DF/HCC Protocol #: 19-524

**TITLE:** A Phase 2 Study of Neoadjuvant Lenvatinib in Locally Advanced Invasive Thyroid Cancer

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Study Exempt from IND Requirements per 21 CFR 312.2(b).

Agent: Lenvatinib (E7080/LENVIMA™), Eisai, Inc

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1. OBJECTIVES

1.1 Study Design

This is a multicenter phase II open-label study of neoadjuvant lenvatinib in patients with locally invasive extrathyroidal differentiated thyroid cancer (DTC). Approximately 30 participants will be enrolled in this trial to examine the efficacy and safety of lenvatinib prior to thyroidectomy, with the goal of achieving more favorable surgical outcomes in patients with locally invasive disease.

All participants will receive either 2, 4, or 6 cycles of lenvatinib prior to surgery, depending on the response. In the landmark SELECT trial investigating lenvatinib in advanced DTC, the greatest degree of tumor shrinkage occurred in the first 2 cycles therapy, however ongoing tumor shrinkage was demonstrated beyond the first 2 cycles in most patients. Thus, in order to allow for optimal surgical timing balancing tumor shrinkage over time with soonest date of surgery, participants in this trial may receive up to 6 cycles of lenvatinib. Participants will undergo restaging in the last week of cycle 2, 4, and 6 (in those participants treated beyond cycle 2).

If response to treatment is deemed by the treating team to be adequate to achieve an R0 resection (clear surgical margins) or R1 resection (microscopically positive surgical margins), lenvatinib will be stopped and the participant should proceed to surgery within 7-14 days from the last dose of lenvatinib.

If the treating team deems there has not been a response sufficient to achieve an R0 or R1, and the participant is tolerating treatment (absence of treatment-related adverse events of grade $\geq 3$ per CTCAE v5.0), an additional 2 - 4 cycles of lenvatinib will be administered followed by surgery that should be performed within 7-14 days from the last dose of lenvatinib.

Given the complexity of the disease, its bilaterality and the cumulative nature of surgical complications especially when bilateral, including both neural and vascular structures, pre-planned staged surgery (i.e. hemithyroidectomy followed by completion thyroidectomy rather than total thyroidectomy) may be an alternative approach for post-neoadjuvant surgery.

If the treating surgeons deems that staged surgery is the best surgical approach, the case should be discussed with the study PI, and if approved by the PI, then hold lenvatinib for at least 1 week before the initial surgery and for at least 2 weeks after initial surgery and until adequate wound healing is achieved. The patient may then resume lenvatinib for approximately 1 month between the initial and 2nd part of the staged surgery. The patient should hold lenvatinib for 7-14 days before the 2nd part of the staged surgery.

If at any time the participant is progressing on lenvatinib, evidenced by scan or clinical examination, surgery will be performed if feasible. If there is significant progression during the treatment and surgery is not deemed feasible, the participant will receive standard of care by treating physician.
Three centers will enroll adult participants who are either initially diagnosed with locally advanced DTC or have experienced persistent or recurrent thyroid and/or cervical nodal recurrent DTC. The three centers are Massachusetts General Hospital/Massachusetts Eye and Ear Infirmary, Memorial Sloan-Kettering Cancer Center, and M.D. Anderson Cancer Center.

**Study Schema**

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### 1.2 Primary Objective

To evaluate the effect of neoadjuvant lenvatinib on surgical resectability in subjects with locally invasive extrathyroidal DTC who are at risk for R2 resection at one or more target interfaces based on preoperative clinical and radiographic assessment. The effect of neoadjuvant lenvatinib will be estimated by the overall R0/R1 resection rate, as defined by proportion of patients who undergo successful surgery with clear (R0) or microscopically positive surgical margins (R1), whether this surgery was definitive or pre-planned staged surgery.

### 1.3 Secondary Objectives

1. To evaluate R0/R1 resection rates in each of 5 pre-specified extrathyroidal anatomic target interfaces:
   - 1- perithyroid muscles (e.g. strap, sternocleidomastoid, inferior constrictor muscles)
   - 2- cartilage (larynx/trachea)
   - 3- esophagus
   - 4- recurrent laryngeal nerve
   - 5- major vessel

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*i initially diagnosed with locally advanced thyroid neoplasm
Persisted or recurrent thyroid and/or cervical nodal recurrent DTC

If disease progressed at any time on lenvatinib:
Participants will be taken off the study drug and receive standard of care which may include surgery, radiation, and any systemic therapy
2. To evaluate whether the surgery involves the resection of 5 pre-specified target interfaces:
   - 1- perithyroid muscles (e.g. strap, sternocleidomastoid, inferior constrictor muscles)
   - 2- cartilage (larynx/trachea)
   - 3- esophagus
   - 4- recurrent laryngeal nerve
   - 5- major vessel

3. To evaluate change in MGH/MEEI-MSK-MD Anderson (MMM) surgical morbidity complexity score (See Appendix A)

4. To evaluate the response rate (RR) prior to primary surgery based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). (See Section 11.1)

5. To evaluate return of laryngeal function by laryngoscopic examination in patients with laryngeal dysfunction at baseline.

6. To assess the safety of lenvatinib
   - Safety assessments will include adverse events based on the revised NCI Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0).
   - Adverse events of special interest include post-operative complications such as significant bleeding which requires operative intervention, infection, delayed wound healing and fistula formation.

7. To identify correlative tissue and blood biomarker determinants of lenvatinib response in pre- and post-neoadjuvant lenvatinib tissue and blood samples. (exploratory)
   - Genomic alterations
   - Gene expression signatures
   - Tissue immune, vascular, and lymphangiogenic factors
   - Circulating blood cytokines and angiogenic factors

2. BACKGROUND

2.1 Study Disease

Surgery represents the mainstay of initial treatment of DTC both in terms of optimizing survival and in preventing consequences of uncontrolled locoregional tumor in the neck\(^1\). Invasive locoregional DTC occurs commonly in 13 to 15 % of patients presenting with DTC\(^2\) and can typically be identified preoperatively by historical (i.e. hemoptysis, voice change), clinical (i.e. mass fixation, vocal cord paralysis), and radiographic parameters (i.e. radiographic evidence of extrathyroidal spread)\(^2-5\). The resection of extrathyroidal, invasive DTC involves resection of extrathyroidal tissues (soft tissue, muscle, nerve, vascular structures, and visceral structures including larynx, trachea and esophagus) and increases surgical complexity, requiring advanced surgical skill sets, increasing surgical morbidity and adversely affecting patients’ quality of life\(^6\). Radiographic criteria used for neoadjuvant therapy for pancreatic cancer surgery are
endorsed by the National Comprehensive Cancer Network for use in all future clinical trials on borderline resectable pancreatic cancer\(^7\). A neoadjuvant approach to improve surgical outcomes in locally advanced DTC has not been systematically studied but warrants investigation.

There is limited information on the rate of R0 resection in patients with advanced thyroid cancer who undergo surgery without preoperative neoadjuvant chemotherapy. Ibrahimpasic et al. reported Memorial’s experience 27 patients with advanced poorly differentiated thyroid cancer, all with gross extrathyroidal extension. Of these, 22% had preoperative radiation but none had preoperative chemotherapy. The R0 resection rate was 7% and the R1/R2 resection rate was 89%, with margin status unknown in 4%\(^8\). In an older study by McCaffrey et al. in patients presenting with locally advanced papillary thyroid cancer without preoperative adjuvant therapy, tumor margins status was not specifically reported but clearance of gross disease was successful in only 56%\(^9\). Very limited experience exists with cytotoxic neoadjuvant regimens in thyroid carcinoma. Besic et al. treated 13 patients with poorly differentiated thyroid cancer with a mean tumor diameter of 9 cm, and 61% having T4 tumors. Cytotoxic neoadjuvant treatment was combined with external beam radiation in 15%. Some degree of tumor regression was seen in all patients, and 38% treated experienced >30% decrease in tumor diameter. Pathologic R0 resection was possible in 38% and R1 resection in 61%\(^{10}\). The same group treated 29 patients presenting advanced T3 or T4 follicular and Hürthle cell cancers with a mean tumor size of 7.3 cm with neoadjuvant vinblastine. 13% were also treated with external beam radiation. Tumor size reduced by >50% in 45% of patients. R0 resections were achieved in 51% and R1 in 34%, with long term local control obtained in 97%\(^{11}\). The same cytotoxic regimen with or without radiation was investigated preoperatively in 16 patients with locally advanced papillary thyroid cancer, 43% of whom had T4 tumors, and mean tumor size was 9.6 cm. Tumor reduction of >50% occurred in 44% of patients, with an R0 resection rate of 12%, and R1 resection in 62%\(^{12}\).

There is no experience with neoadjuvant tyrosine kinase inhibitor (TKI) therapy for DTC. Recently Patel et al. found with preoperative treatment with sunitinib for four weeks, two weeks off prior to cytoreductive nephrectomy in 21 patients with renal cell carcinoma the same rate overall of complications (48 versus 33%) but a higher rate of high-grade complications (28 versus 0%) in the neoadjuvant treated group. Age was an independent predictor of perioperative complications\(^{13}\). Harshman et al. in 14 renal cell carcinoma patients treated with TKI for 17 weeks with two weeks off prior to cytoreductive nephrectomy found no difference in overall perioperative complications (50 versus 40%) or perioperative bleeding (36 versus 34%) but an increased rate of surgical field adhesions (86 versus 58%)\(^{14}\).

