain medications that are associated with a risk for QTc prolongation and/or Torsades de Pointes are not prohibited but should be avoided or replaced with medications that do not carry these risks, if possible. Comprehensive lists of agents that that are associated with a risk for QTc prolongation and/or Torsades de Pointes can be found in Appendix VI.

10.0 TISSUE/SPECIMEN SUBMISSION

NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission. If the patient consents to participate in the tissue/specimen banking in the study, the site is required to submit the patient's specimens as specified in Section 10.0 of the protocol. **Note**: Sites are not permitted to delete the tissue component from the protocol or from the sample consent.

10.1 Tissue/Specimen Submission (6/5/14)

The NRG Oncology Biospecimen Bank at the University of California San Francisco acquires and maintains high quality specimens from NRG Oncology trials. Tissue from each block is preserved through careful block storage and processing. NRG Oncology encourages participants in protocol studies to consent to the banking of their tissue and blood. NRG Oncology Biospecimen Bank provides specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. The NRG Oncology Biospecimen Bank also collects tissue for central review of pathology.

In this study, tissue must be submitted prior to treatment to the NRG Oncology Biospecimen Bank for the purpose of central review of pathology (mandatory), but central review is not required for eligibility. Due to the aggressiveness of this disease, treatment will be started prior to central review. Collection of tissue and blood pre-treatment for banking is recommended, but not required.

10.2 Tissue Collection for Central Review – Mandatory (9/13/16)

The following material must be provided to the NRG Oncology Biospecimen Bank for Central Review:

10.2.1 One H & E stained slide per positive biopsy site (required); the slide can be a duplicate cut stained H&E of the diagnostic slide or block; it does not have to be the diagnostic slide itself. In addition, a digital slide is acceptable in lieu of the H&E.

10.2.2 A paraffin-embedded tissue block of the tumor (preferred), or 10 unstained tumor slides (5 micron thickness per slide), or a 2 mm diameter core of tumor tissue, punched from the tissue block containing the tumor with a skin punch and submitted in a plastic tube labeled with the surgical pathology number. **NOTE**: A kit with the punch, tube, and instructions can be obtained free of charge from the NRG Oncology Biospecimen Bank; see Appendix VIII. Block or core must be clearly labeled with the pathology identification number and block number that corresponds to the Pathology Report.

- The submitted material must be from malignant tumor, not necrotic or fibrotic tissue. If the submitted material is reviewed and is not tumor, the site may be assessed a protocol violation.

10.2.3 A Pathology Report documenting that the submitted block, core, or slides contain tumor; the report must include the NRG Oncology protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

- The submitted material must be from malignant tumor, not necrotic or fibrotic tissue. If the submitted material is reviewed and is not tumor, the site may be assessed a protocol violation.

10.2.4 A Specimen Transmittal (ST) Form stating that the tissue is being submitted for Central Review. The Form must include the NRG Oncology protocol number and the patient's case number.

10.2.5 Central Review will be performed for every case by the Pathology Co-Chair, Ronald A. Ghossein, MD, Memorial Sloan-Kettering Cancer Center. Central review will be performed after the study is closed

10.3 Specimen Collection for Banking – Recommended (2/10/15)

For patients who have consented to participate in the tissue/blood component of the study (See the sample consent form)

See Appendices IX-XI for detailed collection instructions, including information pertaining to collection kits. Note: Kits include a shipping label for frozen biospecimen shipments.

Tissue should be collected pre-treatment. The following must be provided in order for the case to be evaluable for the NRG Oncology Biospecimen Bank:

10.3.1 One H&E stained slide (slide can be a duplicate cut stained H&E of the diagnostic slide or block; it does not have to be the diagnostic slide itself.)

10.3.2 A paraffin-embedded tissue block of the tumor (preferred), or 10 unstained tumor slides (5 micron thickness per slide), or a 2 mm diameter core of tumor tissue, punched from the tissue block containing the tumor with a skin punch and submitted in a plastic tube labeled with the surgical pathology number. **NOTE**: A kit with the punch, tube, and instructions can be obtained free of charge from the NRG Oncology Biospecimen Bank; see Appendix X. Block or core must be clearly labeled with the pathology identification number and block number that corresponds to the Pathology Report.

- The submitted material must be from malignant tumor, not necrotic or fibrotic tissue. If the submitted material is reviewed and is not tumor, the site may be assessed a protocol violation.

If an institution is uncomfortable with obtaining the punches and wants to retain the tissue block, the site can send the entire block to the NRG Oncology Biospecimen Bank, and the Bank will obtain the core punches from the block and return the remaining block to the site. Please indicate this request (to obtain the sections, perform the core punch procedure, and return the block) on the submission form and include a return airbill for the block being returned.

10.3.3 A Pathology Report documenting that the submitted block, or unstained slides, or core contains tumor. The report must include the NRG Oncology protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

10.3.4 A Specimen Transmittal (ST) Form clearly stating that tissue is being submitted for the NRG Oncology Biospecimen Bank documenting the date of collection of the biospecimen; the NRG Oncology protocol number, the patient's case number, and method of storage, for example, stored at -20° C, must be included.

10.3.5 Serum, Plasma, and Whole Blood **(4/19/11)**

Serum, plasma, and whole blood should be collected pre-treatment. The following must be provided in order for the case to be evaluable for the NRG Oncology Biospecimen Bank: A Specimen Transmittal Form documenting the date of collection of the serum, plasma, and whole blood; the NRG Oncology protocol number, the patient's case number, the method and time of storage (for example, stored at -80° C for 3 days).

If the institution does not have any access to centrifuges for serum/plasma separation, it is allowed to submit only whole blood samples which do not require any separation steps (See Appendix IX for processing and shipping instructions.)

Storage Conditions

Store frozen specimens at –80° C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

Please indicate on Specimen Transmittal (ST) Form the storage conditions used and time stored.

