Academic and Community Cancer Research United (ACCRU)

Randomized Double-Blind Phase II Study of Radioactive Iodine (RAI) in Combination with Placebo or Selumetinib for the Treatment of RAI-Avid Recurrent/Metastatic Thyroid Cancers

For any communications regarding this protocol, please contact the protocol resource person on the following page.

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Drug Availability
Drug Company Supplied: Selumetinib (AstraZeneca; IND 074,667)

√ Study contributor(s) not responsible for patient care.

Study Participants	**Date Activated**
ACCRU Membership	May 1, 2015

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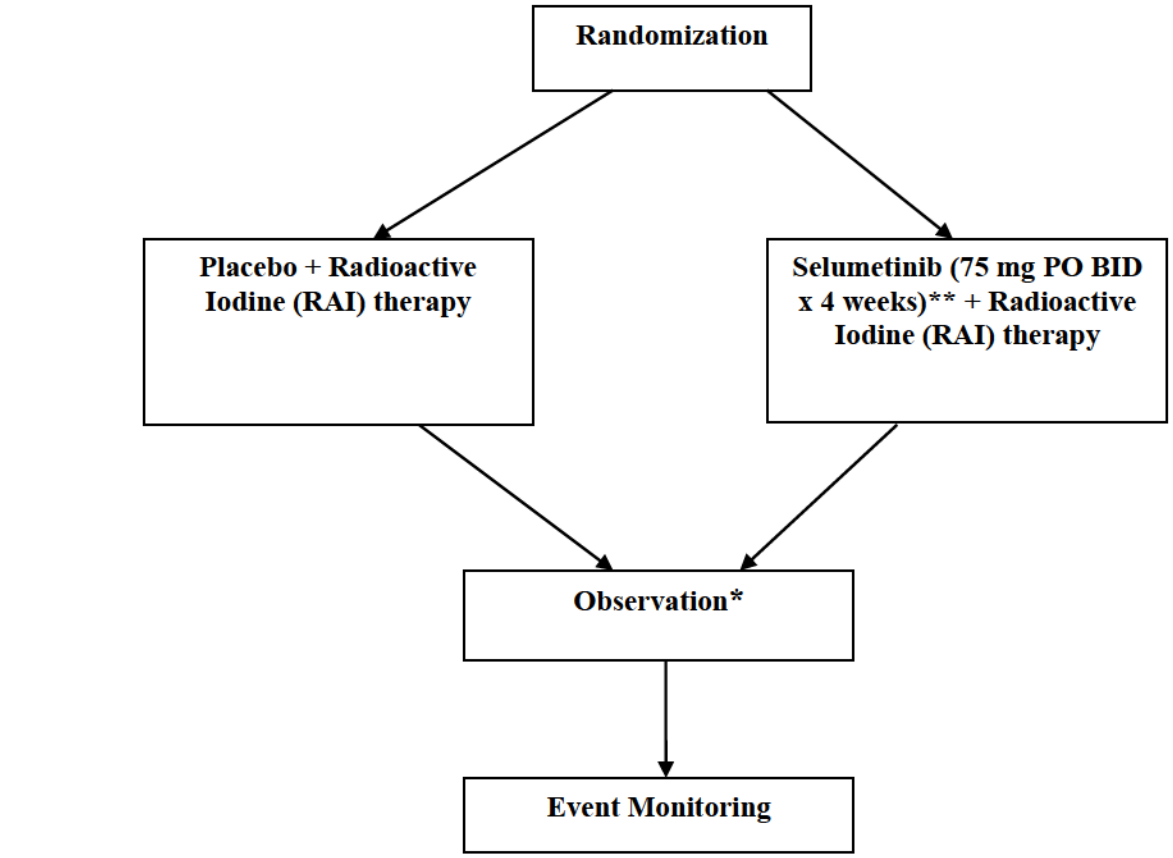
Schema



*Observation time points: 1 and 3 months post-treatment, followed by every 3 months for 12 months post-treatment, followed by every 6 months for a maximum of 2 years from randomization.
**Can be given up to 8 weeks (i.e. the time on treatment including treatment interruptions) (see section 7)

Generic name: Selumetinib Brand name(s): ACCRU Abbreviation: AZD6244 Availability: AstraZeneca	Generic name: Placebo Brand name(s): ACCRU Abbreviation: PLACEB Availability: AstraZeneca

1.0 Background

Utility of ^{131}I therapy for radioiodine-avid thyroid cancers: The majority of thyroid cancers are differentiated carcinomas of follicular origin with papillary thyroid cancer (PTC) being the most common followed by follicular thyroid cancer (FTC) (use of the term "thyroid cancer" in this protocol refers specifically to follicular cell derived thyroid malignancies). Metastatic disease represents the most frequent cause of thyroid cancer-related death (Mazzaferri and Kloos, 2001). Since the ability to transport iodide is retained in thyroid carcinomas of follicular origin and is restricted to only a few cell types, radioactive iodine (RAI or ^{131}I) can be used therapeutically to deliver tumoricidal doses of radiation, eliciting clinical benefit with few side effects and modest long-term toxicity.

^{131}I can be particularly effective for small volume (<1 cm), RAI-avid (RAIA; tumors with detectable RAI uptake) disease with complete remission achieved in reportedly over 50% of patients (Durante et al., 2006). However, ^{131}I efficacy is significantly lower for patients with larger, structurally evident disease. Sabra et al. published a retrospective study evaluating the efficacy of first-line ^{131}I therapy (RAI administered for remnant ablation and evidence of RAIA distant metastasis on post-ablation scan) for patients with metastatic, RAIA thyroid cancer. In 36 patients with structural disease, the response rate of metastatic lesion(s) to initial RAI ablation therapy was 22% (Sabra et al., 2013). This observation is consistent with the 10% to 24% response rates reported in other retrospective series for similar subsets of patients (Durante et al., 2006; Klubo-Gwiezdzinska et al., 2011a; Klubo-Gwiezdzinska et al., 2011b; Tala et al., 2011).

^{131}I efficacy against thyroid metastases is determined by the ^{131}I activity that can be successfully delivered to metastatic lesions (Dorn et al., 2003; Maxon et al., 1992; Maxon et al., 1983; Thomas et al., 1976). Both ^{131}I uptake and retention can be impaired by diminished expression of several thyroid-specific genes, including the sodium iodide symporter (NIS; mediates iodide uptake into thyroid cells) and thyroperoxidase (TPO; critical for iodide retention). Many investigators have searched for drugs to "re-differentiate" metastatic thyroid cancers to restore expression of these genes in an attempt to enhance ^{131}I delivery and efficacy. Unfortunately, such studies have historically reported only modest effects upon ^{131}I action.

Thyroid cancer mutations that activate the MAPK pathway de-differentiate thyroid cancer cells: Mutually exclusive genetic alterations in the growth factor receptor *RET*, the three isoforms of *RAS* (*N, H,* K), and *BRAF* are present in ~70% of PTCs (Cohen et al., 2003; Kimura et al., 2003; Knauf and Fagin, 2009; Soares et al., 2003). These oncoproteins participate in MAPK signaling to activate downstream kinases MEK and ERK (RET->RAS->RAF->MEK->ERK). The $BRAF^{V600E}$ mutation is the most common genetic alteration in PTC (involving about 45% of tumors) (Kimura et al., 2003; Ricarte-Filho et al., 2009). *BRAF* MUT tumors have a more aggressive clinical behavior and are prone to being RAI-refractory (Elisei et al., 2008; Lee et al., 2007). Beyond promoting cellular proliferation and survival, *BRAF* mutations in thyroid cancer have also been implicated in disrupting follicular cell differentiation, including the suppression of key genes involved in iodide metabolism (Durante et al., 2007; Liu et al., 2007; Riesco-Eizaguirre et al., 2006) and iodide uptake, such as *NIS* (Riesco-Eizaguirre et al., 2006). In rat thyroid PCCL3 cells with inducible expression of $BRAF^{V600E}$, treatment with the MEK inhibitor U0126 restored expression of NIS as well as thyroid stimulating hormone (TSH) receptor and thyroglobulin (Liu et al., 2007).

Other MAPK activating alterations common to thyroid cancer can also cause de-differentiation. *RAS* mutations are found in approximately 10-20% of PTCs and 40-50% of FTCs (Nikiforov and Nikiforova, 2011). Recombination events that lead to the fusion of the RET tyrosine kinase receptor with one of several partner genes (known as *RET/PTC* rearrangements) occur in 10-20% of PTCs (Nikiforov and Nikiforova, 2011; Soares et al., 2003; Zhu et al., 2006). Overexpression of either the $HRAS^{V12}$ mutant or *RET/PTC* in thyroid cancer cells suppresses *NIS* expression, which can be restored with MEK inhibitor

treatment (De Vita et al., 2005; Knauf et al., 2003). Hence, genetic alterations that account for MAPK activation in of the vast majority of thyroid cancers can promote MEK-dependent *NIS* suppression, diminished iodide avidity, and resistance to ^{131}I therapy.

MAPK pathway inhibition can restore iodide incorporation in an in vivo thyroid cancer animal model: In a thyroid cancer mouse model with doxycycline (dox) inducible thyroid expression of $BRAF^{V600E}$, Dr. James Fagin's group (Memorial Sloan-Kettering Cancer Center (MSKCC)) demonstrated that dox treatment resulted in $BRAF^{V600E}$ overexpression, MAPK activation, development of PTC, and suppression of several thyroid specific genes, including *NIS* (Chakravarty et al., 2011). Withdrawal of dox to eliminate $BRAF^{V600E}$ expression resulted in suppression of MAPK activation and re-induction of thyroid gene expression, suggesting that oncogenic *BRAF* induced gene patterns can be reversed when *BRAF* activation of MAPK signaling is nullified. This genetic proof of concept was recapitulated with pharmacologic inhibition of BRAF activation: $BRAF^{V600E}$ was induced with one week of dox treatment and subsequently maintained while the animals were treated with the MEK inhibitor PD0325901 (PD901) or the selective oncogenic BRAF inhibitor PLX4720 (Plexxikon/Roche). Inhibition of BRAF signaling with either drug increased RAI incorporation over vehicle treatment, suggesting that inhibiting MAPK signaling with small molecule inhibitors can restore iodide uptake in thyroid tumors driven by a MAPK activating genetic alteration.

Results of a pilot study evaluating the impact of MEK inhibition upon RAI incorporation and ^{131}I efficacy: We translated these preclinical findings into a pilot study evaluating the impact of the AstraZeneca MEK inhibitor selumetinib upon iodide uptake in patients with RAI-refractory thyroid cancers (Ho et al., 2013). A critical component of the study was the utilization of ^{124}I PET/CT lesional dosimetry to precisely quantify drug-induced changes in iodide incorporation within specific lesions (Pentlow et al., 1996; Sgouros et al., 2004) and predict the ^{131}I radiation dose that could be delivered to individual tumors.

Each of the 20 evaluable patients on the study had RAI-refractory disease as defined by one of the following criteria: 1) non-RAI-avid lesion/s on a diagnostic and/or post-therapy RAI scan, 2) RAI-avid lesion/s that remained stable or increased in size after RAI therapy, or 3) fluorodeoxyglucose (FDG)-avid lesion/s by PET scan. In order to optimize iodide uptake, human recombinant TSH (rhTSH or Thyrogen™ from Genzyme) was administered prior to each ^{124}I PET, which was performed before and after treatment with selumetinib for 4 weeks. If the second ^{124}I PET scan predicted that a lesional ^{131}I dose of $\geq$ 2,000 cGy could be achieved, ^{131}I was administered concomitantly with selumetinib. Of the 20 evaluable patients, 12 (60%) had new or increased ^{124}I incorporation after selumetinib. For 8 (40%) patients, the second ^{124}I PET scan predicted that the lesional absorbed ^{131}I radiation dose would equal or exceed 2,000 cGy; these patients were continued on selumetinib and received therapeutic ^{131}I. All 5 patients with *NRAS* MUT tumors on the study exceeded this dosimetry threshold and were treated with ^{131}I.