### 2.2 Study Agent

Lenvatinib 4-[3-Chloro-4-(N’-cyclopropylureido)phenoxy]- 7-methoxyquinoline- 6-carboxamide methanesulfonate (lenvatinib mesilate) is an oral, potent multiple receptor tyrosine kinase (RTK) inhibitor that selectively inhibits vascular endothelial growth factor (VEGF) receptors, VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other pro-angiogenic and oncogenic pathway-related RTKs including fibroblast growth factor (FGF) receptor FGFR1-4, platelet-derived growth factor (PDGF) receptor PDGFR\(\alpha\), KIT, and RET.
Nonclinical studies revealed lenvatinib is a potent antiangiogenesis agent with antitumor activity versus various human cancer xenograft models in athymic mice. A global Phase 1/1b program, in subjects with solid tumors, has been conducted to explore the safety, tolerability, pharmacokinetics (PK), pharmacodynamic biomarkers, and antitumor efficacy of lenvatinib at a wide range of dose levels and with four different dosing schedules: once a day (QD) continuous dosing in Study E7080-E044-101, twice daily (BID) interrupted dosing (Schedule 1 [abandoned before reaching a maximum tolerated dose {MTD}]), BID continuous dosing (Schedule 2), and QD dosing (Schedule 3, melanoma combination cohort) in Study E7080-A001-102, and BID interrupted dosing in Study E7080-J081-103. Modeling of PK data in Studies E7080-E044-101 and E7080-A001-102 demonstrated that progression-free survival (PFS) and response (partial response [PR] and durable stable disease [SD]) significantly increased with higher lenvatinib exposure (based on Cmax and AUC(0-24,ss)).

The MTD from Study E7080-E044-101 (25 mg QD) was correlated with higher drug exposure compared with the MTD from Study E7080-A001-102 (10 mg BID). Consequently, 25mg QD was selected for the future studies, as it was determined to be the safest dose that provides the highest efficacy. A Phase 1b study was performed to investigate the tolerability and safety of lenvatinib up to 24mg, orally, QD on a continuous dose schedule in Japanese subjects with solid tumors that are resistant to standard therapies, or for which no appropriate treatment is available. The 24-mg dose of lenvatinib was determined to be tolerable when administered orally on a once daily continuous dose schedule in Japanese subjects with solid tumor. The adverse events observed are consistent with the VEGF targeted therapy profile and are manageable with dose reductions and interruptions.

2.3 Rationale

In the Phase 3 study E7080-G000-303 (Study 303) in subjects with radioiodine-refractory DTC, lenvatinib treatment demonstrated a statistically significant and clinically meaningful benefit as measured by PFS. Based on Independent Imaging Review (IIR) assessments, lenvatinib prolonged median PFS by 14.7 months compared with placebo (18.3 months vs 3.6 months, respectively). The difference in PFS between the lenvatinib and placebo arms was highly statistically significant (P<0.0001) using both stratified and unstratified log-rank rest. The hazard ratio estimated from the stratified Cox proportional hazard model was 0.21 (99% confidence interval [CI]: 0.14, 0.31) in favor of lenvatinib.

Lenvatinib treatment also resulted in a highly statistically significant effect on response rate (complete response [CR] + partial response [PR]) compared with placebo (64.8% vs 1.5%; P<0.0001). Four subjects in the lenvatinib arm had a complete response, an atypical finding for an antiangiogenic agent. The objective response rate (ORR) of the lenvatinib-treated subjects at 6 months was 57.5% (n=150). Thus, at 6 months, approximately 89% of the subjects who ultimately responded had already achieved a response.\(^{(15,16)}\)

The robust activity of lenvatinib in DTC suggests that neoadjuvant treatment in patients presenting with extrathyroidal locally invasive DTC may facilitate optimal surgical therapy and allow for more oncologically secure surgical margins and perhaps even less aggressive and less morbid initial surgical management. Such improved initial combined medical-surgical
therapeutic efficacy could also decrease rates of locoregional recurrence and potentially, in turn, affect long-term survival in patients presenting with extrathyroidal invasive DTC. In the landmark SELECT trial investigating lenvatinib in advanced DTC, the greatest degree of tumor shrinkage occurred in the first 2 cycles therapy, however ongoing tumor shrinkage was demonstrated beyond the first 2 cycles in most patients. Thus, in order to allow for optimal surgical timing balancing tumor shrinkage over time with soonest date of surgery, participants in this trial may receive up to 6 cycles of lenvatinib before the definitive surgery. If staged surgery is planned and approved by the study PI, then approximately 1 month of lenvatinib may be administered between the initial and the 2nd surgery.

Current systemic therapies for DTC are effective in subgroup of patients and are associated with significant toxicities. Selecting the patients who are most likely to benefit from the treatment is warranted to maximize the treatment efficacy and avoid unnecessary toxicities. Several biomarkers have been suggested as predictive markers for TKIs in thyroid cancer. Germline single-nucleotide polymorphisms (SNPs) of the VEGF-A and VEGFR-2 genes and circulating angiogenic factor have shown correlation with response to sorafenib and lenvatinib treatment, respectively. Yet these markers have not been validated in a prospective manner. Recently, the International Thyroid Oncology Group has recommended that correlative studies should be intrinsic to the design of thyroid cancer clinical trials to offer the best opportunity to advance treatment for patients with advanced and progressive thyroid cancer. In this study, correlative assessments of various tissue- and blood-based angiogenic and immune-related factors will be made in an attempt to identify novel predictive biomarkers.

Given the neoadjuvant setting of this trial, we will explore additional secondary outcomes including change in the MMM surgical morbidity complexity score. We hypothesize that reduction in the MMM score will allow for surgical resection of previously unresectable disease and will decrease the morbidity of surgery. Another outcome includes evaluation for the return of laryngeal function by laryngoscopic examination in patients with laryngeal dysfunction at baseline after receiving neoadjuvant lenvatinib. The Recurrent laryngeal nerve (RLN) is a common site of invasion in patients presenting with bulky thyroid cancer and may be associated with loss of laryngeal function. Return of laryngeal function may be an indicator of reduced disease morbidity and will significantly impact the surgical strategy of managing the disease.

3. PARTICIPANT SELECTION

Participants must meet all the following criteria to be included in this study. Screening assessments must be completed within 28 days of study registration unless otherwise noted.

3.1 Eligibility Criteria

3.1.1 ≥ 18 years of age at the time of informed consent and willing and able to provide written informed consent for the trial.
3.1.2 Adult participants who are either initially diagnosed with locally advanced thyroid neoplasm or have experienced persistent or recurrent thyroid and/or cervical nodal recurrent DTC (participants with M1 disease are allowed, AJCC 8th edition stage I-IVb)), including:

a. Papillary thyroid carcinoma (PTC) - classical and variants
   - Follicular variant
   - Variants including but not limited to tall cell, columnar cell, cribriform-morular, solid, oxyphil, Warthin’s-like, trabecular, tumor with nodular fasciitis-like stroma, Hürthle cell variant of papillary carcinoma
b. Follicular thyroid carcinoma (FTC)
c. Hürthle cell carcinoma
d. Poorly differentiated thyroid carcinoma
e. Cytologically confirmed thyroid neoplasm, Bethesda 3, 4 and 5

3.1.3 Evidence of extrathyroidal extension and/or locally invasive disease and deemed at risk for R2 resection by treating team on clinical and/or fiberoptic examination and/or radiographic evaluation in the primary or recurrent setting. Evidence of “at risk for R2 resection” includes:

a. Vocal cord paralysis by laryngoscopic examination
b. Extrathyroid and/or extranodal extension on CT or MRI, including tracheal and/or laryngeal cartilage invasion, esophageal involvement, and/or involvement of perithyroid muscles (e.g. strap, sternocleidomastoid, inferior constrictor muscles) or bone involvement.
c. Extension into the mediastinum with visceral and/or vascular involvement
d. Involvement of the carotid artery or other major vessel by 180 degrees or more (exclusive of complete encasement)
e. Other factors that make the participant to be “at risk for R2 resection” may be allowed, after discussion with the study’s principal investigator.

3.1.4 Measurable disease by RECIST v1.1.

3.1.5 Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1 and no medical contraindication to surgery.

3.1.6 Adequately controlled blood pressure.
   - Blood pressure ≤150/90 with or without antihypertensive medications at screening

3.1.7 Adequate end-organ function (including bone marrow, coagulation, renal, liver and cardiac) 28 days prior to the study registration as defined below:

   - leukocytes ≥3,000/mcL
   - absolute neutrophil count ≥1,500/mcL
   - platelets ≥100,000/mcL
   - total bilirubin ≤1.5 x institutional upper limit of normal, unless attributed to Gilberts syndrome
   - AST/ALT/Alk Phos ≤3 x institutional upper limit of normal
- INR $\leq 1.5 \times$ institutional upper limit of normal
- creatinine within normal institutional limits
  OR
- creatinine clearance $\geq 30 \text{ mL/min per Cockcroft-Gault formulation.}$

* The cycle 1 day 1 labs need to re-meet eligibility criteria for treatment.

3.1.8 Ability to swallow pills.

3.1.9 Females must not be lactating or pregnant at baseline (as documented by a negative beta-human chorionic gonadotropin [ß-hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

3.1.10 **Note:** All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group and without other known or suspected cause) or have been sterilized surgically (i.e., bilateral tubal ligation, total hysterectomy or bilateral oophorectomy, all with surgery at least 1 month before dosing).

3.1.11 Females of childbearing potential must not have had unprotected sexual intercourse within 30 days before study entry and must agree to use a highly effective method of contraception (e.g., total abstinence, an intrauterine device, a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 30 days after study drug discontinuation. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and must continue to use the same contraceptive during the study and for 30 days after.

### 3.2 Exclusion Criteria

3.2.1 Diagnosis of medullary thyroid carcinoma or anaplastic (undifferentiated) thyroid carcinoma.

3.2.2 Radiographically identified following findings:
   - intraluminal airway tumor
   - complete carotid encasement/infiltration

3.2.3 Active hemoptysis (bright red blood $\geq 1/2$ teaspoon) or other uncontrolled bleeding within 21 days prior to the study registration.

3.2.4 Arterial/venous thromboembolic events in the last 12 months
3.2.5 Treatment within 30 days prior to study registration with anticoagulant or antiplatelet therapy, apart from aspirin 81 mg daily.

3.2.6 Prior radiotherapy to the neck.

3.2.7 Prior treatment with lenvatinib or other VEGFR-directed therapy, including sorafenib.

3.2.8 Known metastasis to central nervous system.

3.2.9 Females who are pregnant or breastfeeding.

3.2.10 If > 1 + proteinuria on urine dipstick testing will undergo 24-hour urine collection for quantitative assessment of proteinuria. Participants with urine protein ≥1g/24 h will be ineligible.