10.3.6 Specimen Collection Summary **(9/13/16)**
Note: See Appendices IX-X for collection kits and instructions.

Specimens for Banking			
Specimens taken from patient:	**Collected when:**	**Submitted as:**	**Shipped:**
Representative H&E stained slides of the primary tumor	Pre-treatment	H&E stained slide Pre-treatment	Slide shipped ambient
A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment, or 10 unstained tumor slides (5 micron thickness per slide), or a 2 mm diameter core of tissue, punched from the tissue block with a punch tool	Pre-treatment	Paraffin-embedded tissue block, or unstained tumor slides, or punch biopsy (must match the H&E slide being submitted)	Block or punch shipped ambient
SERUM: 5-10 mL of whole blood in 1 red-top tube and centrifuge	Pre-treatment	Frozen serum samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials (five)	Serum sent frozen on dry ice via overnight carrier
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/lavender top) and centrifuge	Pre-treatment	Frozen plasma samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials (five)	Plasma sent frozen on dry ice via overnight carrier
DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix	Pre-treatment	Frozen whole blood samples containing 1 mL per aliquot in 1 mL cryovials (three to five)	Whole blood sent frozen on dry ice via overnight carrier

10.3.7 Submit materials for Central Review and Banking as follows: **(9/13/16)**

Courier Address (FedEx, UPS, etc.) For Trackable FFPE and ALL Frozen Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
Questions: 415-476-7864/FAX 415-476-5271; NRGBB@ucsf.edu

10.4 Reimbursement (2/10/15)

NCI funds for reimbursement for protocol-specified biospecimen materials will be distributed per the requirements/methods specified by the new National Clinical Trials Network (NCTN) Program. This information will be made available with the other registration materials in the Oncology Patient Enrollment Network (OPEN) portal system.

10.5 Confidentiality/Storage (4/19/11)

(See the Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/Researchers/BiospecimenResource/BiospecimenResourceFAQs.aspx for further details.)

10.5.1 Upon receipt, the specimen is labeled with the NRG Oncology protocol number and the patient's case number only. The NRG Oncology Biospecimen Bank database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.5.2 Specimens for tissue banking will be stored for an indefinite period of time. Specimens for central review will be retained until the study is terminated. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (2/27/12)

See Appendix I for a summary of assessments and timeframes. **Note**: Clarifications of or exceptions to the study parameters are indicated in Appendix I with an asterisk (*) and are discussed in Sections 11.2-11.7 below.

Laboratory Tests: All laboratory tests (i.e. CBC, serum electrolytes) may be done 1 day prior to scheduled treatment day (e.g. if scheduled in the calendar on a Tuesday, it may be done the day before, on a Monday). Liver function tests may be done up to 2 business days prior to scheduled treatment day.

Urine Tests for Protein/Creatinine: Urine tests may be done up to 2 business days prior to scheduled treatment day. If a 24-hour urine collection for protein has been completed within 5 business days prior, a urine for protein/creatinine ratio is not necessary.

(3/8/12) Patient Education: Institutions must provide patient education regarding the pazopanib/placebo suspension. Patients should be educated regarding swirling the suspension for 30 seconds prior to withdrawing the dose from the bottle, drawing up the prescribed dose, and storage of the suspension. Patients should demonstrate that they can draw up the appropriate daily dose and should be reminded to take the suspension on an empty stomach either 1 hour before or 2 hours after meals. Instructions to the patient for disposal of leftover pazopanib suspension and cleanup of pazopanib suspension spills have been included on the medication diary form **(DP).**

11.2 Pre-Treatment Evaluations (9/30/15)

11.2.1 **Note**: In the event that the patient's condition is deteriorating, lab tests done prior to registration and any other relevant tests should be repeated within 48 hours prior to treatment.

11.2.2 In the review of the patient's medications: Medications must be checked to see if they are listed in Appendices VII and VIII. If the medications are listed in Appendix VI, appropriate changes to the patient's medications must be made.

11.2.3 Systolic blood pressure must be ≤ 140 and diastolic blood pressure must be ≤ 90 on at least 2 separate measurements within 2 weeks prior to treatment, if > 140/90 at baseline.

11.2.4 The recommended (but not required) dental evaluation and, if applicable, prophylaxis, should be performed within 12 weeks prior to treatment.

11.2.5 Imaging of the neck: The CT scan must be done with contrast or if an MRI is done, with gadolinium.

11.2.6 Chest/abdominal imaging: Abdominal imaging must cover the liver and adrenal glands; therefore, separate imaging is not required if these areas are covered by a chest CT scan.

11.2.7 All wounds, whether surgical or other, must be completely healed prior to the initiation of treatment (see Section 4.1.2).

11.2.8 Serum electrolytes should include sodium, potassium, chloride, carbon dioxide, BUN, creatinine, magnesium. Liver function tests include at least serum glutamic oxaloacetic transaminase/aspartate transaminase (SGOT/AST), serum glutamic pyruvic transaminase/alanine transaminase (SGPT/ALT), total bilirubin, and albumin. **Note**: Bilirubin

with fractionation should be done if the total bilirubin is greater than ULN. These definitions pertain throughout the study and in follow up.

11.3 Evaluations During Pre-Radiation Treatment (3/11/15)

11.3.1 On day 1, the CYP3A4-affecting agents (see Appendix VII) that the patient is taking should be recorded.

11.3.2 Day 8 of treatment may be given within 2 days of day 8, if necessary.

11.3.3 Typically, Day 15 (+/- 2 days) of paclitaxel will not take place, and patients will start the concurrent treatment (radiation therapy) on this date. However, there may be an unforeseen delay to starting the radiation therapy after 2 weeks. If this occurs, a 3rd week of treatment (i.e. paclitaxel 80 mg/m^2 on day 15 and pazopanib (or placebo) 400 mg oral suspension daily (unless reduced for safety reasons) until radiation therapy begins may be given after contacting and getting approval from Drs. Sherman, Lee, or Bible (see Section 7.2.1) if radiation therapy is ready to begin by day 17.

11.3.4 Institutions will collect the patient's medication diary for pazopanib/placebo during patient visits. Institutions will keep the medication diary as source documentation and will submit the **DP** form at end of treatment (see Section 12.1).

11.3.5 Serum liver tests must be monitored at Day 1 and at week 3 of treatment if radiation therapy has not begun. **Note**: Bilirubin with fractionation should be done if the total bilirubin is greater than ULN.

11.4 Evaluations During Concurrent Treatment (3/11/15)

11.4.1 Imaging should be done within 2-4 weeks after radiation therapy is completed. If RECIST measurable disease was present prior to the start of treatment, response should be recorded.

11.4.2 Urine protein/urine creatinine only needs to be done on week 1 and then every 3 weeks until end of radiation therapy.

11.4.3 On day 1, an EKG should be performed (see Section 7.6.1).

11.4.4 On day 1 (+/- 3 days), the CYP3A4-affecting agents (see Appendix VII) that the patient is taking should be recorded. This should be repeated every 2 weeks until the end of radiation therapy.