By contrast, 4 out of 9 *BRAF* MUT patients had selumetinib-induced increases in ^{124}I incorporation, but only one achieved the dose threshold to warrant ^{131}I treatment. Two out of 3 *RET/PTC* and 1 out of 3 WT patients also had greater iodide incorporation on the second ^{124}I PET scan, and one of each of those genotypes went on to be treated with ^{131}I. These changes in iodide incorporation translated to clinical benefit as all 8 patients treated with ^{131}I experienced reductions in tumor size. In total, there were 5 confirmed partial responses (cPRs) and 3 with stable disease (SD). Substantial decreases in serum thyroglobulin following RAI therapy were also achieved in all patients.

All evaluable patients completed the full course of selumetinib without dose reduction or delay. Toxicities attributed to selumetinib were Grade 1 or 2, and were consistent with adverse events reported in larger selumetinib studies (Hayes et al., 2012; Kirkwood et al., 2011), including fatigue (80%), maculopapular rash (70%), and acneiform rash (25%). Fourteen (70%) patients experienced Grade 1 elevations in liver transaminases possibly related to selumetinib, which reverted to baseline after drug discontinuation. One patient who was treated with ^{131}I on study was diagnosed with myelodysplastic

syndrome more than 51 weeks later; the disease eventually transformed to acute leukemia. Prior to enrollment, this patient had received three courses of ^{131}I (cumulative pre-study dose of 976.2 mCi) as well as 8640 cGy of external beam radiation for prostate cancer. Hence, this secondary malignancy was attributed to cumulative ^{131}I and external beam radiation toxicities, and not to selumetinib.

Selumetinib(ARRY 142886; AZD6244): Selumetinib is a potent, selective, noncompetitive inhibitor of MEK, licensed for development by AstraZeneca Pharmaceuticals from Array BioPharma. Selumetinib was discovered by Array Biopharma and had the designation ARRY 142886. Other laboratory code names used during the development of this molecule are AR00142886 and AR-142886-X (where X refers to a sequential lot number). Array BioPharma was responsible for the first-into-human study; the remainder of the clinical development program for oncology indications is the responsibility of AstraZeneca. AZD6244 has now been assigned the international nonproprietary name selumetinib.

Selumetinib inhibits the activity of isolated mitogen-activated protein kinase kinase (MEK) to phosphorylate extracellular signal-regulated kinase (ERK) 2 in enzyme assays, with a concentration which resulted in 50% inhibition (IC50) of approximately 10 to14 nM. In contrast, selumetinib was inactive, or only minimally active, against a panel of other kinases. N-desmethyl selumetinib (a pharmacologically active metabolite) was identified to be approximately 3- to 5-fold more active than the selumetinib parent compound. The amide metabolite is up to 50-fold less active than selumetinib, and is therefore unlikely to significantly contribute to biological activity.

As of 31 January 2014, approximately 1940 patients with cancer have received treatment with selumetinib, including approximately 750 patients in AZ-sponsored studies, 57 patients in the Array-sponsored Study ARRY-0401, 62 patients in the Merck-sponsored Study D1532C00028, and approximately 1070 patients in investigator- or collaborative group-sponsored studies. In addition, approximately 120 healthy volunteers have been exposed to selumetinib Hyd-Sulfate.

Selumetinib has been used as both monotherapy and in combination with other anti-cancer agents, in a variety of adult solid tumor settings (e.g., pancreatic cancer, colorectal cancer, melanoma and NSCLC), and pediatric cancer patients.

The formulation taken into the phase I clinical program by Array Biopharma was an extemporaneous preparation of an oral suspension of selumetinib as the free-base in an aqueous solution of sulphobutylether β-cyclodextrin (SBE-CD, Captisol®), referred to as the free-base suspension formulation (mix and drink).

The AstraZeneca phase II monotherapy clinical program also utilized this formulation. Subsequent formulation development resulted in a capsule formulation of selumetinib as the hydrogen sulphate salt (AZD6244 Hyd-Sulfate), which will be used in this study. The maximum tolerated dose (MTD) for the suspension formulation was determined to be 100 mg twice daily, whereas for the capsule, the MTD was determined to be 75 mg twice daily. The emerging safety and tolerability profile of the capsule formulation is broadly consistent with that of the suspension formulation, although a higher frequency of fatigue and nausea has been reported with the capsule formulation compared to the suspension formulation in the phase II monotherapy studies.

Two phase I studies (D1532C00005, D1532C00020) were performed with the Hyd-Sulfate formulation. Comparison of the frequencies from Study D1532C00005 and the AZ-sponsored phase II monotherapy studies described below shows that there are higher percentages of patients reporting the most frequent AEs such as fatigue, dermatitis acneiform, diarrhea, nausea and peripheral edema with the Hyd-Sulfate formulation. This may be due to the higher plasma exposures achieved with the capsule formulation, but may also be in part as a consequence of the more heavily pre-treated patient population in study D1532C00005 having lower tolerances to developing toxicity.

Two hundred and sixty nine (269) patients received selumetinib free base suspension 100 mg twice daily in 4 completed phase II monotherapy studies (D1532C00003, D1532C00008, D1532C00011, and D1532C00012).

- Rashes (including the preferred terms dermatitis acneiform, rash, rash maculopapular, rash macular, rash papular, acne, and folliculitis) were reported in approximately 70% of patients receiving treatment with selumetinib, and dermatitis acneiform was the most common AE term overall (54%). Other commonly reported AEs were diarrhea (49%), nausea (33%) and vomiting (24%). Adverse events of peripheral edema, periorbital edema, and facial edema were reported in 31%, 9%, and 4% of patients, respectively. The AEs of fatigue or asthenia were reported in approximately 30% of patients in this phase II population. Exertional dyspnea or dyspnea was reported in 13% of patients and, in individual studies, exertional dyspnea was reported at a higher incidence in the selumetinib groups than in the comparator chemotherapy groups.

- Serious AEs were reported in 24% of patients receiving selumetinib monotherapy. The most frequently reported serious AEs were vomiting (1.5%), diarrhea, erysipelas, and pulmonary embolism (in 1.1% patients each). Serious AEs of infections (bacterial sepsis, sepsis, infection, and bacterial arthritis) were reported in 2.2% of patients. The most frequently related reported treatment-related SAE was vomiting (3 patients).

- In Study D1532C00003, small increases in blood pressure were observed after 1 week on selumetinib, with mean increases of 7.4 mmHg (systolic, SBP) and 5.3 mmHg (diastolic, DBP) at Week 8, compared with mean increases of 1.1 mmHg (SBP) and 0.5 mmHg (DBP) in the temozolomide comparator arm. The AE of hypertension was reported in 18 patients (6.7%) receiving selumetinib in phase II monotherapy studies; 6 of these patients had hypertension at entry to the study, and a further 5 patients had documented risk factors for hypertension.

- Reversible asymptomatic reduction in left ventricular ejection fraction (LVEF) to below 55% has been reported in a small proportion of patients with advanced cancers in the monotherapy and randomized placebo controlled studies in combination with standard chemotherapies, with both formulations of selumetinib. In both placebo-controlled studies, no patient treated with selumetinib had severe LVEF impairment (< 35%) or symptomatic heart failure. Evidence of reversibility on continuing treatment with selumetinib has been demonstrated in some patients. LVEF scheduled assessments were only included in one phase II study (D1532C00003) and in the selumetinib group to evaluate a possible cardiac etiology of the peripheral edema reported in earlier studies. The median change in LVEF at Week 4 was 1.2 percentage points, and the individual change from baseline ranged from –20 to +19 percentage points. Adverse events of ejection fraction decreased, left ventricular dysfunction, or ventricular dysfunction were reported in a total of 5 patients (3.3%) receiving selumetinib (including 1 patient who had switched from temozolomide treatment after disease progression) versus 1 patient (1%) in the comparator group.

- Review of clinical laboratory parameters in phase II monotherapy studies identified a trend toward increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels after starting treatment with selumetinib. An increase in serum phosphate was observed in some patients after initiation of selumetinib, compared with patients randomized to comparator treatments. There was a trend toward a small mean decrease in albumin relative to the comparator. No other reports of selumetinib-related changes in laboratory parameters were considered to be of clinical relevance at this time. There was no evidence of myelosuppression or renal impairment.

- Adverse events related to visual function have been reported across the program with selumetinib. Most often there were no specific clinical findings reported from patients that underwent ophthalmological evaluation after reporting the AE of visual disturbance. AEs consistent with central serous retinopathy have been reported in a small number of patients receiving treatment with selumetinib, generally in combination with other anti-cancer agents.

- There have been reports of pneumonitis-type events in a small number of patients receiving treatment with selumetinib. An association with selumetinib has not been established.

- Weakness of neck extensor muscles in conjunction with creatine phosphokinase (CPK) increases (reversible on treatment interruption) have been reported in 3 out of 54 patients with uveal melanoma receiving selumetinib 75 mg twice daily in one non-AstraZeneca sponsored study. Increases in CPK levels have been recorded in a small number of patients receiving treatment with selumetinib. CPK elevations are present in some patients with muscle symptoms, although asymptomatic elevations have also been reported. A relationship between selumetinib and elevated CPK levels or myopathy has not been established.

In the pilot study described above where 20 metastatic, RAI-refractory thyroid cancer patients were treated with a 4 week course of selumetinib 75 mg twice daily (the Hyd-Sulfate formulation) to followed by ^{131}I in a subset of patients (Ho et al., 2013), all events attributed to selumetinib were Grade 1 or 2, and included fatigue (80%), maculopapular rash (70%), acneiform rash (25%), elevation in AST (70%; all Grade 1), elevation in ALT (45%; all Grade 1), diarrhea (45%), nausea (40%), limb edema (30%), oral mucositis (35%), constipation (20%), hypoalbuminemia (15%), decreased white blood cell count (15%), face edema (10%), scalp pain (10%), decreased platelet count (1 patient; Grade 1), eye disorder (1 patient; Grade 1 consisting of visual halos and slight blurriness that resolved after therapy stopped), hypertension (1 patient; Grade 1), periorbital edema (1 patient; Grade 1), and vomiting (1 patient, Grade 1). One patient who was treated with ^{131}I was subsequently diagnosed with myelodysplastic syndrome 51 weeks after ^{131}I administration which subsequently evolved into acute leukemia (this was determined to be unrelated to selumetinib and likely related to cumulative RAI toxicity as well as previous external beam radiation therapy).

In the only other study to specifically investigate selumetinib in differentiated thyroid cancer patients (the phase II study of 100 mg bid selumetinib, previous mix-and-drink formulation) in 39 patients with RAI-refractory differentiated metastatic thyroid cancer. In these patients with RAI-refractory disease, common drug-related AEs included rash (77%), fatigue (49%), diarrhea (49%), and peripheral edema (36%). Grade 3 and 4 AEs were consistent with those across the selumetinib program and also included rash (18%), fatigue (8%), diarrhea (5%) and peripheral edema (5%). Twelve patients required dose reductions for reported AEs across the length of the study (the duration of treatment was greater than 16 weeks for 69% of patients). Six patients (15%) discontinued treatment due to adverse events.