3.2.11 Gastrointestinal malabsorption or any other condition that in the opinion of the investigator might affect the absorption of study drug.

3.2.12 Active infection requiring treatment.

3.2.13 Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction, or stroke within 6 months of the first dose of study drug, or cardiac arrhythmia requiring medical treatment.

3.2.14 Prolongation of corrected QT interval (QTc) to > 480 ms as demonstrated by a repeated ECG or any clinically significant ECG abnormality.

3.2.15 History of allergic reactions attributed to compounds of similar chemical or biologic composition to lenvatinib.

3.2.16 Any medical or other condition that in the opinion of the investigators would preclude participant’s participation in a clinical study.

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or
intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at Massachusetts General Hospital by the Coordinating Center. Registrations must occur prior to the initiation of protocol therapy.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.4 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the participating site and forwarded to the Coordinating Center:

- Copy of source documentation for inclusion/exclusion criteria and screening procedures, including but not limited to
  - Pathology report
  - Radiology reports
  - Medical history and physical exam
  - Laboratory reports
  - Concomitant medication list
- Demographics information
- Signed study consent form
- Study Entry Note
- HIPAA authorization form, if applicable
- Eligibility checklist

The Coordinating Center will review the above documentation to confirm eligibility and consent. To complete the registration process, the Coordinating Center will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled Subject Protocol Registration (SOP #:
REGIST-101) and register the participant on the protocol. Once registered, a confirmation email with the participant study number, and if applicable the dose treatment level, will be sent to the participating site.

**Note:** Registrations can only be conducted by the Coordinating Center during the business hours of 8:30 AM and 5:00 PM Eastern Standard Time (or Eastern Daylight Time when applicable), Monday through Friday. A complete registration packet, including all documents listed above, must be received at least 1 business day prior to the anticipated registration to ensure adequate review. Same day treatment registrations will only be accepted with prior notice and discussion with the Coordinating Center.

**Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.**

5. **TREATMENT PLAN**

5.1 **Treatment Regimen**

Lenvatinib will be administered at a starting dose of 24 mg per day with 28 consecutive days defined as a treatment cycle. Lenvatinib will be administered in the form of two 10-mg capsules and one 4-mg capsule.

The study drug cannot be crushed or chewed. If the participant cannot swallow the study drug whole, the study drug can be dissolved in water

- Use a medicine cup to measure about one tablespoon of water or apple juice and place into a small glass.
- Place the lenvatinib capsules into the small glass without breaking or crushing them.
- Leave the capsules in the liquid for at least 10 minutes.
- Stir the contents of the glass for at least 3 minutes.
- Drink the mixture. After drinking, rinse the glass with a small amount of additional water or apple juice and swallow the liquid.

Study drug is to be taken at approximately the same time each morning and may be taken in a fasting state or following a meal. There is no prohibited food with the study drug.

If a dose is missed and cannot be taken within 12 hours, skip that dose and take the next dose at the usual time of administration.

If a participant vomits after taking the daily dose of the study drug, DO NOT repeat dosing and resume regular dosing the next day.

The participant will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each cycle.

Patients will receive either 2, 4, or 6 cycles of lenvatinib with comprehensive preoperative
evaluation before and after lenvatinib. Participants will be assessed for surgical resectability in
the last week of cycle 2, 4 or 6, as applies. If response to treatment after completion of cycle 2, 4
or 6 is deemed by the treating team to be adequate to achieve an R0 resection (clear surgical
margins) or R1 resection (microscopically positive surgical margins), lenvatinib will be stopped
and the participant should proceed to surgery within 7-14 days from the last dose of lenvatinib.

**R classification**
R0 - no cancer cells seen microscopically at the resection margin
R1 - cancer cells present microscopically at the resection margin (microscopic positive margin)
R2 – gross examination by the naked eye shows tumor tissue present at the resection margin
(macroscopic positive margin)

Margin status/R classification criteria is incorporated into standard pathologic reporting. Margin
status/R classification criteria will be determined as per standard pathologic evaluation locally.

If the treating team deems there has not been a response after cycle 2 sufficient to achieve an R0
or R1 resection, and the participant is tolerating treatment (absence of treatment-related adverse
events of grade ≥ 3 per CTCAE v5.0), additional 2 – 4 cycles of lenvatinib will be administered.
If response to treatment after completion of cycle 4 or 6 is deemed by the treating team to be
adequate to achieve an R0 or R1 resection, lenvatinib will be stopped and the participant should
proceed to surgery within 7-14 days from the last dose of lenvatinib. If staged surgery is planned
and was approved by the study PI, then an approximate 1 month of lenvatinib may be
administered between the initial and the 2nd surgery.

If the patient declines further lenvatinib therapy at any point in the trial and wants surgery they
may elect to come off protocol and receive standard of care therapy, which may include surgery,
radiation or other systemic therapy.

Every effort will be made to schedule surgery within the timeline stated above, but if surgery
cannot be scheduled within 7-14 days of the end of the treatment cycle due to unavoidable
reasons, additional bridging therapy will be given to minimize the treatment break, up to an extra
week of study drug to address unavoidable scheduling alterations.

### 5.1.2 Surgical Approach

The surgery represents standard anterior neck approach to the neck base of thyroidectomy and
appropriate nodal resection, most typically a central and or lateral neck dissection. The recurrent
laryngeal nerve and parathyroids are to be preserved. Recurrent laryngeal nerve and associated
viscera are resected in a fashion dictated by their involvement by tumor and reconstructed as per
standard of care. Nerve and visceral resection will be obviated in proportion to lenvatinib’s
effectiveness in tumor reduction.

Given the complexity of the disease, its bilaterality and the cumulative nature of surgical
complications especially when bilateral, including both neural and vascular structures, pre-
planned staged surgery may be an alternative approach for post-neoadjuvant surgery.
If the treating surgeons deems that staged surgery is the best surgical approach, the case should be discussed with the study PI, and if approved by the PI, then hold lenvatinib for 7 – 14 days before the initial surgery, and for at least 2 weeks after initial surgery and until adequate wound healing is achieved. Patients may resume lenvatinib for approximately 1 month between the initial and 2nd part of the staged surgery. The patient should hold lenvatinib for 7 – 14 days before the 2nd part of the staged surgery.

Lenvatinib may increase the risk of surgery. This includes perioperative hemorrhage, wound infection and/or dehiscence. Perioperative complications should be managed according to current surgical standard of care, and will be graded according to CTCAE v5.0. See Section 7 for adverse events reporting requirements.

### 5.2 General Concomitant Medication

Based on a population PK analysis, CYP3A4 inhibitors and inducers were found to have statistically significant but small effects on the apparent clearance (CL/F) of lenvatinib (CPMS-E7080-007R-v1). CYP3A4 substrates known to have a narrow therapeutic index (eg, astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution in subjects receiving lenvatinib. The population PK analysis also indicated that agents that raise gastric pH (eg, H2-blockers, proton pump inhibitors, antacids) do not have a significant effect on the absorption and bioavailability of lenvatinib (CPMS-E7080-007R-v1).

### 5.3 Criteria for Taking a Participant Off Protocol Therapy

Surgery should be performed within 7-14 days after the last dose of lenvatinib. A longer delay may be approved by the study PI. The following stopping rule will be used to monitor delays over what is expected to primary surgery due to excessive neoadjuvant treatment related toxicity: if 3 or more of the first 10 patients who begin neoadjuvant protocol treatment experience treatment related toxicities which cause delays in primary surgery over 4 weeks, accrual to the trial will be suspended to further evaluate the events and decisions made with regard to the overall status of the trial. If the true delay in surgery rate due to toxicity is 10% then the probability of suspending accrual is 7%; if the true rate is 20%, then the probability of suspending accrual is 32.2%; if the true delay in surgery rate due to toxicity is 30% then the probability of suspending accrual is 62%. Adverse events will be continuously monitored throughout the trial by the study team with decisions made accordingly regarding the study status and patient entry throughout the duration of the trial.

Any adverse event(s) attributed to protocol treatment which results in a delay in the planned date of primary surgery exceeding 4 weeks warrants removal of the patient from the study protocol treatment.

In addition to stopping neoadjuvant protocol therapy for delays to time of primary surgery, a participant would be taken off neoadjuvant protocol therapy for:

- Disease progression or recurrence
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition rendering the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment/Off-Study information will be updated in OnCore. The DF/HCC research team will update the relevant Off Treatment/Off Study information in OnCore. The Coordinating Center will update this information for external site participants.

5.4 Duration of Follow Up

Participants who begin neoadjuvant protocol therapy will be followed at 2 and 6 weeks after surgery or removal from protocol therapy for adverse event assessment and survival status, then 6- and 12-months post-surgery by phone for adverse event assessment, additional thyroid cancer treatment (e.g. RAI), and survival status. Participants will have ongoing therapies with standard of care by their treating team, as clinically indicated. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.5 Criteria for Taking a Participant Off Study

Participants will be removed from the study when any of the following criteria apply:
- Completed required follow-up
- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). The DF/HCC research team will update the relevant Off Treatment/Off Study information in the CTMS, OnCore in accordance with DF/HCC policy REGIST-101. The Coordinating Center will update this information for external site participants.

6. DOSING DELAYS/DOSE MODIFICATIONS AND MANAGEMENT OF ADVERSE EVENTS
6.1   Dose delays and modification guideline

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the CTCAE v5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE v5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Dose reduction and interruptions for subjects who experience toxicity will be made according to the guidelines provided in Table below. Dose reductions will occur in succession based on the previous dose level. Any dose reduction beyond 3 levels must be discussed with the sponsor. Once the dose has been reduced, it may not be increased at a later date.