11.4.5 Institutions will collect the patient's medication diary for pazopanib/placebo during patient visits. Institutions will keep the medication diary as source documentation and will submit the **DP** form at end of treatment (see Section 12.1).

11.4.6 Serum liver tests must be monitored in all odd weeks (e.g. 1, 3, 5, 7) of concurrent treatment and at 2 weeks after completion of treatment (+/- 2 days). **Note**: Bilirubin with fractionation should be done if the total bilirubin is greater than ULN.

11.5 Imaging After Completion of Radiation Therapy (3/8/16)

After radiation therapy is completed, imaging studies for staging purposes should be completed. This must include (1) imaging of the neck (CT scan or MRI); (2) imaging of the chest and abdomen by CT scan and (3) imaging of the brain (CT scan or MRI). All CT scans and MRIs should include contrast unless clinically contraindicated. Imaging should take place between 2-4 weeks following the completion of radiation therapy. Imaging of the neck, chest, and adrenal glands should continue every 3 months from the end of RT for 2 years (see Section 11.6).

11.6 Long-Term Follow up (9/30/15)

If/when a subject begins a new type of treatment for anaplastic thyroid cancer, long-term follow up may cease, with the exception of noting whether the subject is alive or dead. To document this, it is not necessary that the patient return for office visits. Follow up may be done through other means (e.g., through telephone calls or registered mail). Note: The Follow-up Form **(F1)** must be submitted as specified in Section 12.1. If a subject dies, the date of death must be recorded and submitted to NRG Oncology.

If a subject comes off treatment due to disease progression or recurrence, or if this happens during long-term follow up, further radiology studies as per protocol are no longer required.

Radiology studies should include imaging of the neck (MRI or CT scan) and chest (CT scan). A PET/CT can be substituted for the CT scans. The first set of follow-up scans and the follow-up visit should be 3 months after the end of radiation treatment, NOT after the prior scans. If the above imaging does not include the adrenal glands, an abdominal CT scan also must be done during follow-up imaging. Patients

may be evaluated +/- 2 weeks of the scheduled follow-up visit during the first 2 years and +/- 1 month during years 3-5. If imaging is required for clinical reasons prior to the per-protocol-scheduled evaluation, all future evaluations may be delayed up to 2 months. Imaging is not required after 2 years but is highly recommended. The patient's evaluation schedule should be modified only after discussion with one of the study co-chairs (Drs. Bible, Lee, or Sherman).

11.7 Measurement of Response (2/27/12)

11.7.1 Measurement of Response Prior to Study Entry

The revised RECIST guideline, v. 1.1 [*European Journal of Cancer*. 45: 228-247, 2009] will be used as applicable to the protocol. See http://ctep.info.nih.gov/protocolDevelopment/docs/recist_guideline.pdf for further details. Additional definitions beyond the RECIST guidelines specific to this protocol are incorporated to define local control as described below.

11.7.2 Response Criteria: Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions; Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

11.7.3 Assessment of Failure Patterns

- *Local or Regional Relapse*
  Relapse is defined as reappearance of tumor after complete response. If possible, relapse should be confirmed by biopsy.
- *Local or Regional Progression*
  Progression is defined as an estimated increase in the size of the tumor (product of the perpendicular diameters of the two largest dimensions) of greater than 25%, taking as reference the smallest value of all previous measurements or appearance of new areas of malignant disease. This should be compared to radiology reassessment done after the completion of radiation therapy.
- *Distant Metastasis Progression*
  Progression (of distant metastasis [lung, bone, brain, liver, etc…]) is defined as an estimated increase in the size of the tumor (product of the perpendicular diameters of the two largest dimensions) of greater than 25%, taking as reference the smallest value of all previous measurements or appearance of new areas of malignant disease. This should be compared to radiology reassessment done after the completion of radiation therapy.

11.8 Criteria for Discontinuation of Protocol Treatment (9/13/16)

- Progression of disease;
- A delay in protocol treatment, as specified in Sections 6.0 and/or 7.0;
- Intercurrent illness that prevents further administration of treatment;
- Unacceptable adverse event(s), as defined in Section 6.0 and/or 7.0;
- Patient noncompliance as determined by the judgment of the investigator that would make further treatment potentially unsafe or make outcomes of the trial difficult to interpret;

- Patient decides to withdraw from the study;
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol. Patients who have received no protocol treatment should be followed for overall survival only.

12.0 DATA COLLECTION (24-FEB-2020)

Data should be submitted to:

NRG Oncology*
50 South 16th Street, Suite 2800
Philadelphia, PA 19102

***If a data form is available for web entry, it must be submitted electronically.**

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission (9/13/16)

Item	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)** Pathology Report **(P1)** Slides/Blocks **(P2)**	Within 2 weeks of study entry
Treatment Form **(TF)**	At the completion of pre-IMRT component and at the completion of concurrent therapy component
Medication diary **(DP)**	At end of treatment
Initial Follow-up Form **(F0)**	3 months from the start of treatment, after re-staging imaging
Follow-up Form **(F1)**	After the F0, q 3 months for years 1 and 2; q 6 months for year 3, then annually; also at death.

12.2 Summary of Dosimetry Digital Data Submission (Submit to TRIAD; see Section 5.0 for account access and installation instructions) (3/25/14)

Item	Due
Preliminary Dosimetry Information (DD) Digital Data Submission – Treatment Plan submitted to NRG Oncology via TRIAD exported from treatment planning machine by Physicist Digital data submission includes the following: • DICOM CT Data • DICOM Structure • DICOM RT Plan • DICOM Dose All required structures MUST be labeled per the specifications in Section 6.5. All digital RT data MUST be in DICOM format. Upon submission of digital data via TRIAD, complete a Digital Data Submission Information Form **(DDSI)** – located at	Within 1 week of start of RT

http://www.rtog.org/CoreLab/RTQASubmissionInformation.aspx

Final Dosimetry Information Within 1 Week of RT End
Radiotherapy Form (T1) Via Web
Daily Treatment Record (T5) [Copy To HQ only]

13.0 STATISTICAL CONSIDERATIONS

13.1 Endpoints (7/15/13)

13.1.1 *Primary Endpoint for Run-In Components* **(2/27/12)**

Grade 4 (CTCAE, v. 4.0) hemorrhage, grade 4 febrile neutropenia, discontinuation of treatment due to toxicity (< 75% of planned radiation therapy delivered), or any Grade 5 adverse event assessed to be definitely, probably, or possibly related to the induction or concurrent treatment components of the protocol regimen (that is not definitely related to disease progression).