Selumetinib is not mutagenic or clastogenic in vitro but produced increases in micronucleated, immature erythrocytes in mouse bone marrow micronucleus studies. Investigatory studies show that this is predominantly via an aneugenic mechanism which is consistent with disruption of normal spindle function as a consequence of the known pharmacological action of a MEK inhibitor. With selumetinib Hyd-Sulfate, a NOEL of 24 mg/kg/day (for 2 days) was established for induction of micronuclei, with plasma exposures significantly above those observed in cancer patients at the maximum tolerated dose of 75 mg twice daily. This suggests that selumetinib will have little potential to cause aneugenicity in dividing cell populations in patients at the proposed clinical dose.

In summary, selumetinib has been shown to have an acceptable profile of side effects, in an extensive safety database for a compound at this stage of development. Further details regarding the safety profile of selumetinib can be found in the Investigator Brochure.

Rationale for evaluating the impact of selumetinib MEK inhibition upon ^{131}I efficacy in RAIA thyroid cancers: We hypothesize that the limited efficacy of ^{131}I alone for patients with structurally evident, RAIA thyroid cancer is in part due to insufficient lesional ^{131}I uptake and retention mediated by aberrant MAPK pathway inhibition. Pathway inhibition with selumetinib is predicted to increase expression of the thyroid-specific genes requisite to enhance ^{131}I lesional delivery and efficacy. To test this hypothesis, we will perform a two-arm, randomized trial in which patients with RAIA, recurrent/metastatic thyroid

cancer are randomized to ^{131}I therapy in combination with approximately 4 weeks of therapy with either placebo or selumetinib. Hence, this study is appropriate only for patients with recurrent/metastatic thyroid cancer for whom ^{131}I therapy is judged to be indicated. The primary clinical objective of the study will be to determine the overall response rate at 6 months following ^{131}I therapy for each treatment arm. Secondary objectives will be to determine the best overall response, progression-free survival (PFS), changes in serum thyroglobulin levels, and safety/tolerability of each of the treatment arms.

1.1 Treatment

1.11 ^{131}I in combination with placebo

1.12 ^{131}I in combination with selumetinib

1.2 Correlative Research

1.21 Therapeutic benefit with ^{131}I in combination with placebo or selumetinib will be correlated to genomic and transcriptomic biomarker analysis of archival tumor tissue specimens.

We will explore the genomic and transcriptomic landscape of RAIA tumors for signatures that correlate to therapeutic benefit achieved in patients with RAI-avid recurrent and/or metastatic thyroid cancer treated with ^{131}I in combination with placebo or selumetinib. Exploratory analysis will include correlating response to tumor genotypes. All tumors will be evaluated for common thyroid cancer gene mutations (BRAF, RAS, PIK3CA, AKT, RET/PTC, PAX8/PPARγ). Descriptive statistics and graphical techniques will be used to summarize this data by treatment arm. Given the small sample size, all these analyses will be considered hypothesis generating and exploratory.

2.0 Goals

2.1 Primary

2.11 To determine the response rate at 6 months following treatment with ^{131}I in combination with placebo or selumetinib for RAIA recurrent and/or metastatic thyroid cancer.

2.2 Secondary

2.21 To determine the best overall response following treatment with ^{131}I in combination with placebo or selumetinib for RAIA recurrent and/or metastatic thyroid cancer.

2.22 To compare the progression-free survival of patients with RAIA recurrent and/or metastatic thyroid cancer treated with ^{131}I in combination with placebo or selumetinib.

2.23 To compare serum thyroglobulin changes for patients with RAIA recurrent and/or metastatic thyroid cancer treated with ^{131}I in combination with placebo or selumetinib.

2.24 To evaluate the safety and tolerability of ^{131}I in combination with placebo or selumetinib for patients with RAI-avid recurrent and/or metastatic thyroid cancer.

2.3 Correlative Research

2.31 To explore the genomic and transcriptomic landscape of RAIA tumors for signatures that correlate to therapeutic benefit achieved with ^{131}I in combination with placebo or

selumetinib.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Age ≥18 years.

3.12 Diagnosis of recurrent and/or metastatic thyroid cancer.

3.13 Histological or cytological confirmation of thyroid carcinoma of follicular origin (including papillary, follicular, or poorly differentiated subtypes and their respective variants).

NOTE: Medullary and anaplastic thyroid cancers are excluded. Hurthle cell carcinomas are excluded (defined as having an invasive tumor composed of >75% oncocytic (Hurthle) cells lacking the nuclear features of papillary carcinoma, tumor necrosis, and marked mitotic activity). Patients with oncocytic (Hurthle cell) variants of papillary thyroid carcinoma (defined as a tumor composed of a majority of oncocytic (Hurthle) cells having the nuclear features of papillary carcinoma) are eligible to participate.

3.14 RAI-avid lesion on a radioiodine scan (a diagnostic, post-therapy, or post-ablation scans) performed ≤24 months prior to registration, which suggests that therapy with ^{131}I is justifiable in the judgment of the investigator.

3.15 Clinically or radiographically evident structural disease. Patients with measureable disease and those with only non-measureable ("non-target") structural disease (according to modified RECIST v1.1 criteria, see Section 11.0) are eligible.

NOTE 1: Modification of the RECIST v1.1 measureable disease criteria includes a change in the definition of what is considered a measureable malignant lymph node. A malignant lymph node is considered measurable if any of the following apply:

1) it is noted to be RAI-avid on radioactive iodine imaging (diagnostic or post-therapy whole body scans acceptable) and it measures ≥1 cm in the long axis,

2) it is pathologically proven to be involved with thyroid cancer (by cytology or pathology) and it measures ≥1 cm in the long axis,

or

3) its short axis is ≥1.5 cm when assessed by CT scan.

NOTE 2: Patients only with biochemical evidence of disease without structural evidence of cancer are not eligible for this study.

3.16 **For patients with non-measureable, structural disease the following must apply:**

1) undetectable thyroglobulin antibody

AND

2) a serum thyroglobulin of 10 ng/ml or greater in the context of suppressed TSH (TSH≤ 0.4 mcU/ml) ≤ 28 days prior to study registration.

Use of any thyroglobulin assay is allowed, though all serum thyroglobulin measurements for study purposes must be conducted with the same thyroglobulin assay.

3.17 ECOG Performance Status (PS) 0, 1 or 2. (Forms are available on the ACCRU web site)

3.18 Able to swallow and retain orally-administered medication with no clinically significant gastrointestinal abnormalities that may alter absorption.

3.19a The following laboratory values obtained ≤ 28 days prior to randomization:

- Absolute neutrophil count (ANC) ≥1500/mm^3
- Platelet count ≥100,000/mm^3
- Hemoglobin >9.0 g/dL
- Total bilirubin ≤1.5 x upper limit of normal (ULN)
- Aspartate transaminase (AST) ≤2.5 x ULN (or ≤5x ULN in presence of liver metastases)
- Creatinine ≤1.5 mg/dL OR calculated creatinine clearance of ≥50 ml/min by either the Cockcroft-Gault formula (see below) or 24-hours urine collection analysis

Cockcroft-Gault Equation:

Creatinine clearance for males = $\frac{\text{(140 - age)(weight in kg)}}{\text{(72)(serum creatinine in mg/dL)}}$

Creatinine clearance for females = $\frac{\text{(140 - age)(weight in kg)(0.85)}}{\text{(72)(serum creatinine in mg/dL)}}$

3.19b Negative pregnancy test performed ≤7 days prior to registration for women of childbearing potential only.

3.19c Provide informed written consent.

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

*Note: During the **Active Monitoring** Phase of a study (i.e., active treatment and observation), participants must be willing to return to the consenting institution for follow-up.*

3.19e Willing to provide mandatory archival tumor tissue (block or minimum of 30 unstained slides from a primary or recurrent/metastatic thyroid cancer) for correlative research purposes (see Section 17.0). NOTE: Patients with less archival tumor tissue available may still be eligible for the study after discussion with ACCRU (refer to Protocol Resource page). Receipt of archival tumor tissue is not required for study registration and initiation of therapy.

3.19f Willing to provide mandatory blood samples for correlative research purposes (see Section 14.0).

3.2 Exclusion Criteria

3.21 ^{131}I therapy ≤6 months prior to registration. Note: ^{131}I administered solely for diagnostic purposes is not considered ^{131}I therapy.

3.22 External beam radiation therapy ≤28 days prior to registration. Note: Previous treatment with radiation is allowed if the investigator judges it will not compromise patient safety on the study.

3.23 Having been treated with a total cumulative (lifetime) ^{131}I therapeutic activity >800 mCi (excluding ^{131}I activity administered for diagnostic scans).

3.24 Treatment with chemotherapy or targeted therapy (e.g. tyrosine kinase inhibitor) ≤28 days prior to registration.

3.25 Prior exposure to MEK, RAS, or RAF inhibitors (Note: previous exposure to sorafenib is allowed) OR history of hypersensitivity to selumetinib, thyrotropin alpha (Thyrogen™), or any excipient agents.

3.26 Unresolved toxicity > CTCAE grade 2 from previous anti-cancer therapy, except for alopecia.

3.27 Cardiac conditions as follows:

- Uncontrolled hypertension (BP ≥150/95 mmHg despite medical therapy)
- Left ventricular ejection fraction <55% measured by echocardiography
- Atrial fibrillation with a ventricular rate >100 bpm on ECG at rest
- Symptomatic heart failure (NYHA grade II-IV)
- Prior or current cardiomyopathy
- Severe valvular heart disease
- Uncontrolled angina (Canadian Cardiovascular Society grade II-IV despite medical therapy)
- Acute coronary syndrome ≤6 months prior to registration.

3.28 Ophthalmological conditions as follows:

- Intra-ocular pressure >21 mmHg, or uncontrolled glaucoma (irrespective of intra-ocular pressure)
- Current or past history of central serous retinopathy or retinal vein occlusion

3.29a Symptomatic or untreated leptomeningeal disease, brain metastasis, or spinal cord compression.

3.29b Unable to follow a low iodine diet or requiring medication with high content in iodide (e.g., amiodarone).

3.29c Received iodinated intravenous contrast ≤2 months of registration. Avoidance of iodinated oral contrast is also preferred but not strictly required for study enrollment. NOTE: Those who have had iodinated intravenous contrast within this time frame may still be eligible if a urinary iodine analysis reveals that excess iodine has been cleared

(defined as urinary iodine documented to be <300 mcg/day by either a spot urinary iodine or 24-hour urinary iodine measurement).

3.29d Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.29e Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3. 29f Immunocompromised patients and patients known to be HIV positive and currently receiving antiretroviral therapy. NOTE: Patients known to be HIV positive, but without clinical evidence of an immunocompromised state, are eligible for this trial.

3.29g Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, hepatitis B infection, hepatitis C infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3. 29h Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm. (NOTE: Performance of investigational ^{124}I PET/CT scans is allowed prior to and during conduct of this study.)

3. 29i Other active malignancy ≤2 years prior to registration that will interfere with conduct of this trial. EXCEPTIONS: Non-melanotic skin cancer or carcinoma-in-situ of the cervix. NOTE: If there is a history of prior malignancy, patients must not be receiving other specific treatment (chemotherapy, hormonal therapy, radiation) for their cancer.

3.29j Not willing to discontinue use of supplemental vitamin E.