<table>
<thead>
<tr>
<th>Study Treatment Dose Reduction and Interruption Instructions</th>
<th>Management</th>
<th>Dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1 or Tolerable Grade 2</strong></td>
<td>Continue treatment</td>
<td>No change. Continue dose level 24 mg QD Two 10 mg capsules plus 4 mg capsule</td>
</tr>
<tr>
<td><strong>Intolerable Grade 2,\textsuperscript{a,d} or Grade 3</strong></td>
<td>Interrupt\textsuperscript{f} until resolved to Grade 0-1 or baseline</td>
<td>Reduce dose level to 20 mg QD Two 10 mg capsules</td>
</tr>
<tr>
<td>First occurrence</td>
<td>Interrupt\textsuperscript{f} until resolved to Grade 0-1 or baseline</td>
<td>Reduce dose level to 14 mg QD One 10 mg capsule plus one 4 mg capsule</td>
</tr>
<tr>
<td>Second occurrence (same toxicity or new toxicity)</td>
<td>Interrupt\textsuperscript{f} until resolved to Grade 0-1 or baseline</td>
<td>Reduce dose level to 10 mg QD One 10 mg capsule</td>
</tr>
<tr>
<td>Third occurrence (same toxicity or new toxicity)</td>
<td>Interrupt\textsuperscript{f} until resolved to Grade 0-1 or baseline</td>
<td>Reduce dose level to 10 mg QD One 10 mg capsule</td>
</tr>
<tr>
<td><strong>Grade 4,\textsuperscript{e}</strong>: Discontinue Study Treatment</td>
<td>Interrupt\textsuperscript{f} until resolved to Grade 0-1 or baseline</td>
<td>Reduce dose level to 10 mg QD One 10 mg capsule</td>
</tr>
</tbody>
</table>

a: A delay of study treatment for more than 28 days (due to treatment-related toxicities) will require a discussion with the PI before treatment can be resumed.
b: Initiate optimal medical management for nausea, vomiting, and/or diarrhea prior to any study treatment, interruption, or dose reduction.
c: Applicable only to Grade 2 toxicities judged by the subject and/or physician to be intolerable.
d: Obese subjects with weight loss do not need to return to baseline weight or Grade 1 weight loss to restart lenvatinib. There should be no weight loss for at least 1 week, and subjects should be started at the lower dose. Normal body mass index should be used for future dose reductions.
e: Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.
f: Doses missed will not be made up

6.2   Management of Hypertension

The following guidelines should be followed for the management of systolic BP $\geq 160$ mmHg or diastolic BP $\geq 100$ mmHg confirmed on repeat measurements after one hour:

- Continue study drug and institute antihypertensive therapy for subjects not already receiving this.
- For those subjects already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or one or more agents of a different class of antihypertensive should be added.

- If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg persists despite maximal antihypertensive therapy, then study drug administration should be interrupted and restarted at one dose level reduction only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.

  - If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs on the first dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then study drug administration should be interrupted and restarted at an additional dose reduction only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.

  - If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs on the second dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then study drug administration should be interrupted and restarted at a third dose reduction dose only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.

  - Additional dose reduction should be discussed with the Principal Investigator.

The following guidelines should be followed for the management of Grade 4 hypertension (life-threatening consequences):

- Institute appropriate medical management

- Discontinue study drug

6.3 Management of Proteinuria

Regular assessment of proteinuria should be conducted as detailed in the Schedule of Procedures/Assessments. Guidelines for assessment and management of proteinuria:

- Initial episode of proteinuria: if proteinuria ≥2+ is detected on urine dipstick testing, study drug will be continued and a 24-hour urine collection for total protein will be obtained as soon as possible within 1 week to verify the grade of proteinuria. Grading according to the CTCAE v5.0 will be based on the 24-hour urinary protein result. Management of study drug administration will be based on the grade of proteinuria according to the “Study Treatment Dose Reduction and Interruption Instructions.”
- Urine dipstick testing for subjects with proteinuria ≥2+ should be performed every 2 weeks (or more frequently as clinically indicated) until the results have been 1+ or negative for 3 consecutive months. Any subsequent increases in the level of proteinuria ≥2+ on urine dipstick testing must be confirmed with a 24-hour urinary protein test which will be assessed and graded according to the Study Treatment Dose Reduction and Interruption Instructions. If a new event of proteinuria ≥2+ occurs, the subject must resume urine dipstick testing for evaluation of proteinuria until results are 1+ or negative for 3 consecutive months.

6.4 Management of Hepatotoxicity

Liver function tests (ALT, AST, bilirubin levels) should be monitored at baseline, every 2 weeks for the first 2 months and monthly thereafter, and as clinically indicated. If signs/symptoms indicating liver injury occur, instructions contained in “Study Treatment Dose Reduction and Interruption Instructions” should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs the study drug must be discontinued.

6.5 Management of Thromboembolic Events

Subjects should be advised to pay attention to symptoms suggestive of venous thromboembolic events, which include acute onset of shortness of breath, dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, DVT signs including lower-extremity swelling, and warmth to touch or tenderness. In case any of these symptoms appear, subjects should be instructed to report such symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in “Study Treatment Dose Reduction and Interruption instructions” should be followed. Appropriate supportive care should be provided together with close monitoring. If a subject experiences life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism, the study drug must be discontinued.

6.6 Management of Posterior Reversible Encephalopathy Syndrome/ Reversible Posterior Leukoencephalopathy Syndrome (PRES/RPLS)

In clinical studies with lenvatinib, events of PRES/RPLS were reported in less than 1% of lenvatinib treated subjects. PRES/RPLS is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. MRI is necessary to confirm the diagnosis of PRES/RPLS. Appropriate measures should be taken to control BP. In subjects with signs or symptoms of PRES, dose interruptions, reductions, or discontinuation may be required.

6.7 Management of Hypocalcemia

Serum calcium should be monitored monthly per the Schedule of Procedures and Assessments. Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v5.0, using the following formula:

\[
\text{Corrected calcium (mmol/L)} = \text{measured total Ca (mmol/L)} + 0.02 \times (40 - \text{serum albumin [g/L]})
\]
The formula is not applicable when serum albumin concentration is normal (≥40 \text{g/L}); in such situations, the total (uncorrected) serum calcium should be used.

Hypocalcemia should be treated per institutional guidelines (eg, using, as appropriate, calcium, magnesium, and Vitamin D supplementation) until resolution.

6.8 Management of “Osteonecrosis of the Jaw (ONJ)

ONJ has been reported in patients receiving lenvatinib. Concomitant exposure to other risk factors, such as bisphosphonates, denosumab, dental disease or invasive dental procedures, may increase the risk of ONJ.

Perform an oral examination prior to treatment with lenvatinib and periodically during lenvatinib treatment. Advise patients regarding good oral hygiene practices. Avoid invasive dental procedures, if possible, while on lenvatinib treatment, particularly in patients at higher risk.

Withhold lenvatinib for at least 1 week prior to scheduled dental surgery or invasive dental procedures, if possible. For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ. Withhold lenvatinib if ONJ develops and restart based on clinical judgement of adequate resolution.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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

7.1 Adverse Events

7.1.1 Adverse Events List of lenvatinib

<table>
<thead>
<tr>
<th>Common lenvatinib-emergent adverse events from SELECT trial</th>
<th>Grade 1–2 (%)</th>
<th>Grade 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenvatinib-emergent adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>67.8</td>
<td>41.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>59.4</td>
<td>8.0</td>
</tr>
<tr>
<td>Fatigue/asthenia/malaise</td>
<td>59.0</td>
<td>9.2</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>50.2</td>
<td>5.4</td>
</tr>
<tr>
<td>Decrease weight</td>
<td>46.4</td>
<td>9.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>41.0</td>
<td>2.3</td>
</tr>
<tr>
<td>Lenvatinib-emergent adverse events</td>
<td>Grade 1–2 (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>35.6</td>
<td>4.2</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>31.8</td>
<td>3.4</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>31.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>28.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Headache</td>
<td>27.6</td>
<td>2.7</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>24.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>18.0</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>16.9</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>16.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Constipation</td>
<td>14.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Myalgia</td>
<td>14.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>13.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>11.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>11.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Alopecia</td>
<td>11.1</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>10.0</td>
<td>0</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>10.0</td>
<td>0</td>
</tr>
</tbody>
</table>

Surgical adverse events that may be related to Lenvatinib include hemorrhage, wound infection, wound dehiscence, and/or fistula. Any of the surgical adverse events noted above that are grade 2 or higher will be reported as a serious adverse event (SAE), as detailed below in Section 7.3.2.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade**: The descriptions and grading scales found in the CTCAE v5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE v5.0. A copy of the CTCAE v5.0 can be downloaded from the CTEP web site [http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

- **For expedited reporting purposes only**:
  - AEs for the levatinib should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.

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

### 7.3 Adverse Event Reporting

In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Overall PI and the Coordinating Center.

Investigators **must** report to the Overall PI and Coordinating Center any AE that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

For Multi-Center Trials where a DF/HCC investigator is serving as the Sponsor, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

#### 7.3.1 DF/HCC Adverse Event Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report AEs to their respective IRB according to the local IRB’s policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Coordinating Center within the timeframes detailed in the table below.

<table>
<thead>
<tr>
<th>Attribution</th>
<th>DF/HCC Reportable Adverse Events (AEs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gr. 2 &amp; 3 AE Expected</td>
</tr>
<tr>
<td>Unrelated</td>
<td>Not required</td>
</tr>
<tr>
<td>Unlikely</td>
<td>Not required</td>
</tr>
<tr>
<td>Possible</td>
<td>Not required</td>
</tr>
<tr>
<td>Probable</td>
<td>Not required</td>
</tr>
<tr>
<td>Definite</td>
<td>Not required</td>
</tr>
</tbody>
</table>

* If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.

* For participants enrolled and actively participating in the study or for AEs occurring within 30 days of the last intervention, the AE should be reported within **1 business day** of learning of the event.
Participating investigators must report each adverse event to the Coordinating Center in accordance with these timeframes. In the event that the participating investigator does not become aware of the adverse event immediately (e.g., participant sought treatment elsewhere) or within the reporting timeframes listed in the table above, the participating investigator is to report the event within 1 business day after learning of it and document the time of his or her first awareness of the adverse event.

7.3.2 **Serious Adverse Event Reporting**

A serious adverse event is any adverse event occurring at any dose or during any use of study drug that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is other important medical event

**Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the investigator in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Sponsor for collection purposes.