13.1.2 *Primary Endpoint for Phase II Component*

Overall survival (OS) at 1 year from study registration

13.1.3 *Secondary Endpoints for Phase II Component* **(6/5/14)**

- Local-regional control at 6 and 12 months;
- Grade 4 (CTCAE, v. 4.0) hemorrhage, grade 4 febrile neutropenia, discontinuation of treatment due to toxicity (< 75% of planned radiation therapy delivered), or any Grade 5 adverse event assessed to be definitely, probably, or possibly related to the induction or concurrent treatment components of the protocol regimen;
- Other adverse events (CTCAE, 4.0) assessed to be definitely, probably, or possibly related to the induction or concurrent treatment components of the protocol regimen;
- Response as per RECIST of the primary site in patients with measurable disease following chemoradiation.

13.2 Background and Sample Size Determination (2/27/12)

13.2.1 Run-in Components

Since there is limited experience with pazopanib added to concurrent chemoradiation for treatment of patients with thyroid cancer, a two-stage design based on binomial distribution will be utilized to monitor safety endpoints. The first stage will be a run-in component enrolling 11 patients to assure that the induction and the concurrent components of the protocol regimen are safe. A safety analysis will be performed after the 11 patients complete radiation therapy. There is particular concern of a possibly unacceptable increase in the incidence of patients with grade 4 bleeding, grade 4 febrile neutropenia, discontinuation of treatment due to toxicity (< 75% of planned radiation therapy delivered), and any grade 5 adverse event (that is not definitely related to disease progression). Discontinuation of treatment due to toxicity is defined as discontinuation of treatment by a treating physician due to a grade 3 or 4 toxicity/toxicities that are possibly, probably, or definitely related to treatment and causes < 75% of planned radiation therapy to be delivered. This incidence is assumed to be no greater than 20%; an increase of 25% or more is considered unacceptable. Eleven patients will be initially entered on the run-in component to guard against the possibilities that disease may progress during treatment or a patient withdraws consent. Patient accrual then will be suspended until the analysis of the run-in component is completed. With 9 evaluable patients, if 4 or fewer patients experience the adverse events of concern, then the induction and the concurrent components will be judged to be safe. If 5 or more patients with such events are observed, then the induction and the concurrent components will be judged as too toxic. The run-in component may be repeated following dose modification. The data that will be collected for analysis will include all the adverse events reported through 4 weeks after the completion of concurrent chemoradiation, as well as dose delays, dose modifications, and delays in initiating radiation therapy. The probability of the induction and the concurrent components being judged to be too toxic when the true toxicity rate is 45% or higher is at least 84%. If the true toxicity rate is 20% or lower, the probability that the therapy will be safe is 95%. The second stage of the analysis will be done when 30 patients have been randomized on the phase II component, given the trial is not stopped at the first analysis. With 15 more patients and total of 24, if 8 or fewer patients

experience the adverse events of concern, then the induction and concurrent components will be judged to be safe. Otherwise, the trial will be stopped due to the toxic nature of the therapy. The data that will be collected for analysis will include all the adverse events reported through 4 weeks after the completion of concurrent chemoradiation, as well as dose delays, dose modifications, and delays in initiating radiation therapy. For this second analysis, accrual to the study will be not suspended. Analysis results of the run-in components will be reviewed by the NRG Oncology Data Safety Monitoring Board (DSMB) and shared with CTEP. Analysis results of the phase II component will be reviewed by the NRG Oncology Data Monitoring Committee (DMC).

13.2.2 Phase II Screening Component **(10/28/10)**

After the run-in component is completed, the study will be a randomized phase II screening trial as proposed by Rubinstein, et al. (2005). It is designed as a one-sided test to detect a ≥ 37.5% reduction of the hazard rate associated with overall survival (OS) favoring the addition of pazopanib. The type I (alpha) is set at 0.15 while the statistical power is set at 0.80. There is a paucity of outcome data available for this study population. Currently, the best available data comes from a population-based study that reported a 1-year survival rate of 19% with standard of care treatment (Goutsouliak 2005). It should be noted that this rate is consistent with the long-term experience at Memorial Sloan-Kettering (personal communication, Sherman). OS will be assumed to follow an exponential distribution for planning purposes. East® software for group sequential design was used in calculating the sample size with one planned interim analysis for early efficacy and futility testing (East 2005). The O'Brien-Fleming boundary for efficacy and futility were utilized. The interim analysis will occur when there are 35 deaths seen from both arms. If the p<=0.0418, this result will be interpreted as an indication of pazopanib in improving overall survival in these patients. If p>=0.5324, we will declare futility. If either boundary is crossed, further patient accrual will be discontinued, and the result will be reported. If no boundary is crossed, the final analysis will occur when there are 71 deaths. The significance level 0.1379 for the final analysis was derived in order to preserve a 0.15 significance level for the entire study. If the resulting p-value is < 0.1379, the result will be interpreted as an indication of pazopanib tending to improve overall survival in these patients. In order to have 71 deaths (total from both arms combined), 79 analyzable patients are targeted for phase II portion of this trial. Assuming that up to 10% of patients may be ineligible or lost to follow up, **the sample size required for the phase II screening portion of the trial will be 88 patients.** The analysis will be restricted to eligible patients with follow-up data and may possibly exceed 79 patients.

13.3 Patient Accrual (2/27/12)

Patient accrual is projected to be 2 per month after the first 2 months in which institutions are obtaining IRB approval. At this rate, it will take approximately 8 months to complete accrual for each run-in component. Analysis will begin 4 weeks after the last subject has completed radiation therapy. The total duration of each component will be 14 months, including 4 months to finish the proposed treatment and 2 months for data collection and data analysis. The data will be provided to CTEP for review prior to starting the phase II component of the study. For the randomized phase II component, it will take approximately 44 months to complete accrual for a total of 88 patients, with 12 months follow up and six month for data collection and analysis.

13.4 Randomization (2/27/12)

For the randomized phase II component, the treatment allocation scheme described by Zelen (1974) will be used as it balances patient factors other than treating institution. The randomization ratio between the 2 arms will be 1:1. Additionally, patients will be stratified according to presence of metastatic disease (M0 vs. M1 vs. Mx).