4.0 Test Schedule

(Week designations may change if there are interruptions in study treatments/assessments)

Tests and procedures	**≤28 days prior to registration [12]**	**Prior to treatment initiation**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Observation Phase: 1 month post-^{131}I therapy (+/- 1 wk)**	**Observation Phase:** **• 3 months post-^{131}I therapy (+/- 1 wk) *then*** **• every 3 months (± 1 week) until 12 months post^{131}I therapy,** ***followed by*** **• every 6 months (± 2 weeks) until 2 years (± 3 months) post randomization**
Selumetinib or placebo[1]			X	X	X	X		
Adherence to low iodine diet[2]					X	X		
Thyrogen™[3]						X		
Administration of therapeutic ^{131}I[5]						X		
Informed consent	X							
History and exam, wt, ECOG PS	X		X		X		X[15]	
Height	X							
Pulse and blood pressure	X		X		X			
Adverse event assessment[16]	X		X[4]	X	X	X	X[15]	X
Hematology: CBC/ differential	X		X[13]		X		X[15]	
Chemistry: SGOT (AST), SGPT (ALT), alk phos, T. bili, creatinine, calcium, phos, glucose, Na, K	X		X[13]		X		X[15]	
TSH, free T4, serum thyroglobulin, thyroglobulin antibody[18]	X						X[15]	X
Radiologic evaluation for disease assessment (CT(s) and/or MRI(s))[6] NO IODINATED CONTRAST IS ALLOWED (REQUIRED)[14]	X							X

AVOIDANCE OF IODINATED ORAL CONTRAST IS ALSO PREFERRED BUT NOT STRICTLY REQUIRED[14]								
ECG	X							
Echocardiogram[17]	X							
Ophthalmological examination[7]	X							
Pregnancy test (serum beta HCG)[8]	X					X		
Mandatory research blood sample (see Section 14.0)[9, R]		X						
Mandatory archival tissue collection[10] (see Section 17.0)	X							
Patient Medication Diary (**Appendix II**)[11]			X	X	X	X		

1. Placebo or selumetinib 75 mg orally twice daily will be started on Week 1, Day 1 and continued through 2 days after therapeutic ^{131}I therapy has been administered. Ideally, placebo or selumetinib dosing/treatment should be maintained for at least 7 days prior to and throughout administration of therapeutic ^{131}I (this is not a requirement). Extending the time on placebo or selumetinib (i.e. extending time on treatment and/or instituting treatment interruptions) and/or rescheduling/repeating study assessments/procedures/treatments (though therapeutic ^{131}I should be administered only once) is/are allowed to fulfill the criteria discussed above at the investigator's discretion. The period of time on placebo or selumetinib (i.e. extending time on treatment and/or instituting treatment interruptions) is not to exceed 8 weeks.
2. Patients should adhere to a low iodine diet for 5 days prior to the start of Thyrogen™-stimulated administration of therapeutic ^{131}I processes. The low iodine diet will be continued through 1 day after ^{131}I is given. Please see Appendix III for details of the low iodine diet.
3. Thyrogen™ 0.9 mg IM will be administered once daily for 2 consecutive calendar days, with the last dose given 1 calendar day prior to ^{131}I ingestion.
4. These Adverse Event assessments are meant to denote that study placebo or drug adverse events should be monitored throughout the treatment. No formal visits are required for these assessments, with the exception of Week 3, which is a mandatory visit.
5. Patients <70 years of age will be treated with 150 mCi ^{131}I (+/- 5 mCi). Patients ≥70 years of age can be treated with a ^{131}I activity from 100 mCi up to and including 150 mCi (+/- 5 mCi for 100 mCi or 150 mCi administered activities); for these patients, the activity to be

administered must be determined by the investigator at the time of study registration. Though performing whole blood and body dosimetry to determine maximum tolerated activity (MTA) is NOT required, for centers at which this evaluation is done prior to therapeutic ^{131}I study administration (Week 4), lower 131I activities than what is recommended here may be administered if the MTA is calculated to be lower than the lower limit of what is allowed per protocol or what has been determined to be given (for patients >70 years of age). ***Examples*** (these are only applicable in instances in which dosimetry was performed prior to therapeutic ^{131}I administration): *1) Patients <70 years of age:* If the dosimetry-determined MTA value is less than 150 mCi, then a RAI activity less than 150 mCi may be administered; *2) Patients >70 years of age:* If the dosimetry-determined MTA value is less than the activity that was determined to be given at the time of study registration, then a lower RAI activity may be administered, even activities less than 100 mCi if the MTA is below this threshold. Dosimetry can NOT be used to justify administering therapeutic 131I activities higher than what has been recommended per this protocol. Administration of Thyrogen™ and/or therapeutic ^{131}I at a facility other than the participating site is allowed if documentation of the dates and amount/activity of drug /radioisotope administered is provided to verify adherence to protocol requirements. Performance of post-therapy iodine scans is not required, but is allowed per institutional practice.

6. CT(s) WITHOUT CONTRAST (refer to footnote 14) and/or MRI(s) for tumor(s) assessment is/are to be done prior to study registration, about 3 months (+/- 1 week) after ^{131}I therapy, and then every 3 months (+/- 1 week). After 12 months post-^{131}I therapy, follow up scans are to be done every 6 months (+/- 1 week) for a maximum of 2 years (+/- 3 months) from study randomization. The schedule of radiographic assessments may be altered in order to maintain the tumor assessment intervals detailed here in the event unscheduled assessments are performed. Every effort must be made to have the 6 month post-^{131}I therapy assessment(s) performed.
7. Ophthalmological examination should be performed by an ophthalmologist and include best corrected visual acuity, intraocular pressure measurement, slit-lamp funduscopy. OCT scan should be considered only if deemed clinically appropriate. It is recommended that patients with ongoing retinal abnormality at the time of discontinuation of Selumetinib or placebo should have a follow-up ophthalmological assessment approximately 1 month after drug/placebo discontinuation (the purpose of this is to document reversibility, but should only be considered if the patient is fit enough to have the assessment done).
8. For women of childbearing potential only. Must be done ≤7 days prior to registration. On the week therapeutic ^{131}I given, a pregnancy test will be performed ≤2 days prior to administration of the ^{131}I.
9. Collection of 10 ml of blood (in lavender top tube with EDTA) for research purposes should not be collected and submitted until *after* the patient is registered onto the study, but *prior* to the initiation of placebo or selumetinib therapy (see Section 14.3).
10. ≤60 days from registration. NOTE: Receipt of archival tumor tissue is not required for study registration and initiation of therapy.
11. The diary must begin the day the patient starts taking the medication and returned to the treating institution after its completion OR compliance must be documented in the medical record by any member of the care team.
12. "Pre-registration assessments" need to be completed ≤ 28 days prior to study registration unless otherwise specified.
13. This blood work is to be completed prior to starting therapy with placebo or selumetinib. These tests do not need to be repeated if the pre-registration blood work was performed ≤7 days prior to the initiation of placebo or selumetinib.
14. Iodinated intravenous contrast is not allowed for radiologic evaluations done during screening and prior to administration of RAI. It is also preferred that iodinated oral contrast (e.g. Omnipaque) be avoided during screening and prior to RAI (alternatives such as barium or other agents may be used), but this is not a requirement. Iodinated intravenous and oral contrast for radiologic evaluations in the Observation Phase is allowed.

15. These tests and assessments are only required for the 1 month post ^{131}I therapy visit.
16. Adverse events for selumetinib will be monitored for up to 30 days after discontinuation of drug.

17. If an ongoing reduction in left ventricular ejection fraction of ≥10% and to below 55% at time of selumetinib or placebo discontinuation is noted, then a follow-up echocardiogram, single ECG, and vital sign assessment should be considered approximately 1 month after drug/placebo discontinuation.
18. For patients with non-measureable/non-target lesions and lymph nodes, serum TG measured in the context of TSH suppression (TSH ≤ 0.4 mcU/ml) will be used as part of disease response assessment. For the primary endpoint, serum TG must be assessed with TSH ≤ 0.4 mcU/ml at baseline (pre-treatment) and at the 6-month assessment of response (6 months s/p RAI). For all other measurements of serum TG in these patients, it is preferred that the TSH ≤ 0.4 mc U/ml, but it is not an absolute requirement. If the 6-month serum TG is initially measured in the context of a TSH >0.4 mcU/ml, then every effort should be made to repeat this assessment until a serum TG value is obtained in the context of a TSH ≤0.4mcU/ml, even if it requires obtaining the measurement outside of the protocol-defined +/- 1 week window. Serum TG values that have to be obtained outside this protocol-defined window to ensure it is measured in the context of TSH ≤0.4 mcU/ml will still be used for the primary assessment of response. **IMPORTANT**: Use of any thyroglobulin assay is allowed, though all serum thyroglobulin measurements for study purposes must be conducted with the same thyroglobulin assay. These requirements do not apply to patients with measureable disease.

R "Research funded" (see Section 19.0)

*Note: ***Observation Phase***: *Part of the Active Monitoring Phase of a study. The time period following the active treatment phase when the participant continues to receive cycles of evaluation in compliance with the Test Schedule and may be required to return to the consenting site. Participants will be required to return to the consenting site for follow-up.*

5.0 Stratification Factors:

This Phase 2 randomized study will compare radioactive iodine (RAI) in combination with placebo or selumetinib for the treatment of RAI-avid recurrent/metastatic thyroid cancers. A 1:1 randomization will be used, where the Pocock-Simon algorithm (Pocock SJ et al, 1975) will be used to balance the arms with respect to the following stratification factors, along with the registering membership:

- Prior thyroid cancer treatment with systemic chemotherapy and/or molecularly targeted inhibitors: Yes vs. No
- Age ≥70 years: Yes vs. No
- Bone Metastases present: Yes vs. No
- Previous ^{131}I therapy given for thyroid remnant ablation prior to this study: Yes vs. No
- Measureable disease (as defined by this protocol): Yes or No

6.0 Registration/Randomization Procedures

6.1 Registration Procedures

6.11 To register a patient, access the ACCRU web page atwww.accru.org, go to the Application section and click on "registration" and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the Academic and Community Cancer Research United (ACCRU) Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

Instructions for the registration/randomization application are available on the above web page under the Study Resources section, "Application Training."

Prior to initiation of protocolintervention, this process must be completed in its entirety and an ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office [redacted]. If the patient was fully registered, the ACCRU Registration Office staff can access the information from the centralized database and confirm registration.
- Refer to www.accru.org; click on "Registration, Installation & Entry Instructions.

6.12 Correlative Research

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.19c, 3.19d, 14.1 and 17.1).

6.13 Documentation of IRB approval must be on file with ACCRU before an investigator may register any patients. Approvals should be uploaded through the online ACCRU Regulatory Management System (ARMS).

In addition to submitting initial IRB approval documents, ongoing IRB approval

documentation must be on file with ACCRU no less than annually. Approvals should be uploaded through the online ACCRU Regulatory Management System (ARMS). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

Submission of annual IRB approvals to ACCRU is required until the study is closed through your IRB.

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

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

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

- Patient has/has not given permission to store and use his/her sample(s) for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- Patient has/has not given permission for ACCRU to give his/her sample(s) to outside researchers.

6.16 Treatment cannot begin prior to registration and must begin ≤7 days after registration.

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

6.18 All required baseline symptoms (see Section 10.5) must be documented and graded.

6.19 Treatment on this protocol must commence at an ACCRU/ITOG institution under the supervision of a medical oncologist or endocrinologist for the administration and management of placebo/selumetinib therapy. Collaboration with a nuclear medicine physician will also be necessary to coordinate the conduct and administration of ^{131}I therapy.