- A new cancer (that is not a condition of the study);
- Events associated with an overdose.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any participant must be reported within 24 hours to the Coordinating Center if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the study drug, must be reported within 24 hours to the Coordinating Center.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to study drug that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported with 24 hours to the Coordinating Center who will report the SAE to Eisai within one working day.
7.4 Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Coordinating Center, on behalf of the Overall PI, will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA’s criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.5 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

7.6 Routine Adverse Event Reporting

All Adverse Events must be reported in routine study data submissions to the Overall PI on the toxicity case report forms. AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.

8. PHARMACEUTICAL INFORMATION

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

8.1 Lenvatinib

8.1.1 Description

- Test drug code: E7080
- Generic name: lenvatinib
- Chemical name: 4-[3-Chloro-4-(N’-cyclopropylureido)phenoxy]-7-methoxyquinoline6-carboxamide methanesulfonate
- Molecular formula: C21H19ClN4O4•CH3SO3H
- Molecular weight: 522.96
- Structural formula:

![Structural formula of lenvatinib](image)

Based on a population PK analysis, CYP3A4 inhibitors and inducers were found to have statistically significant but small effects on the apparent clearance (CL/F) of lenvatinib (CPMS-
E7080-007R-v1). CYP3A4 substrates known to have a narrow therapeutic index (eg, astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution in subjects receiving lenvatinib. The population PK analysis also indicated that agents that raise gastric pH (eg, H2-blockers, proton pump inhibitors, antacids) do not have a significant effect on the absorption and bioavailability of lenvatinib (CPMS-E7080-007R-v1).

8.1.2 Form

Capsule Therapy Pack, Oral:

- Lenvima 10 MG Daily Dose: 10 mg (30 ea)
- Lenvima 14 MG Daily Dose: 10 mg & 4 mg (60 ea)
- Lenvima 20 MG Daily Dose: 2x10 mg (60 ea)
- Lenvima 24 MG Daily Dose: 2x10 mg & 4 mg (90 ea)

8.1.3 Ordering

The study drug will be provided through Eisai.

8.1.4 Storage and Stability

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator (if regionally required, the head of the medical institution) or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the trial and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

8.1.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

Do not open the capsule. Avoid repeat exposure to contents of the capsule.

8.1.6 Drug supplies and Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator’s Handbook for Procedures for Drug Accountability and Storage.)
Drug accountability will be reviewed during site visits and at the completion of the study.

8.1.7 Destruction and Return

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Do not open the capsule. Avoid repeat exposure to contents of the capsule.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Exploratory biomarker research will be conducted on the pre-, on- and/or post-treatment tumor tissues and blood samples using proteomic, genomic and transcriptional analyses to assess the effects of lenvatinib therapy on vascular and immunologic biomarkers. Samples may be retained up to 10 years. Participating sites are responsible for purchasing all correlative lab supplies and related shipping costs.

Assays may include but are not limited to:

9.1 Research Blood biomarker & DNA studies

Key blood biomarkers to be collected pre-treatment and on treatment (in the last week of the last dose, whether that is cycle 2, 4 or 6) (see Section 10: Study Calendar for specific timing of sample collection):

a. Circulating blood biomarkers to correlate with response (suggested list of potential biomarkers to examine):
   i. VEGF-a, short VEGF-a isoforms, neuropilin-1, IL-8, Ang2, soluble KIT
   ii. PIGF, VEGF-D
   iii. CXCR-4 expressing circulating endothelial cells VEGF-R1
   iv. FGF-23

b. Germline DNA analysis: a lavender top EDTA tube (10 mL) will be collected and used as a germline control for the planned DNA analyses of the tumor tissues.

9.1.1 Collection and handling of specimen(s)

- During the screening period, collect 3 x 10 mL of peripheral venous blood in lavender top tubes (1 tube will be used to confirm the germline DNA, while the remaining 2 tubes will be used to study -mainly but not limited to- circulating blood biomarkers).
- During other timepoints beyond the screening period, collect only 2 x 10 mL of peripheral venous blood in lavender top tubes to study -mainly but not limited to- circulating blood biomarkers.
- Invert the tubes approximately 8-10 times to mix the EDTA and then centrifuge at room temperature for 15 minutes at 2500 x g (or in accordance with the centrifuge manufacturer’s instructions).
- Aliquot approximately 1.0 mL of plasma into each 2.0 mL cryovial (total of 10 cryovials).
- Immediately label and freeze cryovials at −70°C or colder. If −70°C or colder freezer is not available, temporary storage on dry ice or at −20°C prior to shipping is acceptable for up to approximately 48 hours. Labels should include the following information:
  - Study #
  - Participant ID
  - Collection Date
  - Visit time point
- Sites must maintain a current Biospecimen log to track the collection, storage and shipping of all specimens.

9.1.2 Site Performing Correlative Study

All correlative studies will be performed by the Fagin laboratory at Memorial Sloan Kettering Cancer Center (MSKCC).

An inventory list including a complete list of samples with study #, participant ID and sample timepoint must be included with each shipment. Prior to shipping, email the Coordinating Center and the Lab to notify them of a pending shipment and include the inventory list.

These samples will be shipped overnight on dry ice (Monday-Thursday shipping only to avoid samples potentially being delivered over a weekend). An inventory list including a complete list of samples with study #, participant ID and sample timepoint must be included with each shipment. Prior to shipping, email the Coordinating Center and the Lab to notify them of a pending shipment and include the inventory list. All samples must be stored -70°C or colder, or on dry ice for up to 48 prior to time of shipment.

Shipping Address:

Memorial Sloan-Kettering Cancer Center
Attention: Katherine Berman, room: Z-519
408 East 69th Street (between York & First Avenues)
New York, NY 10065

Tel: 646-888-2647 (Fagin Lab Phone)
Cell:646-606-7111 (Gnana Krishnamoorthy)

Contacts:
Katherine Berman: sfogliak@mskcc.org
Gnana Krishnamoorthy: krishnag@mskcc.org
9.2 Tissue biomarker studies

Key tissues biomarkers to be analyzed in baseline and post-lenvatinib tumor samples. Both fixed and frozen tissues will be collected whenever feasible for both MEE/MGH and MSKCC (these biopsies are optional for participants at MDACC).

9.2.1 Fixed tissues
a. Vasculature
   i. Immunofluorescence (IF) microscopy (IFM) with 3D reconstruction and/or immunohistochemistry (IHC) staining for vascular markers, including but not limited to CD31, HIF1alpha, alpha smooth muscle actin (alphaSMA).

b. Immune infiltrate
   i. IF staining for PD-1, FOXP3, CD4 and CD8
   ii. IF staining for CD45, F480
   iii. Multispectral IHC: Multispectral fluorescent IHC protocol to analyze in situ co-expression of multiple immune markers (will be performed at MSKCC or University of Colorado (Dr. Jenna French)).

c. Lymphatics
   i. IF staining for LYVE1

9.2.2 Fresh tissue:
a. FACS
   i. Immune characterization of myeloid and lymphoid cells

9.2.3 Any tissue: DNA/RNA will be extracted from fixed and/or frozen tumor.
a. DNA: Next Generation Sequencing platform (MSK-IMPACT) and/or whole exome analysis.
   i. Germline DNA (from normal tissue or blood collection)
   ii. Tumor DNA: somatic mutations

b. RNA (Q-PCR and RNA Seq)
   i. VEGF-C
   ii. VEGFRs, RTKs
   iii. Immune deconvolution

Lenvatinib does not inhibit the proliferation of most thyroid cancer cell lines directly \(^{(20, 21)}\), but can elicit tumor regressions in xenograft models \(^{(21-24)}\), implicating the tumor microenvironment (TME) as the primary drug target. In those experiments, lenvatinib efficacy correlated to decreased microvessel density (MVD) \(^{(21-24)}\). In this trial, 28 thyroid cancer patients will be enrolled and treated with lenvatinib for 4-6 months, and then taken to surgery. Assuming 3 patients do not go on to undergo surgery at all, 25 will be available for this pre- and post-therapy tissue analysis. Pre-lenvatinib biopsies will be performed, analyzed, and compared to surgically resected tumors (post-lenvatinib specimens). The tumors will be evaluated by immunofluorescence microscopy for CD31+ (marker of endothelial cells) vessels to calculate MVD, which will be quantified as %CD31. Slides will be probed with fluorescent antibodies directed against CD31 and digitally scanned using Pannoramic Flash 250 (3DHistech, Hungary) using Zeiss...
20x/0.8NA objective. Regions of interest will be drawn and exported to tif images using CaseViewer (3DHistech, Hungary), then images will be analyzed using custom made macro written in ImageJ/FIJI. After thresholding each channel with appropriate value, the area of CD31 signal will be measured and normalized to the area of all CD31 signal, allowing calculation of %CD31 observed over the entire tumor area. The percentage change in MVD (%CD31(post)-%CD31(pre) X 100) will be calculated for each patient. The percentage change in MVD will be compared between patients achieving radiologic CR/PR (“responders”) and those with SD or PD (“non-responders”) as best response. We predict greater decreases in MVD among responders compared to non-responders. Change in MVD levels from before to after surgery will be tested for association with response using t-test. Assuming 25 patients on the trial and 63% response rate, if the MVD measurements will be normalized to have mean 0 and standard deviation of 1, we will be able to detect the difference in mean MVD change of 1.5 between responders and non-responders with 94% power and 5% 2-sided type 1 error.

9.2.4 Collection and handling of Specimen(s)

Biospecimens will be collected from all participating sites whenever feasible (except for MDACC where biopsies are optional):
Core biopsy will be obtained prior to lenvatinib therapy (preferably 3-6 cores). Tissue will be divided for formalin fixation and flash freezing in liquid nitrogen. For paraffin embedded samples, fixation will be done per institutional guidelines, and a block provided. If tissue is limited. For flash frozen samples, the biopsy sample will be placed into a cryovial that will immediately be submerged in a liquid nitrogen bath until the tissue is frozen. The Principal Investigator and the Treating Investigator(s) will determine what types of samples will be taken (ie, just frozen or frozen and formalin fixed).