13.5 Analysis Plan (06-MAR-2020)

13.5.1 Statistical Methods

Overall survival rates will be estimated using the Kaplan-Meier method (1958) and rates of local-regional control (LRC) by the cumulative incidence method (Kalbfleisch 1980) to account for the competing risk of death without local-regional failure. The distributions of the overall survival times will be compared between treatment arms with a one sided log rank test (Mantel, 1966). If the resulting p-value for OS is < 0.1379 with all patients, the result will be interpreted as an indication of pazopanib in improving overall survival of these patients Failure for LRC is

defined as local regional progression in the thyroid bed or regional lymph nodes. For overall survival, death from any cause will be considered a failure. All failure times will be measured from the date of study registration to the date of failure or last follow up.

For the endpoints in Sections 13.1.1 and 13.1.3, only adverse events (AEs) assessed to be definitely, probably, or possibly related (if relationship is missing, it will be assumed to be definitely, probably, or possibly) to protocol treatment will be considered. The rates of adverse events, discontinuation of treatment, and response will be estimated using a binomial distribution along with their associated 95% confidence intervals and will be compared using Fisher's exact test.

13.5.2 Interim Analysis to Monitor Study Progress **(2/27/12)**

Interim reports will be prepared twice each year until the final analysis has been accepted for presentation or publication. In general, these reports will contain information about the accrual rate with projected completion date for the accrual phase, exclusion rates and reasons, pretreatment characteristics of patients accrued, compliance rate of treatment delivered with respect to the protocol prescription, and the frequency and severity of AEs. This study will be monitored by the Clinical Data Update System (CDUS), version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Analysis results of the run-in components will be reviewed by the NRG Oncology Data Safety Monitoring Board (DSMB). Analysis results of the phase II component will be reviewed by the DMC twice a year in conjunction with the NRG Oncology semi-annual meetings with respect to patient accrual and morbidity. The DMC also will review this study on an "as needed" basis between meetings.

13.5.3 Special Interim Analysis to Monitor Adverse Events

Since there is limited experience with the experimental regimen, a two stage interim analysis of AEs will be performed to assure that there are no unexpected problems. This analysis will occur after 9 analyzable patients are entered into the run-in component and 15 patients are entered into the experimental arm. If 4 or fewer and 8 or fewer patients experience the AEs of concern at the first and second interim analysis, then the induction and the concurrent components will be judged to be safe. After reviewing the results from each analysis, the study chairs and study statistician will make a recommendation to the NRG Oncology Head and Neck Steering Committee, the NRG Oncology DSMB, and the corporate sponsor for their consideration. These committees and individuals jointly will decide the future course of action for the study.

13.5.4 Significance Testing for Early Termination and Reporting **(8/24/11)**

One interim treatment comparison will be performed when 50% (35 deaths) of the 71 required number of failures are observed. Only the primary endpoint will be tested in the interim analysis. The efficacy will be tested using O'Brien-Fleming boundaries of 0.0418 for the interim tests and 0.1379 for the final analysis to preserve an overall alpha level of 0.15 for the study. The futility will be tested using the lower boundary at P>0.5324. The results will be reported to the NRG Oncology DMC with the treatment blinded. The responsible statistician may recommend early reporting of the results and/or stopping accrual (if applicable) of the trial if the treatment effect with respect to OS is highly significant or if it is not likely to be; that is, if the p-value is less or greater than the nominal value specified in a sequential design for either efficacy or futility. If the resulting p-value for efficacy is <0.1379, this result will be interpreted as an indication of pazopanib in improving overall survival in these patients.

13.5.5 Analysis for Reporting the Initial Treatment Results

The analysis to report the initial results of treatment was originally planned when 71 events (total from both arms) have been reported for the primary endpoint, OS, unless the criteria for early stopping are met. However, not enough OS events have been observed with the projected follow-up time, and the required number of OS events (71) for this final analysis will not be obtained given that the number of eligible patients at risk of death is lower than the required number of OS events due to a higher than projected ineligibility rate and consent withdrawals. Given that, the final analysis will now be time driven and will be done after all eligible patients had been potentially followed for 3 years. This change was done in a blinded fashion regarding the clinical outcomes. A sensitivity analysis based on all randomized patients at risk of anaplastic thyroid cancer death (after excluding one patient with renal cell carcinoma histology) will also be done.

The time from opening this trial to patient entry to this analysis is projected to be approximately 5.5 years if the projected accrual rate is realized. Only eligible patients with both on-study and

follow-up information will be included. Eligible patients that do not start protocol treatment will be included in this intent-to-treat analysis. The usual components of this analysis are:

- Tabulation of all cases entered, and any excluded from analysis with reasons for exclusion;
- Patient accrual rate;
- Institutional accrual;
- Distribution of important baseline prognostic variables;
- Frequency and severity of adverse events;
- Observed results with respect to the endpoints described in Sections 13.1.1 and 13.1.2.

The difference in OS between the control arm and the experimental arm will be tested using the one sided log-rank statistic at the significance level of 0.1379 given that the one interim analysis is carried out and shows no statistical significance. If the resulting p-value for efficacy is <0.1379, this result will be interpreted as an indication of pazopanib in improving overall survival in these patients.

13.6 Gender and Minorities (7/15/13)

Both men and women of all races and ethnic groups are eligible for this study. In conformance with the National Institutes of Health Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have considered the possible interactions (treatment by race and treatment by gender). The study was designed under the assumption of the same results between the gender and among the races. Based on Gilliland (1997), we project that 32% of patients enrolled on this study will be male, 87% white, and 3% Hispanic. The following table provides the projected number of patients in each race, ethnicity, and gender group.

Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	2	1	3
Not Hispanic or Latino	79	39	118
Ethnic Category: Total of all subjects	81	40	**121**
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	0	0	0
Asian	0	0	0
Black or African American	11	6	17
Native Hawaiian or other Pacific Islander	0	0	0
White	70	34	104
Racial Category: Total of all subjects	81	40	**121**

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APPENDIX I, STUDY PARAMETER TABLE: PRE-TREATMENT ASSESSMENTS (9/30/15)
*See Sections 11.2 through 11.7 for details and exceptions

Assessments	Within 10 Days Prior to Registration Unless Otherwise Noted	Prior to Treatment
Tissue for central review		X
History/physical	2 weeks	
BP	X*	
EKG	X	
CT or MRI of Neck*	4 weeks	
Imaging of Chest, Abdomen, Liver and Adrenal glands*	4 weeks	
Performance status	X	
PT/INR/PTT	X	
CBC w/ diff & ANC	X	
Liver function tests*	X	
Serum electrolytes*	X	
Urine protein & urine creatinine	X	
Serum pregnancy test (if applicable)	X	
Documentation of QTC history	X	
Wound healing		X
Review/recording of medications	X*	
PET/CT Dental evaluation Nutritional evaluation TSH suppression	Recommended, not required	

APPENDIX I, STUDY PARAMETER TABLE: ASSESSMENTS DURING TREATMENT (6/5/14)

*See Sections 11.2 through 11.7 for details and exceptions

Assessments	During Pre-IMRT Treatment			During Concurrent Treatment	
	Day 1	Day 8 (+/- 2 days)	*Day 15-see Section 11.3	Weekly during Treatment	2 weeks after completion of Treatment (+/- 2 days)
History/physical	X	X	X	X	X
BP	X	X	X	X	X
EKG				Day 1*	
CT or MRI of Neck* and Brain					X*
Imaging of Chest, Abdomen, Liver and Adrenal glands*					X*
Performance status				X	X
CBC w/ diff & ANC	X	X	X	X	X
Serum electrolytes*	X	X	X	X	X
Serum liver tests*	X		X	In all odd weeks	X
Urine protein & urine creatinine			X	X*	X
Serum thyroglobulin, thyroglobulin antibodies, & thyroid stim. hormone	X				
Review/recording of medications	X*			*Day 1 (+/- 3)	
Medication diary		X			X
Adverse event eval	X	X	X	X	X

APPENDIX I, STUDY PARAMETER TABLE: ASSESSMENTS IN FOLLOW UP (3/8/16)

*See Sections 11.2 through 11.7 for details and exceptions

Assessments	Long-Term Follow up
	q 3 mos. for years 1-2; q 6 months for year 3, then annually
History/physical	X
BP	X
CT or MRI of Neck*	X*
Imaging of Chest, Abdomen, Liver and Adrenal glands*	X*
Performance status	X
CBC w/ diff & ANC	X
Serum electrolytes*	X
Serum thyroglobulin, thyroglobulin antibodies, & thyroid stim. hormone	X
Adverse event eval	X

APPENDIX II: ZUBROD PERFORMANCE SCALE AND CLASSIFICATION OF CARDIAC DISEASE

ZUBROD PERFORMANCE SCALE

0	**Fully active, able to carry on all predisease activities without restriction**
1	**Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work**
2	**Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours**
3	**Capable of only limited self-care, confined to bed or chair 50% or more of waking hours**
4	**Completely disabled. Cannot carry on self-care. Totally confined to bed**
5	**Death**

NEW YORK HEART ASSOCIATION CLASSIFICATION OF CARDIAC DISEASE

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

APPENDIX III: AJCC STAGING SYSTEM (7/15/13)

Edge, SB, ed. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.

HEAD & NECK

ANAPLASTIC THYROID CANCER

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	
T1	
T2	
T3	
T4a	Intrathyroidal anaplastic carcinoma—surgically resectable
T4b	Extrathyroidal anaplastic carcinoma—surgically unresectable

REGIONAL LYMPH NODES (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastasis to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)
N1b	Metastasis to unilateral, bilateral, or contralateral cervical or superior mediastinal lymph nodes

DISTANT METASTASIS (M)

M0	No distant metastasis
M1	Distant metastasis
MX	Distant metastasis cannot be assessed

STAGE GROUPING

Stage IVA	T4a, Any N, M0
Stage IVB	T4b, Any N, M0
Stage IVC	Any T, Any N, M1

APPENDIX IV: MANAGEMENT OF DENTAL PROBLEMS IN IRRADIATED PATIENTS

Dental Care for Irradiated Patients

Goals for a dental care program include: 1) To reduce incidence of bone necrosis; 2) To reduce incidence of irradiation caries; 3) To allow proper fitting of dentures following treatment.

Pre-irradiation Care and Procedures

The patients may be grouped into four groups in accordance with the problems they present prior to irradiation.

Group 1

Includes edentulous patients. They may require surgical removal of any symptomatic cysts, infected retained root tips, or alveolar hyperplasia. These patients require hygiene instruction and precautionary instruction about trauma with premature use of a prosthesis.

Group 2

Includes those with poor dental hygiene, including those patients whose teeth are beyond repair by ordinary dental procedure, those with generalized oral sepsis, those with generalized periodontal disease, and those with chronic periapical abscesses or granulomas.

Procedures performed on this group include removal of all remaining teeth prior to irradiation with primary closure and surgical preparation of the alveolar ridges to laterally support a prosthesis. There should be antibiotic coverage during the healing stage and adequate time prior to the start of radiation therapy. These patients need complete hygiene instruction and precautionary instruction about premature use of a prosthesis.

Group 3

Includes those in whom dental condition is fair, including those patients whose teeth are restored, ordinary dental procedures, periodontal pockets are less than 3 mm deep, carious lesions are not in proximity to the pulp, and no more than 20 restorable carious lesions are present. X-ray examinations show at least 1/2 of the bone still present around root surfaces. These patients require removal of any teeth that are non-salvageable in accordance with the above and restorations of the remaining teeth as required. The patients are instructed for dental prophylaxis and the patients utilize custom-made fluoride carriers.

Group 4

Includes those in whom dental hygiene is good. This includes patients who do not have severe malocclusion in whom few carious lesions are present. Carious lesions are not in close proximity to the pulp and are correctable by conventional methods. These patients require periodontal evaluation and dental prophylaxis training, restorations as needed, no extractions prior to radiation therapy, and fitting for custom carriers.

Extraction of Teeth

If extraction of teeth is necessary prior to radiation therapy, the bone must be contoured so that closure at the extraction site is possible. All loose spicules and sharp projections must be removed. The approximation of the gingival tissue must be such that the closure is neither too loose nor too tight. At least 10 days are required for adequate healing prior to initiation of therapy.

Causative Factors

The major causative factors appear to be the reduction of the amount of saliva and secondarily, reduced pH in the mouth. This occurs following high dose radiation to the major salivary glands using parallel opposed fields. The decay process usually occurs in the first year following radiation therapy. It tends to occur more quickly in teeth which have a large amount of root cementum exposed to those teeth with large amounts of plaque formation present. Doses of radiation in excess of 20 Gy to salivary tissue place the teeth at risk.