6.2 Randomization Procedures

6.21 The factors defined in Section 5.0, together with the registering membership, will be used as stratification factors.

6.22 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which

balances the marginal distributions of the stratification factors between the treatment

groups (Pocock-Simon ref – see below).

- Radioactive iodine (RAI) plus placebo
- Radioactive iodine plus selumetinib

6.3 Procedures for Double-Blinding the Treatment Assignment

6.31 AstraZeneca will supply selumetinib or placebo to Clinical Research Services, a division of Rx Crossroads by McKesson for distribution to participating sites. No blinded starter supplies will be available for this study. Blinded, patient-specific clinical supplies will be sent to the registering investigator at the time of randomization and should arrive within 3-5 days. This randomization will be performed by the ACCRU Statistical and Data Center. The assigned ACCRU Patient ID number must be recorded by the registering institution for proper bottle dispersion. Once a patient has been registered, ACCRU will electronically transmit a clinical drug request for that patient to Clinical Research Services, a division of Rx Crossroads by McKesson. This request will be entered and transmitted by ACCRU the day the patient is registered and will be processed and shipped by Clinical Research Services, a division of Rx Crossroads by McKessonthe same business day if received before 2 pm ET. If the request is received after 2 pm ET, drug will be shipped the following business day. Shipments will be sent via FedEx Priority Overnight.

6.32 Each blinded, patient-specific supply will be labeled with:

- The study protocol number (i.e., ACCRU RU241306I)
- The patient study ID number
- The patient's initials
- The number of capsules
- Administration instructions (i.e., 'Administer as directed per Protocol ACCRU RU241306I')
- Drug Identification (i.e., Selumetinib 25 mg OR Placebo)
- Expiration Date
- Storage instructions ("Store at controlled room temperature, 25°C (77°F)")
- Date dispensed
- IND caution statement and/or local regulatory statements
- Emergency contact instructions

6.33 Please see section 15.18 for more information on how to re-order more supplies, if needed.

7.0 Protocol Treatment

(Please refer to the table in Section 4.0 for schedule of all protocol treatments and assessments)

7.1 Treatment Schedule

Agent	Dose Level	Route	Day	ReRx
Selumetinib or Placebo*	75 mg	PO	BID	None
Thyrogen™	0.9 mg	IM	Daily for 2 days prior to RAI for therapy	
RAI (^{131}I)	100-150 mCi**	PO	Once	None

* The twice daily doses of selumetinib should be scheduled 12 hours apart (+/- 2 hours). If a participant misses a scheduled dose by more than 2 hours, that dose should not be given and the next dose administered at the regularly scheduled time. It is not required to extend the time on Selumetinib or placebo to make up missed doses unless extending time (i.e. extending time on treatment and/or instituting treatment interruptions) is deemed necessary to comply with instructions detailed below. The period of time on placebo or selumetinib (i.e. the time on treatment including treatment interruptions) is not to exceed 8 weeks.

** Patients < 70 years of age will be treated with 150 mCi ^{131}I (+/- 5 mCi). Patients ≥70 years of age can be treated with a ^{131}I activity from 100 mCi up to and including 150 mCi (+/- 5 mCi for 100 mCi or 150 mCi administered activities); for these patients, the activity to be administered must be determined by the investigator at the time of study registration. Though performing whole blood and body dosimetry to determine maximum tolerated activity (MTA) is NOT required, for centers at which this evaluation *is* done prior to therapeutic ^{131}I study administration (Week 4), lower therapeutic ^{131}I activities than what is recommended here may be administered if the MTA is calculated to be lower than the lower limit of what is allowed per protocol or what has been determined to be given (for patients ≥ 70 years of age). ***Examples*** (these are applicable only in instances in which dosimetry was performed prior to therapeutic ^{131}I administration): 1) *Patients <70 years of age:* If the dosimetry-determined MTA value is less than 150 mCi, then an RAI activity less than 150 mCi may be administered; 2) *Patients ≥70 years of age:* If the dosimetry-determined MTA value is less than the activity that was determined to be given at the time of study registration, then a lower RAI activity may be administered, even activities less than 100 mCi if the MTA is below this threshold. Dosimetry can NOT be used to justify administering therapeutic ^{131}I activities higher than what has been recommended per this protocol.

Administration of Thyrogen™ and/or therapeutic ^{131}I at a facility other than the participating site is allowed if documentation of the dates and amount/activity of drug /radioisotope administered is provided to verify adherence to protocol requirements. Performance of post-therapy iodine scans is not required, but is allowed per institutional practice.

Placebo or Selumetinib

Continuous dosing of placebo or selumetinib 75 mg orally twice daily will be started on Week 1, Day 1 and continued through 2 days after therapeutic ^{131}I therapy has been administered.

Below are recommendations to be followed for therapy with both selumetinib and placebo:

Selumetinib/placebo should be taken twice a day on an empty stomach (1 hour before or 2 hours after a meal), 12 hours (± 2 hours) apart with a glass of water.

- Patients should avoid excessive sun exposure and use adequate sunscreen protection if sun exposure is anticipated.
- Patients should not donate blood during the study.
- Unless clinically indicated, patients should avoid changes to, or the addition of, concomitant medications, in particular any that may affect the metabolism of selumetinib (e.g., CYP1A2, CYP2C19 or 3A4 inhibitors/inducers).

The pharmacokinetics of Selumetinib were investigated in study D1532C00086, conducted in the UK involving healthy volunteers of Asian ethnicity (defined as being born in an Asian country, and expatriate for not longer than 5 years, and with maternal and paternal grandparents of Asian ethnicity). The subjects who received Selumetinib in Study D1532C00086 were of the following ethnicities: Japanese, Chinese, Filipino, Malay, Malaysian, Maldivian, Singaporean, Thai, Indian and Vietnamese, and it is not known in these groups whether Selumetinib exposure will be similar to Western subjects or to subjects of the specific Asian ethnicities included in Study D1532C00086.

The pharmacokinetic findings from study D1532C00086 do not support excluding subjects of Asian ethnicity from studies of Selumetinib. However, as it is possible that Asian subjects may experience higher Selumetinib plasma exposure (than would be expected in Western subjects receiving the same dose of selumetinib), there could be a potential for a higher risk of adverse events.

The number of Asian patients with advanced cancer who have received treatment with Selumetinib is very low. Emerging information from ongoing study D1532C00067 of Japanese patients receiving selumetinib + docetaxel for second-line treatment of NSCLC suggests that febrile neutropenia may occur more commonly in Japanese patients (3 of 8 patients treated, although comparative data in Japanese patients receiving docetaxel monotherapy is not available) than might be predicted from studies conducted in Western subjects.

Patients of Asian ethnicity are not excluded from studies evaluating Selumetinib. However, when considering enrolling an individual of Asian ethnicity to a Selumetinib clinical study, investigators should make a clinical judgment as to whether the potential risk of experiencing higher Selumetinib plasma levels outweighs the potential benefit of treatment with Selumetinib. The Patient Information and Consent form for studies of Selumetinib includes information on the possibility of higher Selumetinib plasma levels and occurrence of adverse events in Asian subjects than in subjects who are not of Asian origin. Investigators should be aware of the potentially higher risk of adverse events when monitoring patients of Asian ethnicity receiving treatment in clinical studies of Selumetinib.

As reproductive toxicology data indicate that selumetinib has adverse effects on embryofoetal development and survival at dose levels that do not induce maternal toxicity in mice, the following restrictions apply:

Selumetinib/placebo should not be administered to pregnant or breast-feeding women and conception while on treatment must be avoided. Female patients of child-bearing potential will be required to use reliable methods of contraception for the duration of the study and until

4 weeks after the last dose of Selumetinib. Of note, patients may be requested to maintain contraception and avoid pregnancy for a longer period of time after ^{131}I administration according to institutional guidelines.

Male patients with sexual partners who are pregnant or who could become pregnant (i.e., women of child-bearing potential) should use acceptable methods of contraception for 3 months after the last dose of selumetinib/placebo to avoid pregnancy and/or potential adverse effects on the developing embryo. Of note, patients may be requested to maintain contraception and avoid pregnancy for a longer period of time after ^{131}I administration according to institutional guidelines.

Selumetinib/placebo capsules contain vitamin E in the form of D-α- Tocopheryl polyethylene glycol 1000 succinate (TPGS), a water-soluble form of vitamin E which acts as a formulation excipient. The maximum daily dose of vitamin E that a study subject may receive from selumetinib/placebo is approximately 261.6 mg/day. Therefore:

Patients should not take any supplemental vitamin E. High doses of vitamin E have been reported to cause bleeding and interrupt blood coagulation processes.

Selumetinib/placebo should be administered with caution in patients who are also receiving concomitant Coumadin anticoagulant medications, e.g. warfarin. These patients should have their INR monitored/anticoagulation assessments conducted more frequently and the dose of the anticoagulant should be adjusted accordingly.

^{131}I Therapy

Patients <70 years of age will be treated with 150 mCi ^{131}I (+/- 5 mCi). Patients ≥70 years of age can be treated with ^{131}I activity from 100 mCi up to and including 150 mCi (+/- 5 mCi for 100 mCi or 150 mCi administered activities); for these patients, the activity to be administered must be determined by the investigator at the time of study registration.

These ^{131}I activities are within the 100-200 mCi range for empiric RAI treatment of metastatic thyroid cancer recommended by the 2015 American Thyroid Association (ATA) guidelines (Haugen et al, 2015) Allowing activities <150 mCi for patients ≥70 years of age as detailed above acknowledges that the ^{131}I maximum tolerable activity (MTA) tends to decline among the elderly population (Tuttle et. al., 2006); (Kulkarni et. al, 2006).

Though performing whole blood and body dosimetry to determine maximum tolerated activity (MTA) is NOT required, for centers at which this evaluation is done (performed during the study or within 6 months of study enrollment), lower therapeutic ^{131}I activities than what is recommended here may be administered if the MTA is calculated to be lower than the lower limit of what is allowed per protocol (i.e. for patients with MTA values < 150 mCi for patients <70 years of age or <100 mCi for patients ≥ 70 years of age). Dosimetry can NOT be used to justify administering therapeutic ^{131}I activities higher than what has been recommended per this protocol. Performance of post-therapy iodine scans is not required, but certainly allowed per institutional practice.

Administration of Thyrogen™ and/or therapeutic ^{131}I at a facility other than the participating site is allowed if documentation of the dates and amount/activity of drug /radioisotope administered is provided to verify adherence to protocol requirements.

Any form of oral ^{131}I (e.g., capsule or liquid) is allowed on the trial.

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

7.3 For this protocol, the patient must return to the consenting ACCRU institution for evaluation during treatment and during observation (Active Monitoring Phase) according to the table in Section 4.0.

7.4 Treatment by a local medical doctor: Administration of Thyrogen™ and/or therapeutic ^{131}I at a facility other than the participating site is allowed if documentation of the dates and amount/activity of drug /radioisotope administered is provided to verify adherence to protocol requirements.

7.5 Breaking Codes in Double-Blinded Studies

The treatment code cannot be broken except in the event of an emergency for an individual patient.

In the event of an emergency, call the ACCRU Registration Office at [redacted] to break the code on Monday through Friday, 8:00 a.m. to 4:30 p.m. Central Time. If the code must be broken after hours, assume the patient was assigned to active treatment and treat accordingly. Place a call to the ACCRU Registration Office and leave a message informing them of the need to un-blind a patient. Provide your contact information so that ACCRU Registration Office personnel can return the call the next business day.