Post-lenvatinib tumor tissue:
Tumor will be obtained from the surgical specimen as the post-lenvatinib sample for analysis. A fixed tissue block of at least 1 cm$^3$ will be collected. At least a 1-2 cm$^3$ frozen sample will also be collected (can be taken from same tissue as in 3b-Ebendorf tubes snap frozen liquid N$_2$).

If the disease is judged unsuitable for surgery by the treating team after completion of 4 to 6 cycles, repeat core biopsies will be performed for biomarker studies whenever feasible.

Additional tests for tissue collected from MSKCC only:
If there are opportunities to obtain fresh tissue for immediate analysis, this will be conducted for flow-cytometry based analyses (only to be performed if feasible and sufficient tissue is available).

Storage and shipping instructions:
Samples should be labeled with the following information:
  o Study #
  o Participant ID
  o Collection Date
o Visit time point

These samples will be shipped overnight on dry ice (Monday-Thursday shipping only to avoid samples potentially being delivered over a weekend). An inventory list including a complete list of samples with study #, participant ID and sample timepoint must be included with each shipment. Prior to shipping, email the Coordinating Center and the Lab to notify them of a pending shipment and include the inventory list. All frozen tumor samples and lavender EDTA tube of blood will be stored at -80°C until time of shipment (packaging to prevent breakage during shipment would be advisable).

Sites must maintain a current Biospecimen log to track the collection, storage and shipping of all specimens.

Prepared samples should be shipped to:

**Shipping Address:**

Memorial Sloan-Kettering Cancer Center  
Attention: Katherine Berman, room: Z-519  
408 East 69th Street (between York & First Avenues)  
New York, NY 10065

**Contacts:**  
Katherine Berman: sfogliak@mskcc.org  
Gnana Krishnamoorthy: krishnag@mskcc.org

**10. STUDY CALENDAR**

Screening evaluations are to be conducted within 4 weeks (28 days) prior to study registration. Procedures done within a week of study registration do not need to be repeated to establish baseline. Scans must be done ≤4 weeks prior to the start of therapy. Laboratory evaluations do not need to be repeated to meet eligibility criteria on cycle 1 day 1 if they were done within 3 days of the first treatment dose. In an event that the participant’s condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. In such situations where the study samples were obtained after registration but the participant becomes ineligible for the study, treatment may proceed at investigators’ discretion. Each treatment cycle in this study is 28 days long.
### Treatment Period (28 days cycles)

<table>
<thead>
<tr>
<th>Trial Period</th>
<th>Screening Period</th>
<th>Treatment Period (28 days cycles)</th>
<th>Post-surgery Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td>D-28 to D-1</td>
<td>D1</td>
<td>D8</td>
</tr>
<tr>
<td>Scheduling Window (Days)</td>
<td>±3</td>
<td>±3</td>
<td>±3</td>
</tr>
<tr>
<td>Informed consent</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staging</td>
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<tr>
<td>Lenvatinib</td>
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<tr>
<td>Physical exam</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ECOG P.S.</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Vital signs</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Height</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>X</td>
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</tr>
<tr>
<td>Serum B-HCG</td>
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</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
<td>Urine analysis</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Coagulation test</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>TSH/free T4</td>
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<td>X</td>
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</tr>
<tr>
<td>ECG</td>
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<tr>
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</tr>
<tr>
<td>CT and MRI</td>
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<td>Laryngoscopic exam</td>
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</tr>
<tr>
<td>Tissue biomarkers</td>
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</tr>
<tr>
<td>MMM score</td>
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<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

- AEs = adverse events, CT = computed tomography, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, MRI = magnetic resonance imaging, P.S. = performance status, Postop = postoperative

**a.** If response to treatment is deemed by the treating team to be adequate to achieve an R0 resection (clear surgical margins) or R1 resection (microscopically positive surgical margins), the participant should proceed to surgery within 7-14 days from the last dose of lenvatinib. If the treating team deems there has NOT been a response sufficient to achieve an R0/R1, additional 2-4 cycles of lenvatinib will be administered followed by surgery within 7-14 days from the last dose of lenvatinib.
b. Surgery is expected to be performed 7-14 days after the last dose of lenvatinib. A longer delay may be approved by the study PI. This surgery is either the definitive surgery or the initial surgery of a staged surgery after receiving the PI approval.

c. Post-surgery follow-up at post-operative D14 (±3 days) and D42 (±3 days) will be done to assess acute surgical complications and survival status.

d. Long-term follow up for survival and long-term toxicity evaluation will be made on D180 (± 14 days) and D360 (± 14 days) by phone.

e. Female participants of childbearing potential.

f. Serum chemistry refers to complete metabolic panel. The cycle 1 day 1 labs need to re-meet eligibility criteria for treatment. Both CBC and chemistry will be handled locally per each participating institution policies.

g. If proteinuria is detected on urine analysis, study drug will be continued and a 24-hour urine collection for total protein will be obtained as soon as possible within 72 hours to verify the grade of proteinuria.

h. The thyroid function test does not need to be resulted prior to study treatment.

i. Both CT scan with contrast and dynamic contrast-enhanced (DCE) MRI scan are recommended for all participants for clinical assessment of response and changes in tissue perfusion. CT scans with contrast should be obtained and used for comparison at the specified time points. MRI scans are optional depending on availability.

j. Scans and laryngoscopic exam will be used in decision making for each subject to either proceed with definitive surgery or receive additional 2 - 4 cycles of lenvatinib.

k. Research blood biomarkers refer to circulating blood biomarkers of response mentioned in section 9.1 of the protocol, samples to be handled as per guidance of section 9 in the protocol.

l. Baseline FNA and core-biopsy (at least 3 cores are required whenever feasible). Biopsies are optional at MDACC.

m. Both fixed and frozen specimen should be prepared. At least 1 fixed and multiple frozen specimen are required whenever feasible. If the disease is judged unsuitable for surgery by the treating team after completion of 4 to 6 cycles, repeat core biopsies will be collected whenever feasible.

n. A blood draw will be collected and used as a germline control for the planned DNA analyses of the tumor tissue (Section 9.1.1 & 9.2.3).

o. In case of staged surgery was planned and was approved by the study PI, then hold lenvatinib for 7 – 14 days before the initial surgery and for at least 2 weeks after initial surgery and until adequate wound healing is achieved. Patients may resume lenvatinib for around 1 month between the initial and 2nd part of the staged surgery. The patient should hold lenvatinib for 7 – 14 days before the 2nd part of the staged surgery.

p. In case of a definitive non-staged surgery, the MMM score will be assessed using surgical notes and pathology reports of the surgery performed. In case of staged surgery, the MMM score will be assessed after the 2nd surgery by combining data of the 2 surgeries.

q. Blood biomarker samples will be drawn once at pre-treatment and once on treatment (on the last week of the last dose, whether that is cycle 2, 4 or 6).
11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect

For the purposes of this study, participants should be re-evaluated for response at the end of cycle 2, cycle 4 and cycle 6 prior to surgery. Response and progression will be evaluated in this study using the RECIST v1.1 [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.
Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

11.1.3 Methods for Evaluation of Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI. CT scans with contrast should be obtained and used for comparison at the specified time points. MRI scans are optional depending on availability. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease.
Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

Anatomical MRI (axial T1-Weighted, T2-Weighted imaging) and DCE- MRI scans will be performed in participants at MGH and MSKCC at baseline and during therapy prior to surgery on the 1.5T or 3T clinical MRI scanners. The anatomical MRI scan will be followed by DCE-MRI with administration of Gadolinium based contrast agent (CA). The slice will be selected that cover sboth the entire tumor and the feeding artery in the same field of view (FOV). T1w DCE images will be acquired using three-dimensional (3D) spoiled gradient-recalled echo (SPGR) sequence. All attempts will be made to use the same MR parameters for data acquisition and avoid geometrical mismatch between anatomical and functional MR images. Before contrast agent administration, precontrast T1w images will be acquired with 3 flip angles (30°, 15°, and 5°). The precontrast T1w acquisition parameters are follows: TR=5.4ms, TE=2.7 s, BW=31.25 kHz, imaging matrix=256×128, NEX=2. Dynamic volume images (40-50 phases) before, during and after CA injection will be acquired with flip angle of =15° at a high temporal resolution (<10 s) with the same parameters as that of precontrast T1w images with NEX =1.

The DCE data will be analyzed using the extended Tofts model (25) which provides the parametric estimates of the volume transfer constant from blood to tissue, $K_{\text{trans}}$ (min$^{-1}$), extracellular volume fraction, $v_e$, and blood plasma volume fraction, $v_p$. $K_{\text{trans}}$ reflects quantitative measure of perfusion/permeability of tumor vessels. DCE data analysis will be central at MSKCC and all data analysis will be performed using an inhouse developed software package, MRI-QAMPER (Quantitative Analysis Multi-Parametric Evaluation Routines) implemented in MATLAB (The MathWorks, Natick, MA, USA).

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later data and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy. The laryngoscopic examination will be performed in all subjects at time points mentioned in the study calendar table (baseline; end of C2, C4 & C6 if applicable) to assess the vocal cord function and to document return of laryngeal function. While the utilization of these techniques for objective tumor evaluation is not advised, return of laryngeal function may be an indicator of reduced disease morbidity and will significantly impact the surgical strategy of managing the disease.

Tumor markers. Tumor markers including thyroglobulin and anti-thyroglobulin antibody alone cannot be used to assess response. If markers are initially above the upper normal limit, they
must normalize for a participant to be considered in complete clinical response.

11.1.4 Response Criteria

11.1.4.1 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 the 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.

11.1.4.2 Evaluation of Non-Target Lesions

**Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

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

**Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

**Progressive Disease (PD):** Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

11.1.4.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor
(for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

<table>
<thead>
<tr>
<th>For Participants with Measurable Disease (i.e., Target Disease)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target Lesions</strong></td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
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<tr>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
</tr>
<tr>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
</tr>
<tr>
<td>Any</td>
</tr>
</tbody>
</table>

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

**Note:** Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration.” Every effort should be made to document the objective progression even after discontinuation of treatment.
For Participants with Non-Measurable Disease (i.e., Non-Target Disease)

<table>
<thead>
<tr>
<th>Non-Target Lesions</th>
<th>New Lesions</th>
<th>Overall Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>Non-CR/non-PD</td>
<td>No</td>
<td>Non-CR/non-PD*</td>
</tr>
<tr>
<td>Not all evaluated</td>
<td>No</td>
<td>not evaluated</td>
</tr>
<tr>
<td>Unequivocal PD</td>
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<tr>
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<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

* ‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

11.1.4.5 Evaluation of Overall Survival

Overall Survival: Overall Survival (OS) is defined as the time from study registration to death due to any cause, and otherwise censored at date last known alive.