Preventive Program

The rationale behind the use of fluoride treatments is to make the tooth surfaces less susceptible to the decay process. This is accomplished by a combination of increasing fluoride concentration on the tooth surface and by the effect of fluoride on the plaque and flora that are present in the oral cavity. Adequate results are obtained by: 1) cleansing the teeth thoroughly, followed by a good home care dental prophylaxis program, 2) construction of
fluoride carriers, custom-made mouth guards, which provide local application of fluoride solution to the gingiva and tooth surfaces. Fluoride carriers are made individually with the use of casts. Material used for making a mouth guard is "Sta-Guard" plastic used in conjunction with vacutrole unit produced by Jelrus Technical Products, Corp., both of which are available through local dental supply. This material is molded to the cast impression and allowed to harden. A fluoride solution prepared at the M.D. Anderson Hospital is now available from the Emerson Laboratories, Inc., Dallas, Texas 75221. It has been used to coat the plastic carrier for use in the mouth. The patients are instructed to cleanse their teeth prior to placement of the carrier. It is then worn in place for 5 minutes each day. The patients are instructed to rinse their mouths thoroughly following the use of the carrier. This will be continued for an indefinite period of time. Close follow-up is necessary.

Results

In the 5-1/2 year program at the M.D. Anderson Hospital beginning in 1966, a study of 304 patients shows that the incidence of necrosis of the jaw was reduced to approximately 21% compared to 37% prior to initiation of the study. Groups 3 and 4 patients randomized with and without fluoride treatment showed reduction in radiation carries from 67% to 34% among Group 3 patients, and from 65% to 22% among Group 4 patients.

Failure to Control Decay

Management of failure to control radiation decay includes silver fillings with continued use of fluoride treatments. If the decay process is sufficiently advanced that a filling will no longer stay in place, these teeth are merely smoothed so that there will be no sharp, irritating edges. The mere existence of such a decayed tooth is not necessarily reason for extraction, for it must be remembered that extraction could lead to complications such as bone necrosis.

Pulp exposure resulting from the decay process can usually be handled by use of antibiotics and/or root-canal therapy.

Hypersensitivity of Teeth

Occasionally, a patient will exhibit extreme sensitivity of the teeth secondary to diminished amounts of saliva. This has been shown to be reduced in incidence with the fluoride treatments. Should this problem become manifest, increasing the fluoride treatment to 10 to 15 minutes 3 times a day is recommended.

Infections

Infections occurring in patients under or after radiation therapy are best managed conservatively with good oral hygiene, irrigation and flushing procedures, and systemic antibiotics.

Bone Necrosis

The patients receiving radiation therapy to a high dose to the head and neck region have increased susceptibility to bone necrosis for several reasons including: impairment of normal metabolism, increased susceptibility to infection and severely limited repair process. Bone necrosis occurs most often after dental or oral surgery in patients who have been previously radiated. Conservative management should be tried first, though in more aggressive lesions a more radical approach may ultimately be necessary.

APPENDIX V: ORAL ANTIHYPERTENSIVE MEDICATIONS

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

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

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

APPENDIX VI: DRUGS THAT PROLONG, MAY PROLONG, OR ARE UNLIKELY TO PROLONG THE QTC

Please note that this list is frequently updated. For the most current list of medications, users should be directed to the following website: http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm.

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

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

	Sunitinib /Sutent®	
	Tacrolimus /Prograf®	
	Tamoxifen /Nolvadex®	
	Telithromycin /Ketek®	
	Tizanidine /Zanaflex®	
	Vardenafil /Levitra®	
	Venlafaxine /Effexor®	
	Voriconazole /VFend®	
	Ziprasidone /Geodon®	

APPENDIX VII: DRUGS KNOWN TO BE METABOLIZED BY SELECTED CYP450 ISOENZYMES

CYP2C8/9

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

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

APPENDIX VII (Continued)

DRUGS THAT MAY HAVE POTENTIAL INTERACTIONS WITH CYP2C8/9

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

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

Inducers			
Carbamazepine	Phenobarbital	Primidone	Rifapentine
Fosphenytoin	Phenytoin	Rifampin	Secobarbital

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

APPENDIX VII (Continued)

SELECTED POTENTIAL CYTOCHROME P450 (CYP) DRUG INTERACTIONS

CYP3A4

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

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

APPENDIX VII (Continued)

DRUGS THAT MAY HAVE POTENTIAL INTERACTIONS WITH CYP3A4

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

APPENDIX VII (Continued)

DRUGS THAT MAY HAVE POTENTIAL INTERACTIONS WITH CYP3A4 (Continued)

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

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

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

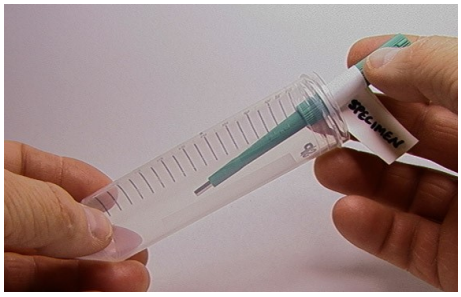
(1) Malhorta *et al*. (2000). Clin Pharmacol Ther. 69:14-23

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

APPENDIX VIII: NRG ONCOLOGY FFPE SPECIMEN PLUG KIT INSTRUCTIONS (9/13/16)

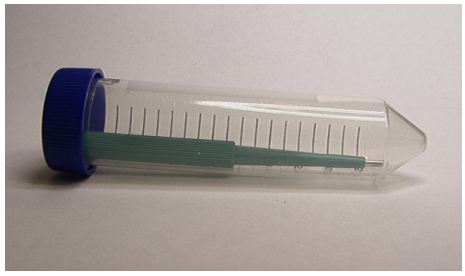
This Kit allows sub-sampling of an FFPE block for submission to the NRG Oncology Biospecimen Bank. The plug kit contains a shipping tube and a punch tool.

Step 1
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.



Step 2
Label the punch tool with the proper specimen ID and block number. DON'T remove specimen from the punch.

Use a separate punch tool for every specimen. Call or e-mail us if you have any questions or need additional specimen plug kits.



Step 3
Once punch tool is labeled, place in shipping tube and mail to address below. Please do not mix specimens in the same tube.

We will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID.