If in the judgement of the attending physician, it would be helpful for the future clinical care of the individual patient, the code may be broken after the patient has completed the study. That is, after the patient has been fully evaluated and all evaluation information has been recorded by the attending physician and the patient (if appropriate), the ACCRU Registration Office may be called to find out which study therapy the patient was receiving.

8.0 Dosage Modification Based on Adverse Events

For all adverse events reported in this study considered at least partly causal to the administration of selumetinib, the following dose modification guidance should be applied.

ALERT: *ADR reporting may be required for some adverse events (See Section 10)*

8.1 Dose Levels (Based on Adverse Events in Section 8.2)

Dose Level	Selumetinib
0	75 mg PO BID
-1	50 mg PO BID

Dose level 0 refers to the starting dose.

8.2 Guidelines for Dose Modifications/Interruptions

For adverse events (AEs) that are considered at least partly due to administration of selumetinib

the following dose reduction/adjustment guidance may be applied:

Treatment with selumetinib/placebo should be temporarily interrupted if one of the following adverse events occurs **despite optimal supportive care**:

- Any intolerable adverse event regardless of grade
- Any adverse events ≥ CTCAE Grade 3 (despite optimal supportive care) (exception: patients with ≥ Grade 3 lymphopenia or asymptomatic biochemistry laboratory abnormalities may be continued on study treatment at the same dose level without interruption based upon investigator judgment).

  On improvement of the adverse event to CTCAE grade 1 (or to CTCAE grade 2 for rash) or baseline, selumetinib may be restarted at the same dose or may be reduced as described in

  section 8.1 at the discretion of the investigator. One dose reduction is allowed before permanent discontinuation of therapy.

- If a further episode of the same AE subsequently requires dose interruption, selumetinib may be restarted at the next dose level down on improvement of the AE.
- If a different AE subsequently requires dose interruption, selumetinib may be restarted at the same dose or at the next dose level down on improvement of the AE.
- Selumetinib should not be re-escalated to an earlier dose level on improvement of an AE.
- Ideally, placebo or selumetinib dosing/treatment should be maintained for at least 7 days prior to and throughout administration of therapeutic ^{131}I; however, this is not a requirement. If necessary, study procedures and/or ^{131}I therapy may be rescheduled/repeated (^{131}I therapy should be administered only once) at the discretion of the investigator to achieve this. Extending the time on placebo or selumetinib (i.e. extending time on treatment and/or instituting treatment interruptions) and/or rescheduling protocol assessments/treatments is allowed in order to comply with this approach at the investigator's discretion.
- The period of time on placebo or selumetinib (i.e. extending time on treatment and/or instituting treatment interruptions) is not to exceed 8 weeks.
- NOTE: missing less than 7 doses of placebo or selumetinib for reasons other than toxicity will not be considered a violation of the protocol.

9.0 Ancillary Treatment/Supportive Care

All management of adverse events is left to the Investigator's discretion. **Appendix IV** includes guidelines for the management of some common selumetinib-related adverse events. Compliance with those guidelines is recommended, but not required.

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

9.2 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. J Clin Oncol 2006; 24:3187-3205.

9.3 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical

conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.4 Rash: early initiation of treatment for rash is strongly recommended to minimize the duration and severity of the adverse event. All patients should be given emollient cream to take home for prophylactic use once study treatment has been initiated (see **Appendix IV**).

9.5 Diarrhea: early initiation of treatment for diarrhea is strongly recommended to minimize the duration and severity of the adverse event. Treatment provision will be according to Investigator discretion according to local practice and regulations (see **Appendix IV**).

9.6 Dyspnea: new or worsening dyspnea has been reported during treatment with selumetinib; investigation to determine the underlying cause is recommended (see **Appendix IV**).

9.7 Reduction in LVEF: asymptomatic reductions in LVEF have been reported in some patients receiving selumetinib; treatment may be recommended depending on the magnitude of the LVEF reduction (see **Appendix IV**).

9.8 Visual disturbances: symptoms, including blurred vision, occur commonly during treatment with selumetinib, and AEs of central serous retinopathy and retinal vein occlusion have been reported in studies of other MEK inhibitors. Investigation to determine the underlying cause of visual disturbance is recommended, including ophthalmological examination. Patients with an ongoing retinal abnormality at the time of selumetinib discontinuation should have a follow-up ophthalmological assessment approximately 28 days after discontinuation. This assessment is recommended to document reversibility, but should be performed only if the patient is fit enough to have the assessment (see **Appendix IV**).

Extra assessments are recommended for investigation of specific adverse events that occur during treatment with selumetinib:

Adverse event	**Assessment**
Clinically significant LVEF reduction (by ≥10 percentage points and to below 55%)	**Single ECG** **Troponin levels (isoform according to institutional norm)**
Cardio-respiratory AEs of non-obvious cause	**Single ECG** **Troponin levels (isoform according to institutional norm)**
New or worsening respiratory symptoms (such as dyspnea, cough)	**Single ECG**

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be

utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.3). With this information, determine whether the event must be reported as an expedited report (see Section 10.4). Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.5 and 18.0).

10.12 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

NOTE: A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

- The determination of whether an AE is expected is based on agent-specific information provided in Section 15.0 of the protocol.
- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of the protocol.

NOTE: "Unexpected adverse experiences" means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

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

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.31 Special Situations for Expedited Reporting

Exceptions to Expedited Reporting: EXPECTED Serious Adverse Events

An expedited report may not be required for specific Grade 1, 2 and 3 Serious Adverse Events where the AE is **EXPECTED**. Any protocol specific reporting procedures MUST BE SPECIFIED BELOW and will supersede the standard Expedited Adverse Event Reporting Requirements:

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditiously reported.
General disorders and administration site conditions	Edema face	≤ Grade 3
	Edema trunk	
	Fatigue	
	Fever	
Skin and subcutaneous tissue disorders	Dry skin	≤ Grade 3
	Rash acneiform	
	Rash maculo-papular	
	Stevens-Johnson syndrome	
Respiratory, thoracic and mediastinal disorders	Dyspnea	≤ Grade 3
Eye disorders	Blurred vision	≤ Grade 3
Vascular disorders	Hypertension	≤ Grade 3
Investigations	Alanine aminotransferase increased	≤ Grade 3
	Aspartate aminotransferase increased	
Gastrointestinal disorders	Diarrhea	≤ Grade 3
	Nausea	
	Vomiting	
	Mucositis oral	
	Dry mouth	
Infections and infestations	Nail infection	≤ Grade 3

Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

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

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol or to administer protocol-directed treatment (*i.e.* ^{131}I therapy)
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry

10.311 **Persistent or Significant Disabilities/Incapacities**

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormities or birth defects, must be reported immediately if they occur at any time following treatment with an agent under an IND/IDE since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

10.312 **Death**

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

- **Reportable categories of Death**

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

10.313 **Secondary Malignancy**

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

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

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

10.314 **Second Malignancy**

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

10.4 Expedited Adverse Event Reporting Requirements for IND/IDE Agents

10.41 **Late Phase 2 and Phase 3 Studies:** Expedited Reporting via the **ACCRU Adverse Event Expedited Report Form** for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

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

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥24 hrs	7 Calendar Days			24-Hour; 3 Calendar Days
Not resulting in Hospitalization ≥24 hrs	Not required		7 Calendar Days	

NOTE Protocol specific exceptions to expedited reporting of serious adverse events are found in section 10.31 of the protocol.

Expedited AE reporting timelines are defined as:

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

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

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

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

Effective Date: May 5, 2011

Additional Instructions:

1. Any event that results in persistent or significant disability/incapacity, congenital anomaly, or birth defect must be reported via expedited mechanisms if the event occurs following treatment on a trial under an IND.

2. Use the ACCRU protocol number and the protocol-specific patient ID provided during trial registration on all reports.

   The above expedited reports (24-hour and 3 or 7 day) must be submitted via the **ACCRU Adverse Event Expedited Report Form**.

3. Mayo Clinic Cancer Center (MCCC) Institutions: Provide copies, along with the UPIRTSO cover sheet, by fax [redacted] to the MCCC Regulatory Affairs Unit (RAU) Regulatory Affairs Specialist, who will determine and complete IRB reporting. The RAU will submit to the ACCRU SAE Coordinator and the ACCRU IND Coordinator to determine if FDA submission is needed.

4. Non-Mayo ACCRU Sites: Submit reports to ACCRU Safetyviaemail at: [redacted]

   Once ACCRU Safetyr receives the report viaemail, ACCRU Safety will forward a copy of the above expedited reports to the ACCRU IND Coordinator, who will notify the FDA as warranted by the event and stipulated in the U.S. Code of Federal Regulations.

<u>Reporting serious adverse events to AstraZeneca</u>

All Serious adverse events that meet the criteria for regulatory reporting should be copied to AstraZeneca at the same time that they are reported to regulatory authorities. The notification to AstraZeneca should include a copy of the regulatory submission and a cover page that indicates the following:

- "Notification from an Investigator-Sponsored Study"
- Study title and reference number (preferably with ISSIS reference number)
- Investigator name and address
- IND number or equivalent

Notification to AstraZeneca should also include the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE per local requirements.

Send SAE report and accompanying cover page by way of fax to **AstraZeneca's designated fax line:** [redacted].

In the case of blinded trials, AstraZeneca may request that the Sponsor either provide a copy of the randomization code/ code break information or unblind those SAEs which require expedited reporting.

Reporting pregnancy events to AstraZeneca

If pregnancy occurs, treatment with placebo or Selumetinib should be discontinued, and AstraZeneca should be informed of the pregnancy within one business day of the investigator or site personnel becoming aware of the pregnancy.

The outcome (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) of all pregnancies occurring during treatment with placebo or Selumetinib must be followed up and documented even if the patient was discontinued from the study.

NOTE: The Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form is not being used for this study.

10.5 Other Required Reporting

10.51 Adverse events to be graded at each evaluation and pretreatment as specified in the Test Schedule (Section 4.0). The CTCAE v4.0 grading should be used unless an alternate grading method is indicated in the table below:

System Organ Class (SOC)	Adverse event/ Symptoms	Baseline	Each evaluation	Grading scale (if not CTCAE)
General disorders and administrations site conditions	Fatigue	X	X	
	Weight loss	X	X	
	Localized edema	X	X	
Gastrointestinal Disorders	Diarrhea	# of stools per day	X	
	Dyspnea	X	X	
	Nausea	X	X	
	Vomiting	X	X	
Eye Disorders	Blurred vision	X	X	
Vascular disorders	Hypertension	X	X	
Investigations	Alanine aminotransferase increase Aspartate aminotransferase increase	X	X	
Skin and subcutaneous tissue disorders	Rash acneiform	X	X	
	Rash maculopapular	X	X	

10.52 Submit via appropriate Academic and Community Cancer Research United (ACCRU) Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.5:

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

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

10.523 Grade 5 AEs (Deaths)

10.5231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.53 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation Using RECIST Guideline

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

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1) (Eisenhauer et al., 2009) with some modifications as detailed below.

Patients with measureable tumors and patients with only non-measureable tumors ("non-target" disease only) are eligible for enrollment and will have response assessed as detailed below **(see Sections 11.43 and 11.44)**.

11.1 Schedule of Evaluations: For the purposes of this study, patients should be reevaluated about 3 months (+/- 1 week) after ^{131}I therapy and then every 3 months (+/- 1 week). After 12 months post-treatment, scans should be done every 6 months (+/- 2 weeks) for a maximum of 2 years (+/- 3 months) from study randomization.