11.2 R0/R1 resection rate assessment

Local pathology review at each of the participating centers will determine the R status (clear (R0) or microscopically positive surgical margins (R1)).

If staged surgery is planned, then the cumulative results of the 2 surgeries will be used to assess the R0/R1. This can be done by pooling the surgical notes and the pathology of both surgeries to provide an accurate judgement of R0/R1 resection.

11.3 MGH/MEEI-MSK-MD Anderson (MMM) Surgical Morbidity Complexity Score assessment

The MMM score will be determined by the site PI who is also the investigator who performed the surgery and most fluent with the parameters involved in determination. (See Appendix A)

Each patient on neoadjuvant thyroid cancer clinical trial will have at least 3 MMM scores as follows:
1. At baseline (prior to initiation of neoadjuvant therapy).
2. At the completion of cycle(s) 2, 4, 6, and in the preoperative visit (if possible).
3. After surgery*.

* If staged surgery is planned, then the cumulative results of the 2 surgeries will be used to assess the MMM score. This can be done by pooling the surgical notes and the pathology of both surgeries to provide an accurate judgement of the MMM score.

12. DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1.1 Method

The DF/HCC Office of Data Quality (ODQ) will collect, manage, and audit data for this study. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

12.1.2 Responsibility for Data Submission

Investigative sites are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multi-Center Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix B.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.
13. STATISTICAL CONSIDERATIONS

13.1 Study Design

The proposed study will be a multicenter, phase II, open-label trial of neoadjuvant lenvatinib in patients with locally invasive extrathyroidal differentiated thyroid cancer (DTC).

This is a one arm phase II trial. The primary endpoint is to estimate the proportion of patients who undergo successful thyroidectomy, defined by clear (R0) or microscopically positive surgical margins (R1).

A two-stage design (Simon’s minimax design) will be used to minimize the number of patients enrolled. Twelve eligible patients who start protocol treatment are to be accrued in the first stage. If there are ≤ 3 patients with clear (R0) or microscopically positive surgical margins (R1), accrual to this trial will be closed with the expectation that there is little evidence that the R0/R1 resection rates would reach 50%. The probability that the trial will close early is 49% if the true rate is 30%. If there are ≥4 patients with R0/R1 rates, accrual will continue until a total of 28 eligible patients who start protocol treatment are entered. If there are ≥12 patients with R0/R1 resection rates among 28 eligible patients who began protocol treatment, further testing of this regimen will be considered. If the true rate is 50%, the probability of concluding the regimen is effective is 80%, if the true rate is 30%, the probability of concluding the regimen is effective is 9.5%. Allowing for patients to be declared ineligible or to not start protocol treatment after registration, a total of 30 patients will be entered.

The primary efficacy population includes all eligible patients who begin protocol treatment. The R0/R1 rate will be summarized as a proportion with a corresponding exact 95% confidence interval (CI).

For stopping rule and secondary objectives:

- Surgical margin status (R0/R1 vs R2) in 5 anatomic subsets (1-muscle, 2- RLN, 3-cartilage (larynx/trachea), 4-esophagus, 5-major vessel) and determination if the extrathyroidal invasive target interface posing the R2 risk was resected or not. These will be summarized as frequency (%).

- Change in MMM Surgical Morbidity Complexity Score (see appendix A) and conversion rate from unresectable to resectable disease as determined by the treating team. The change in SMCS will be reported as the median value. The conversion rate will be summarized as frequency (%).

- Response rate via RECIST (just prior to primary surgery) will be summarized as a proportion with a corresponding exact 95% confidence interval (CI) (noting that a ‘modified’ version (no confirmation of initial CR or PR) of RECIST will be used for patients whose disease initially achieves a CR or PR: the patients’ tumor will be resected prior to confirming the CR
or PR at least 4 weeks after initial response).

- Adverse events will be classified and graded according to the CTCAE v.5.0. Frequencies of adverse events will be summarized among patients who begin protocol therapy.

- Surgery (whether definitive or staged) should be performed within 7-14 days after the last dose of lenvatinib. A longer delay may be approved by the study PI. The following stopping rule will be used to monitor delays over what is expected to primary surgery due to excessive neoadjuvant treatment related toxicity: if 3 or more of the first 10 patients who begin neoadjuvant protocol treatment experience treatment related toxicities which cause delays in primary surgery over 4 weeks, accrual to the trial will be suspended to further evaluate the events and decisions made with regard to the overall status of the trial. If the true delay in surgery rate due to toxicity is 10% then the probability of suspending accrual is 7%; if the true rate is 20%, then the probability of suspending accrual is 32.2%; if the true delay in surgery rate due to toxicity is 30% then the probability of suspending accrual is 62%. Adverse events will be continuously monitored throughout the trial by the study team with decisions made accordingly regarding the study status and patient entry throughout the duration of the trial.

• The distributions of time-to-event endpoints will be estimated using the Kaplan-Meier method with corresponding 95% confidence intervals for the median or time-specific event time.

• Several correlative studies are also planned. Given the small sample size of this trial, these studies are exploratory. Samples will be collected at baseline and at post-baseline timepoints as outlined in the Study Calendar. Assuming 25 evaluable patients with baseline and a post-baseline value provides 81% power to detect .61 SD mean difference (Wilcoxon sign rank test two-sided 0.05 alpha level) in any given continuous marker.

With an estimated monthly accrual of 2 patients, the first stage is estimated to complete accrual in approximately 6 months. Due to possible delays in initiation of approval and/or in initiation of accrual itself, accrual to the first stage could take longer. As is customary with this type of design, accrual will be suspended after the first stage (n = 12 eligible patients who begin protocol therapy) in order to assess outcome; however, this suspension is also dependent on the actual observed accrual rate and the number of patients with confirmation of R0/R1 status while the first stage of the trial is accruing.

13.2 PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of
Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.
REFERENCES

APPENDIX A

MGH/MEEI-MSK-MD Anderson (MMM) Surgical Morbidity Complexity Score

The aim of the MMM score is to understand the surgical complexity, potential for complications, expected patient morbidity and/or change of function from the resection. Any alteration in MMM score will be considered meaningful, as it will either allow for surgical resection of a previously unresectable disease or will decrease the morbidity of surgery. Ideally, neoadjuvant therapy can help by reducing the number of structures needed to be surgically resected, surgical complexity, surgical complications in addition to reducing the frequency of loss/change of function associated with organ resection.

Investigators at each participating institutions will assess the MMM score at baseline (hypothetical structures that needs to be resected if the patient underwent surgery at that time point before starting neoadjuvant Lenvatinib); after receiving neoadjuvant therapy but before surgery; and after surgery (actual structures surgically resected after receiving Lenvatinib).

**MMM Score will be assessed by each site investigator (or the treating surgeon) at the following time points:**

1. At baseline (prior to initiation of neoadjuvant therapy).
2. At the completion of cycle(s) 2, 4, 6, and in the preoperative visit (if possible).
3. After surgery*.

* If staged surgery is planned, then the cumulative results of the 2 surgeries will be used to assess the MMM score. This can be done by pooling the surgical notes and the pathology of both surgeries to provide an accurate judgement of the MMM score.

The MMM score is a secondary endpoint of this study.

**MMM Surgical Morbidity Complexity Score**

In order to categorize patients into morbidity/complexity groupings, we have worked collectively with colleagues at Massachusetts Eye & Ear Infirmary/Massachusetts General Hospital, Memorial Sloan Kettering and MD Anderson Cancer Center to develop the “MMM (MGH/MEE-MSK-MDACC) Surgical Morbidity Complexity Score” which will be utilized in multiple neoadjuvant thyroid clinical trials moving forward. The granularity of this scoring system will allow a thorough assessment of surgical morbidity and complexity.

The MMM Score gives a score for each structure judged to be requiring resection, which is associated with surgical complexity, a higher potential for complications, more patient morbidity and a resultant change of function from the resection. The higher the MMM Score, the more likely it is that the participant will have a more complex resection with greater surgical morbidity. Ideally, neoadjuvant therapy can help by reducing the number of structures needed to be surgically resected, hence, lowering the score.
The MMM Surgical Morbidity Complexity Score will be determined using the following criteria:

**Baseline MMM Score**  
*(To be calculated prior to initiation of neoadjuvant Lenvatinib therapy)*

<table>
<thead>
<tr>
<th>Structure(s) expected to be resected</th>
<th>Points</th>
<th>Patient hypothetical score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross muscle, mild: (SCM, strap muscles) *</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Gross muscle, advanced: (limited pharyngeal constrictor muscle and/or esophageal muscularis) *</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Jugular vein</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Unilateral RLN/Vagus #</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>11th, and/or 12th cranial nerve</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Superior mediastinal extension (sternotomy required) and/or subclavian vein involved</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Visceral, mild: limited laryngeal cartilage resection, tracheal resection &lt; 4 cm</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Bilateral RLN and/or vagus nerves # $</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Visceral, advanced: (total laryngectomy, tracheal resection &gt; 4 cm, and/or segmental esophageal (mucosa) resection) **</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Carotid/innominate artery 360-degree encasement, prevertebral fascia involvement, brachial plexus/floor of the neck involvement</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td><strong>Total score</strong></td>
<td>34</td>
<td></td>
</tr>
</tbody>
</table>

Notes:

* Individual gross muscle involvement in this category is not additive, e.g., a patient who has both strap muscle and SCM muscle involvement would receive only one point.

# Recurrent laryngeal nerve involvement includes significant radiographic disease in the tracheoesophageal groove, such that in the opinion of the surgeon and radiologist, the recurrent laryngeal nerve is at significant risk of resection or if there is vocal cord paralysis evident.