***NOTE:** If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the NRG Oncology Biospecimen Bank and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.
Ship specimen plug kit, specimen in punch tool, and all paperwork to the address below. For Questions regarding collection/shipping or to order an FFPE Specimen Plug Kit, please contact the NRG Oncology Biospecimen Bank by e-mail: NRGBB@ucsf.edu or call 415-476-7864/Fax 415-476-5271.

U.S. Postal Service Mailing Address: For Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For All Frozen Specimens or Trackable shipments
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

APPENDIX IX: NRG ONCOLOGY BLOOD COLLECTION KIT INSTRUCTIONS (9/13/16)

This Kit is for collection, processing, storage, and shipping of serum, plasma, or whole blood *(as specified by the protocol)*:

Kit contents: NOTE: SITES MUST PROVIDE THEIR OWN BLOOD DRAW TUBES.

- Fifteen (15) 1 ml cryovials
- Biohazard bags (3) and Absorbent shipping material (3)
- One Styrofoam container (inner) and Cardboard shipping (outer) box per case
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal Form (ST) and Kit Instructions

PREPARATION AND PROCESSING OF SERUM, PLASMA AND WHOLE BLOOD:

(A) Serum (if requested): Red Top Tube (One 10 ml or two 5 ml Red Top tubes)

- ❑ Label as many five (5) 1mL cryovials for the serum collected. Label them with the NRG Oncology study and case number, collection date, time, and time point, and clearly mark cryovials "serum".

Process:

1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST Form.
3. Aliquot a minimum of 0.5 ml serum into five (5) cryovials as are necessary for the serum collected labeled with NRG Oncology study and case numbers, collection date/time, protocol time-point collected (e.g. pretreatment, post-treatment), and clearly mark specimen as "serum".
4. Place cryovials into biohazard bag and immediately freeze tubes upright at -70 to -90° C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90° C until ready to ship on dry ice. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the ST Form.

(B) Plasma (If requested): Purple Top EDTA tube #1 (One 10 ml or two 5 ml Red Top tubes)

- ❑ Label five (5) 1ml cryovials for the plasma collected. Label them with the NRG Oncology study and case number, collection date, time, and time point, and clearly mark cryovials "plasma".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST Form.
3. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot a minimum of 0.5 ml plasma into five (5) cryovials for the plasma collected (5 to 10) labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as "plasma". Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag and immediately freeze tubes upright at -70 to -90°C.
6. Store frozen plasma until ready to ship on dry ice.
7. See below for storage conditions.

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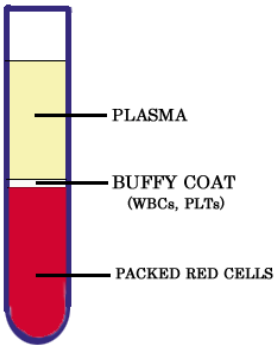

(C) <u>Whole Blood for DNA (if requested): Purple Top EDTA tube #2 (One 5 ml or one 10ml EDTA tube)</u>

- ❑ Label as many 1ml cryovials (3 to 5) as necessary for the whole blood collected..Label them with the NRG Oncology study and case number, collection date/time, and time point, and clearly mark cryovials "blood".

<u>Process</u>:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1.0 ml blood into as many cryovials as are necessary for the blood collected (3 to 5) labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as "blood".
3. Place cryovials into biohazard bag and freeze tubes upright immediately at -70 to -80° Celsius.
4. Store blood samples frozen until ready to ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on ST Form.

<u>Freezing and Storage</u>:

- ☐ Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- ❑ Store at –80°C (-70°C to -90°C) until ready to ship.
  If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

  <u>OR</u>:
  - Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only; Canada: Monday-Tuesday only).

  <u>OR</u>:
  - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- ❑ Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

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APPENDIX IX (9/13/16)
NRG Oncology BLOOD COLLECTION KIT INSTRUCTIONS (continued)

Shipping/Mailing:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all NRG Oncology paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- ❑ Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- ❑ *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ **For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail NRGBB@ucsf.edu or call (415)476-7864.**

Shipping Address:

Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
For questions, call 415-476-7864 or e-mail: NRGBB@ucsf.edu

APPENDIX X: PREPARATION OF 50 MG/ML OF PAZOPANIB ORAL SUSPENSION (6/5/14)

Pazopanib Powder for Oral Suspension is presented with a label claim of 5 grams per bottle in a 200 mL amber type III glass bottle. This powder is to be reconstituted into a 50 mg/mL suspension using 90 mL of purified or sterilized water. This suspension must be refrigerated and should be used within 35 days.

The label claims of 5 grams/bottle (50 mg/mL) refers to 5 grams (50mg/mL) of pazopanib hydrochloride-free base.

Reconstitution Instructions for Pazopanib Powder for Oral Suspension with Purified or Sterilized Water.

1. Tap the sides of the Powder in Bottle to loosen the powder. **Add 90 mL of the room-temperature Purified or Sterilized Water** to the bottle. Replace the cap tightly and **shake vigorously with inversion for at least 2 minutes** to ensure complete powder reconstitution.

2. Allow the bottle to sit for at least 3 minutes to allow any foam to dissipate. The suspension is now ready for use as an elegant white suspension with Lemon flavor. This suspension is designed for multiple uses and may be used for up to 35 days when refrigerated (2 – 8^{o}C).

Dosing Instructions for 50 mg/mL Pazopanib Multi-Use Oral Suspension

3. Immediately prior to the removal of the required dose for administration, **swirl gently for at least 30 seconds** to ensure homogeneity of the suspension.

4. Insert a **Baxa "Press-In-Bottle Adapter (PIBA®)** into the neck of the bottle. **Please ensure that the lip of the Adapter fits snugly with the top of the bottle.**

5. Remove the require dose using a suitable graduated syringe:
    a. Ensure that the syringe plunger is fully pushed into the barrel.
    b. Insert the syringe tip into the Adaptor, then invert the bottle and dispense at least 5 mL of suspension into the syringe and then pump the entire suspension back into the bottle to purge the syringe of any air bubbles. Repeat this step until the syringe is free from air bubbles.
    c. Withdraw the required dosing volume. Then re-invent the bottle and remove the syringe from the Adapter and administer the dose to the patient as soon as possible. **For example, 8 mL aliquot of suspension contains 400 mg pazopanib.**

6. Store the suspension refrigerated (2 – 8^{o}C). Do not freeze. ***The suspension may be used for up to 35 days after reconstitution*.**