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

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

11.212 A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.213 A malignant lymph node is considered measurable if 1) it is noted to be RAI-avid on radioiodine imaging (diagnostic or post-therapy whole body scans acceptable) and it measures ≥1 cm in the long axis, 2) it is pathologically proven to be involved with thyroid cancer (by cytology or pathology) and it measures ≥1 cm in the long axis, or 3) its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

11.214 Tumor lesions in a previously irradiated area are considered measurable disease under the following conditions: there has been evidence of tumor progression in the irradiated area prior to study registration.

11.22 Non-Measurable Disease

11.221 All other lesions (or sites of disease (e.g., visible pulmonary nodules <1 cm in longest diameter)) are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

- FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A 'positive' FDG-PET scanned lesion is defined as one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered 'negative.' New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

  a. Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

  b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

     i. If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT or MRI, this is PD.

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

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

11.33 Measurement at Follow-up Evaluation:

- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

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

  Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.

- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the long or short axis of all the target lymph nodes (if the lymph node qualified as a target lesion based upon a long axis of $\geq$1 cm, then the long axis will be used for the baseline and post-baseline assessments; if the lymph node qualified as a target lesion based upon a short axis of $\geq$1.5 cm, then the short axis will be used for baseline and post-baseline assessments) will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the long or short axis of all the target lymph nodes (if the lymph node qualified as a target lesion based upon a long axis of $\geq$1 cm, then the long axis will be used for post-baseline assessments; if the lymph node qualified as a target lesion based upon a short axis of $\geq$1.5 cm, then the short axis will be used for post-baseline assessments) will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be part of the response assessment as detailed in Section 11.433 or 11.442.

11.43 RESPONSE CRITERIA FOR PATIENTS WITH MEASUREABLE TARGET LESIONS/LYMPH NODES

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

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

11.432 Evaluation of Target Lesions

- Complete Response (CR): All of the following must be true:

  a. Disappearance of all target lesions.

  b. Each target lymph node must have reduction in short axis to <1.0 cm (if short axis being used for measurement) or have reduction in long axis to < 0.7 cm (if long axis is being used for measurement).

  c. For patients without detectable thyroglobulin antibodies, serum thyroglobulin on suppression must be measured to be <0.2 ng/ml. If a center does not have a thyroglobulin assay that reads to <2 ng/ml, then a TSH-stimulated Tg <1 ng/ml would be required to confirm complete response. For patients with detectable thyroglobulin antibodies, assessment of thyroglobulin will not be necessary for assessment of complete response.

- Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the long or short axis of all the target lymph nodes (depending on which axis is being used for assessments) at current evaluation) taking as reference the BSD (*see* Section 11.41).

- Progression (PD): At least one of the following must be true:

  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis and is deemed to be malignant during follow-up.

  b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the long or short axis of all the target lymph nodes (depending on which axis is being used for assessments) at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

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

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

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

- Complete Response (CR): All of the following must be true:

  a. Disappearance of all non-target lesions.

  b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.

  c. For patients without detectable thyroglobulin antibodies, stimulated serum thyroglobulin must be measured to be undetectable. For patients with detectable thyroglobulin antibodies, assessment of thyroglobulin will not be necessary for assessment of complete response.

- Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.

- Progression (PD): At least one of the following must be true:

  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis and is deemed to be malignant during follow-up.

  b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

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

11.434 **Overall Objective Status for Patients with <u>Measureable Target Lesions/Lymph Nodes</u>**

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables. Serum thyroglobulin measurements will <u>not</u> be used in determining overall response, <u>except</u> for designating a complete response (as detailed in Section 11.432 and in the table below):

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

* CR designation may also require serum thyroglobulin assessment as detailed in Section 11.432.

** See Section 11.431

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

11.44 RESPONSE CRITERIA FOR PATIENTS WITH NON-MEASUREABLE, NON-TARGET LESIONS/LYMPH NODES ONLY

11.441 Lesions and lymph nodes should be followed by CT or MRI at time points specified in Section 11.1.

11.442 Structural Evaluation of Non-Target Lesions & Non-target Lymph Nodes

These guidelines inform how non-target lesions and non-target lymph nodes should be assessed for all patients enrolled on trial.

- Complete Response (CR): All of the following must be true:

  a. Disappearance of all non-target lesions.

  b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.

  c. For patients without detectable thyroglobulin antibodies, serum thyroglobulin on suppression must be measured to be < 0.2 ng/ml.

If a center does not have a thyroglobulin assay that reads to ≤ 2 ng/ml, then a TSH-stimulated TG <1 ng/ml would be required to confirm complete response. For patients with detectable thyroglobulin antibodies, assessment of thyroglobulin will not be necessary for assessment of complete response.

- Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.

- Progression (PD): At least one of the following must be true:

  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis and is deemed to be malignant during follow-up.

  b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

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

11.443 **Overall Objective Status for Patients with Non-Measureable, Non-Target Lesions/Lymph nodes**

The overall objective status for an evaluation is determined by:
- Structural assessment of lesions/lymph nodes as detailed in Section 11.442.
- For the "non-CR/non-PD" structural category, measurement of the serum TG in the context of suppressed TSH (and negative TG antibody) will be used to determine the final response designation (the exception is for the assessment of complete response, which requires measurement of a stimulated TG, see chart below).

Non-Target Lesions & Non-Target Lymph Nodes	Serum Thyroglobulin (TG)* (or TG antibody)	New Sites of Disease	Overall Objective Status
CR	TG <0.2 ng/ml on TSH suppression* OR stimulated TG < 0.1 ng/ml (see 11.442)	No	CR
CR	TG ≥ 0.2 ng/ml on TSH suppression* OR stimulated TG > 0.1 ng/ml (see 11.442)	No	Assess as per Non-CR/Non-PD
Non-CR/Non-PD	50% or more reduction compared to baseline Tg WITHOUT a 25% or more increase compared to the lowest TG measured on study (baseline or nadir)*	No	PR
Non-CR/Non-PD	25% or more increase compared to the lowest TG measured on study* (baseline or nadir)	No	PD
Non-CR/Non-PD	Less than 50% reduction compared to baseline TG WITHOUT a 25% or more increase compared to the lowest TG measured on study* (baseline or nadir)	No	SD
Non-CR/Non-PD	New detection of TG antibody	No	PD
Not All Evaluated	25% or more increase compared to lowest TG measured on study Tg* (baseline or nadir)	No	PD

Non-Target Lesions & Non-Target Lymph Nodes	Serum Thyroglobulin (TG)* (or TG antibody)	New Sites of Disease	Overall Objective Status
Not All Evaluated	WITHOUT 25% or more increase compared to lowest TG measured on study Tg* (baseline or nadir)	No	NE
Unequivocal PD	Any serum TG result or TG antibody result, including failure to complete the measurement as per protocol	Yes or No	PD
CR Non-CR/Non-PD Not All Evaluated	Any serum TG or TG antibody result, including failure to complete the measurement as per protocol	Yes	PD
CR Non-CR/Non-PD Not All Evaluated	TG was not evaluated or not evaluated in the context of TSH suppression*	No	NE

* TG will be measured in the context of a suppressed TSH (≤ 0.4 mcU/ml) and negative TG antibody, except for the designation of CR which may require TG measurement in the context of TSH stimulation (see 11.442). For the primary endpoint, the serum TG value designated for the 6-month assessment (6 months after therapeutic ^{131}I is administered) will be used. If the 6-month serum TG is initially measured in the context of a TSH >0.4 mcU/ml, then every effort should be made to repeat this assessment until a serum TG value is obtained in the context of a TSH ≤0.4mcU/ml, even if it requires obtaining the measurement outside of the protocol-defined +/- 1 week window. Serum TG values that have to be obtained outside this protocol-defined window to ensure it is measured in the context of TSH ≤0.4 mcU/ml will still be used for the primary assessment of response.

11.45 **NOTE**: On this study, patients with clinical, radiographic, or biochemical (i.e., thyroglobulin, if applicable) evidence of progression of disease (as described above) on assessments prior to the 6-month disease evaluation (i.e. the scans and evaluations performed 6 months after therapeutic ^{131}I is administered) will be allowed to continue on study treatment and/or evaluations given the potentially delayed therapeutic benefit of ^{131}I, effects of Thyrogen™, etc. For patients with clinical, radiographic or biochemical evidence of progression of disease on assessments prior to the 6 month disease evaluation, the final objective response assessment at 6 months will be based

upon a comparison between the 6 month radiologic scan(s)/evaluations and the baseline, pre-treatment radiologic scans (and serum thyroglobulin measurements if applicable).

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

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

12.0 Descriptive Factors

12.1 Number of prior ^{131}I treatments: 0 vs. 1 vs. 2 vs. 3 vs. 4 or more.

12.2 Previous chemotherapy/targeted therapy for thyroid cancer: Yes vs. No.

12.3 Prior RT: Yes vs. No.

12.4 Thyroid histology: (papillary, follicular, poorly differentiated, and other respective variants).

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who are CR, PR, or SD will continue treatment/assessment per protocol. Patients that are non-PD after completing treatment will be followed during the observation phase as outlined in Section 4.0: 1 month post-treatment, 3 months post-treatment, followed by every 3 months until 12 months post-treatment when patients will be followed every 6 months for a maximum of 2 years (+/- 3 months) from randomization.

13.2 Patients who develop PD while receiving therapy or undergoing protocol assessment will be followed in the event monitoring phase (see section 18). However, it is possible that patients will have PD early in the study and still demonstrate benefit from the study treatment later in the study for several reasons: 1) selumetinib alone prior to RAI may not have significant clinical efficacy, 2) Thyrogen™ stimulation can transiently increase tumor size which can be mistaken for disease progression; 3) the therapeutic effects of RAI can be delayed; and 4) evidence of progression may be evident prior to administration of RAI. Hence, patients with evidence of radiographic, clinical or biochemical (i.e. thyroglobulin, if applicable) PD noted prior to the 6-month disease evaluation (i.e. the scans and evaluations performed 6 months after therapeutic ^{131}I is administered) may remain on treatment/assessment at the discretion of the treating physician. If, in the opinion of the treating physician, these patients are unlikely to demonstrate benefit with subsequent clinical assessments, the patients will be classified as having PD and will be followed in the event monitoring phase (see Section 18.0).

13.3 Patients who go off protocol treatment for reasons other than PD will go to the event-monitoring phase per Section 18.0.

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

These patients should receive treatment if deemed clinically indicated by the treating physician(s).

13.5a A patient is deemed ineligible if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

13.5b A patient is deemed a major violation, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated such that evaluation of the primary end point is significantly compromised. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.5c A patient is deemed a cancel if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood/Blood Products to Be Collected for This Protocol

Indicate if specimen is mandatory or optional	Collection tube description and/or additive (color of tube top)	Volume to collect per tube (number of tubes to be collected)	Blood product being processed and submitted by participating site	Pre-Treatment (prior to starting placebo or selumetinib)	Additional processing required at site after blood draw?	Storage /shipping conditions[1]
Mandatory	Lavender	10 ml (1)	Blood	X	No	Refrigerated

(Requisition form located on the ACCRU web site.)

14.2 No kits will be required for this study.

14.3 Samples should be collected Monday through Thursday. However, if the subject can only be seen on Friday, notify the Biospecimen Resource Manager listed in the in the protocol resource page of the sample, study ID and tracking number and Saturday arrangements will be made to stabilize the sample over the weekend. Do not collect specimens the day before a federal holiday. NOTE: Research blood samples should not be collected and submitted until *after* the patient is registered onto the study, but *prior* to the initiation of placebo/selumetinib therapy.