$ Bilateral RLN and/or vagus nerves involvement includes RLN at significant risk (e.g., radiographic disease in the tracheoesophageal groove) in the setting of a known contralateral nerve paralysis.

** For patients with advanced visceral involvement, RLN and/or vagus nerves and/or tracheal involvement are not additive, e.g., a patient with laryngeal/cricoid involvement who needs a laryngectomy does not receive additional points for RLN or tracheal involvement.
### On Treatment: MMM Score

*(To be calculated using data of the last week of cycle 2, 4 and 6 before undergoing surgery)*

<table>
<thead>
<tr>
<th>Structure(s) expected to be resected</th>
<th>Points</th>
<th>Patient hypothetical score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross muscle, mild: (SCM, strap muscles) *</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Gross muscle, advanced: (limited pharyngeal constrictor muscle and/or esophageal muscularis) *</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Jugular vein</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Unilateral RLN/Vagus#</td>
<td>2</td>
<td></td>
</tr>
<tr>
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<td></td>
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<tr>
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<td></td>
</tr>
<tr>
<td>Visceral, advanced: (total laryngectomy, tracheal resection &gt; 4 cm, and/or segmental esophageal (mucosa) resection) **</td>
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</tr>
<tr>
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<td></td>
</tr>
<tr>
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<td></td>
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</tbody>
</table>

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** For patients with advanced visceral involvement, RLN and/or vagus nerves and/or tracheal involvement are not additive, e.g., a patient with laryngeal/cricoid involvement who needs a laryngectomy does not receive additional points for RLN or tracheal involvement.
**Postoperative MMM Score**  
*(To be calculated after surgery)*

<table>
<thead>
<tr>
<th>Structure expected to be resected</th>
<th>Points</th>
<th>Patient actual score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross muscle, mild: (SCM, strap muscles)*</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Gross muscle, advanced: (limited pharyngeal constrictor muscle and/or esophageal muscularis)*</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Jugular vein</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Unilateral RLN/Vagus#</td>
<td>2</td>
<td></td>
</tr>
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<td></td>
</tr>
<tr>
<td>Superior mediastinal extension (sternotomy required) and/or subclavian vein involved</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Visceral, mild: limited laryngeal cartilage resection, tracheal resection &lt; 4 cm</td>
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<td></td>
</tr>
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<td></td>
</tr>
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<td>7</td>
<td></td>
</tr>
<tr>
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</tr>
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## APPENDIX B

### PERFORMANCE STATUS CRITERIA

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

Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan

1.0 INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP should serve as a reference for any sites external to DF/HCC that will be participating in the research protocol.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions DF/HCC Multi-Center Protocol:

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children’s Hospital (BCH), Brigham and Women’s Hospital (BWH)) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the Overall Principal Investigator who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies. The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority
and responsibility for the overall conduct of the study.

**Coordinating Center:** The entity that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines. In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

**DF/HCC Office of Data Quality:** A group within DF/HCC responsible for ensuring high quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring.

**DF/HCC Research Informatics for Operations (RIO):** A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

### 2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

#### 2.1 DF/HCC Sponsor

The DF/HCC Sponsor, Gregory Randolph, MD, will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial’s conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with FDA (investigator-held IND trials).
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual...
2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions.
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Review and approve Participating Site informed consent forms
- Conduct and document initial and ongoing protocol training
- Oversee the data collection process from Participating Institutions.
- Maintain documentation and cumulative reports of Serious Adverse Event (SAE) reports and Deviations/Violations across all sites and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out approved protocol monitoring plan either by on-site or remote monitoring.
- Maintain essential regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federal wide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites, and protocol training documentation
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc.) and maintain documentation all relevant communications.

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements. The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their institutional IRB.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related
Submit Serious Adverse Event (SAE) reports to local IRB per institutional requirements and to the Coordinating Center, in accordance with DF/HCC or other sponsor requirements.

Submit protocol deviations and violations to institutional IRB per local requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.

Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.

Have office space, office equipment, and internet access that meet HIPAA standards.

Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.

Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3.0 DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution’s responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions**: Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes**: Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds**: Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.
3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for Investigator-Sponsored Multi-Center Protocols. This document will be provided separately to each Participating Institution.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that for all interventional drug, biologic, or device research, only attending physicians may obtain initial informed consent and any re-consent that requires a full revised consent form.

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution’s IRB.
- Participating Institution’s IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals. The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information.
The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e., Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

All participants must be registered with DF/HCC prior to conducting any research-related procedures

3.7.1 Participant Registration

Please refer to protocol Section 4.0: Registration Procedures

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before receiving treatment. Treatment may not be initiated until the Participating Institution receives confirmation of the participant’s registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.3 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

3.8 DF/HCC Protocol Case Number

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.8.1 Protocol Deviations, Exceptions and Violations
Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms “violation”, “deviation” and “exception” to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.8.2 Definitions

**Protocol Deviation**: Any departure from the defined procedures set forth in the IRB approved protocol which is prospectively approved prior to its implementation.

**Protocol Exception**: Any protocol deviation that relates to the eligibility criteria, e.g., enrollment of a participant who does not meet all inclusion/exclusion criteria.

**Protocol Violation**: Any protocol deviation that was not prospectively approved by the IRB prior to its initiation or implementation.

3.8.3 Reporting Procedures

**DF/HCC Sponsor**: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

**Participating Institutions**: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution’s IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission. The deviation may not be implemented without all required approvals.

All protocol violations must be sent to the Coordinating Center in a timely manner. Participating sites must also maintain a log of all minor violations and submit the log to the Coordinating Center each month. The Coordinating Center will provide training for the requirements for the reporting of violations.

**Coordinating Center**: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for
review. Subsequently, the Participating Institution’s IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

3.9 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated treatment will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 7.3.5: Serious Adverse Event Reporting.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

3.9.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

3.10 Data Management

The DF/HCC RIO develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. The DF/HCC RIO provides a web-based training for eCRF users.

3.10.1 Data Forms Review
Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

4.0   REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol section 8.1.3: Ordering Investigational Product.

Participating Institutions should order their own agent regardless of the supplier.

If the agent is commercially available, check with the local Director of Pharmacy and/or the Research Pharmacy to ensure that the agent is in stock. If the agent is not stocked, ensure that the agent can be ordered once the protocol is approved by the local IRB.

If the agent is investigational, ensure that the pharmacy will be able to receive and store the agent according to state and federal requirements. The local IRB should be kept informed of who will supply the agent (i.e., NCI or a pharmaceutical company) so that any regulatory responsibilities can be met in a timely fashion.

5.0   MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the ODQ provides quality control oversight for the protocol.

5.1   Ongoing Monitoring of Protocol Compliance

All Participating Institution will be monitored and are subject to on-site as well as remote monitoring conducted by the Coordinating Center. Participating Institutions will be required to submit relevant participant source documents to the Coordinating Center for monitoring.

The Coordinating Center will implement ongoing monitoring activities to ensure that
Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring will occur before the clinical phase of the protocol begins, continue during protocol performance and through study completion. Monitoring practices include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study drug administration/treatment, regulatory files, protocol departures, pharmacy records, response assessments, and data management.

All DF/HCC sites and Participating Institutions will undergo on-site monitoring by the Coordinating Center within 4 months of enrollment of the first patient at each site. Combination on-site and remote monitoring will occur every 4-6 months thereafter with at least 1 on-site visit every 12 months while the site is actively accruing and treating patients.

Once all site participants are off treatment and have completed the post-treatment Safety Follow-Up Visit, the follow-up monitoring schedule will be revised to a combination of remote and on-site monitoring conducted every 6 months, with at least one on-site visit every 18 months for confirmation of long term follow-up data. Once all subjects have completed follow-up at a given site, monitoring will be limited to annual, remote review of overall survival data, confirm off-study data entry and to verify regulatory review.

Additional monitoring may be conducted for cause or at the discretion of the Principal Investigator.

For remote monitoring visits, Participating Institutions will be asked to provide remote electronic medical record access to the monitor or will be required to forward de-identified copies of participants’ medical record and source documents to the Coordinating Center to aid in source data verification. The participants and CRFs to be reviewed at the visit will be communicated at least 2 weeks in advance of the scheduled monitoring visit. Source documentation can be provided to the Coordinating Center via an encrypted memory stick or via a secure file transfer system. During remote monitoring visits, the Site Specific File will be reviewed in lieu of the site regulatory binder.

On-Site Monitoring will be scheduled several weeks in advance and will be conducted over a 2-3 day period. During an on-site monitoring visit 2-4 participants will be monitored. Source documentation verification (SDV) will be conducted by having access to participants’ complete medical record and source documents. Participating Institutions will be expected to coordinate the necessary resources for the monitor, including a desk, access to all participant medical and research records (electronic and hard copy), the regulatory binders and access to a photocopier. The Participating Institution will also be asked to assist in scheduling a pharmacy visit and a brief exit interview on the final day of the visit with the Study Coordinator and the Site investigator.

All Participating Institutions will be required to participate in monthly Coordinating Center initiated teleconferences. Once all participants have completed treatment, teleconferences will be scheduled as needed.
5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports for on-site and remote monitoring of Participating Institutions to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations. Participating Institutions may also be subject to an audit as determined by the DF/HCC Sponsor.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. For Phase II studies, sites are expected to accrue at least 3 participants annually, with the exception of rare disease groups. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

6.0 AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. Its main focus is to measure whether standards and procedures were followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 Audit Plan: NCI Sponsored Trials

Not applicable

6.2 Audit Plan: DF/HCC Sponsored Trials

One on-site audit will be scheduled by the ODQ, assuming at least three participants have been treated on protocol at the site. Approximately 3-4 participants would be audited at the site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.3 Audit Notification

It is the Participating Institution’s responsibility to notify the Coordinating Center of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.4 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans if applicable.
The Coordinating Center must forward these reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.5 Participating Institution Performance

The DF/HCC Sponsor and the DFCI IRB is charged with considering the totality of an institution’s performance in considering institutional participation in the protocol.

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site’s participation if it is determined that a site is not fulfilling its responsibilities as described above.