14.31 Label the specimen tube with protocol number, ACCRU subject ID number, and time and date blood is drawn.

14.32 Ship the EDTA tube with a properly prepared cold pack.

14.33 Ship specimens via FedEx Priority Overnight service.

14.34 Ship samples to:
BAP Freezer
[redacted]

14.35 BAP Receiving will receive the samples and forward specimens to the ACCRU Research Base BAP Shared Resource, [redacted].

14.4 Study Methodology and Storage Information

14.41 Blood/blood product samples will be collected for the following research:

14.411 DNA extraction, storage, and analysis of DNA will be performed in BAP using standard laboratory protocols. These samples will be used as a normal control for the genomic analysis conducted upon the archival tumor tissue and may be analyzed in future pharmacogenetic assays. Remaining DNA will be stored frozen at -70ºC by BAP, according to patient consent information until specific analyses are identified. As protocols are developed, they will be presented for ACCRU, IRB, and ITOG review and approval. (This collection is part of a general strategy of investigation for the majority of ACCRU/ITOG studies.)

14.412 As part of ongoing ACCRU/ITOG research, we will collect white blood cells/plasma for future research studies, according to patient consent information. Samples will be stored frozen at −70ºC by BAP until specific analyses are identified. As protocols are developed, they will be presented for ACCRU, ITOG, and IRB review and approval.

14.5 Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

If, at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

15.0 Drug Information

Investigator Brochure: The most current version of the Investigator Brochure will be maintained in the study folder on the ACCRU website. Updated Investigator's Brochures should be obtained from the study folder as they become available.

Each investigator should obtain a copy of the Investigator's Brochure prior to initiation of the study.

15.1 Selumetinib (AZD6244 Koselugo™) or selumetinib-matched placebo

15.11 **Background**: The RAS/RAF/MEK/ERK pathway is an important mediator of many cellular processes including proliferation, survival, differentiation, apoptosis, motility and metabolism. This pathway is often aberrantly activated in human tumors due to the overexpression of activated K-RAS, mutant b-Raf, or other growth factor receptors. Selumetinib is a selective mitogen-activated protein kinase (MEK) inhibitor. By inhibiting MEK, selumetinib inhibits ERK phosphorylation. Thus, selumetinib may inhibit oncogenic growth signaling in tumor cells by targeting the RAS/RAF/MEK/ERK pathway.

15.12 **Formulation:**
The drug product consists of a series of plain, HPMC capsules containing 10 mg (white) and 25 mg (blue) selumetinib (expressed as free-base) for oral administration. Selumetinib capsules are supplied in white, HDPE bottles with desiccant, a tamper evident induction seal membrane and child resistant screw closure.

The 10 mg capsule is presented as either a plain white capsule with a center band, or white to off-white capsule with a center band marked with 'SEL 10' printed in black ink.

The 25 mg capsule is presented as either a plain blue capsule with a center band, or blue capsule with a center band marked with 'SEL 25' printed in black ink.

Apart from the markings, plain and marked capsules are identical in all other aspects.

The capsules contain selumetinib Hyd-Sulfate and Vitamin E polyethylene glycol succinate (also known as TPGS - a water soluble form of vitamin E)Placebo composition is consistent with the composition of drug product, with the absent drug substance being replaced by Vitamin E polyethylene glycol succinate. The same HPMC capsule shells are used for both placebo and active drug products.

Both selumetinib and placebo are supplied in 25 mg capsules in bottles containing 60 capsules each.

15.13 **Preparation and Storage:** Store the selumetinib or placebo capsules in the original packaging until use at room temperature (20° C-25° C). Brief excursions are permitted between 15° C and 30° C. For further information refer to the investigational product label.

15.14 **Administration:** Selumetinib should be taken on an empty stomach, 1 hour before or 2 hours after a meal. Take capsules with water only.

15.15 **Pharmacokinetic information**:
Absorption - Selumetinib was absorbed relatively quickly across all dose levels, with a median t_{max} of 1 to 1.5hours across the dose range (25 to 100 mg).
Distribution - Following the peak, selumetinib concentrations declined multi-exponentially, with a mean $t_{1/2}$ ranging from 5 to 7 h, which is consistent across dose levels. CL/F and V_{ss}/F also remained largely consistent across the dose range, with mean values ranging from 12 to 23 L/h and 87 to 126 L respectively. Plasma N-desmethyl selumetinib concentrations followed a similar pharmacokinetic profile to selumetinib, although exposure was much lower, with C_{max} and AUC values generally <15% of parent, within each patient. The median t_{max} was around 1.5 hrs and $t_{1/2}$ was around 9 to 13 hours.

Metabolism -
Cytochrome P450 3A4 is the predominant isoform responsible for selumetinib oxidative metabolism with CYP2C19, CYP1A2, CYP2C9, CYP2E1, and CYP3A5 involved to a lesser extent. Its active metabolite, N-desmethyl selumetinib is approximately 3-5 times more potent than selumetinib, and generated primarily by CYP1A2, CYP2C19, CYP2C9 and CYP2C8 and metabolized through the same routes as selumetinib.
Special Populations – Renal impairment is expected to have minimal effect on exposure to selumetinib. Patients with moderate and severe hepatic impairment may experience higher exposures of approximately 1.5-and 3-fold, respectively. It is recommended that investigators take this information into consideration if patient experience moderate or severe hepatic impairment during the study treatment.

15.16 **Potential Drug Interactions**: High vitamin E doses may potentiate the anticoagulant activity of warfarin. Monitor PT/INR more frequently in patients receiving both selumetinib and warfarin.

The concomitant intake of supplemental vitamin E should be avoided in all subjects receiving selumetinib.

Avoid co-administering selumetinib with medicinal products that are strong inhibitors of CYP3A4 (eg, clarithromycin, grapefruit juice, oral ketoconazole) and CYP2C19 (eg, ticlopidine). If co-administration is unavoidable, patients should be carefully monitored for AEs. No dose adjustment is necessary for

use of selumetinib with moderate CYP3A4 or CYP2C19 inhibitors. Patients should be carefully monitored for AEs when co-administered with moderate CYP3A4 or CYP2C19 inhibitors.

Avoid concomitant use of strong CYP3A4 inducers (eg, phenytoin, rifampicin, carbamazepine, St. John's Wort) or moderate CYP3A4 inducers with selumetinib.
Selumetinib may be an inhibitor of OAT3 and the potential for a clinically relevant effect on the PK of concomitantly administered substrates of OAT3 cannot be excluded.

Based on *in vitro* data and SimCYP simulations, selumetinib is considered unlikely to cause clinically significant drug-drug interaction via inhibition or induction of CYP enzymes

15.17 **Known potential toxicities**:

Very Common Adverse Events, (>10%)
Cardiovascular: Peripheral edema
Central nervous system: Fatigue, headache
Dermatologic: Rash acneiform, rash maculo-papular
Endocrine & metabolic: Creatine phosphokinase (CK) increased
Gastrointestinal: Diarrhea, nausea, vomiting, abdominal pain, constipation.
Respiratory: Exertional dyspnea

Common Adverse Events, (1 to <10%)
Cardiovascular: Hypertension
Central nervous system: Fever, dizziness, insomnia, depression
Dermatologic: Dry skin, pruritus, rash
Endocrine & metabolic: Hypoalbuminemia, hypomagnesemia, hyperphosphatemia
Eye: Periorbital edema, blurred vision
Gastrointestinal: upper abdominal pain, abdominal distension, stomatitis, anorexia, decreased appetite, dry mouth
Hematologic: Thrombocytopenia, anemia
Hepatic: AST increased, ALT increased
Neuromuscular & skeletal: Back pain, arthralgia, asthenia
Respiratory: Dyspnea, cough
Miscellaneous: Alopecia, Low blood potassium

Rare Adverse Events (Important or life-threatening), <1%
Left ventricular systolic dysfunction, Liver injury/failure

15.18 **Drug procurement:**
AstraZeneca will supply selumetinib or placebo to Clinical Research Services, a division of Rx Crossroads by McKessonfor distribution to participating sites. No blinded starter supplies will be available for this study. Blinded, patient-specific clinical supplies will be sent to the registering investigator at the time of randomization and should arrive within 3-5 days. This randomization will be performed by the ACCRU Statistical and Data Center. The assigned ACCRU Patient ID number must be recorded by the registering institution for proper bottle dispersion. Once a patient has been registered, ACCRU will electronically transmit a clinical

drug request for that patient to Clinical Research Services, a division of Rx Crossroads by McKesson. This request will be entered and transmitted by ACCRU the day the patient is registered and will be processed and shipped by Clinical Research Services, a division of Rx Crossroads by McKessonthe same business day if received before 2 pm ET. If the request is received after 2 pm ET, drug will be shipped the following business day. Shipments will be sent via FedEx Priority Overnight.

If additional supplies are needed, contact a member of the Clinical Research Services team:

Clinical Research Services, a division of Rx Crossroads by McKesson
Clinical Research Services
[redacted]

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

15.19 Nursing Guidelines

15.191 Medication should be taken on an empty stomach with no food or drink other than water for 1 hour before and 2 hours after dosing.

15.192 Gastrointestinal side effects were the most commonly reported side effects with this agent (including nausea, diarrhea, constipation, dyspepsia and vomiting). Manage symptomatically and assess for effectiveness of intervention.

15.193 Patients experienced acneiform rash. Instruct patient to report this rash and manage symptomatically.

15.194 Dyspnea has been reported. Instruct patient to report any shortness of breath to the study team. Rarely interstitial lung disease has been seen with agent.

15.195 Hypertension has been seen. Assess blood pressure according to study requirements.

15.196 Instruct patients to report any limb swelling (usually legs) to the study team. Rarely LVEF dysfunction has been seen.

15.197 Monitor LFT's.

15.198 Monitor CBC w/diff. Instruct patients to report any unusual bruising or bleeding to the study team.

15.199a Patients may experience increased fatigue. Instruct patients in energy conserving lifestyle.

15.199b Warn patients of possible alopecia.

15.199c Instruct patients to report any blurred vision or periorbital edema to the

study team.

15.199d Assess patient's concomitant medications as there are numerous drug to drug interactions.

15.2 Thyrogen™ (rhTSH, thyrotropin alfa for injection)

Effective conduct of RAI therapy requires stimulation by TSH in order to maximize RAI uptake by thyroid cells. Recombinant human TSH (rhTSH or Thyrogen™) will be used to stimulate iodide uptake according to the manufacturer's recommendation (0.9 mg intra-muscular injection for 2 days prior to the RAI administration according to the Section 4.0). This allows patients to avoid the hypothyroidism state, since they can maintain their routine thyroid hormone supplementation. Patients or clinicians choosing withdrawal of thyroid hormone treatment for this purpose will be ineligible for this study.

15.21 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.3 Radioactive iodine (RAI)

15.31 Therapeutic RAI dose (^{131}I)

Patients <70 years of age will be treated with 150 mCi ^{131}I (+/- 5 mCi). Patients ≥70 years of age can be treated with a ^{131}I activity from 100 mCi up to and including 150 mCi (+/- 5 mCi for 100 mCi or 150 mCi administered activities); for these patients, the activity to be administered must be determined by the investigator at the time of study registration.

Though performing whole blood and body dosimetry to determine maximum tolerated activity (MTA) is NOT required, for centers at which this evaluation *is* done prior to therapeutic ^{131}I study administration (Week 4), lower ^{131}I activities than what is recommended here may be administered if the MTA is calculated to be lower than the lower limit of what is allowed per protocol or what has been determined to be given (for patients ≥70 years of age). ***Examples*** (these are applicable only in instances in which dosimetry was performed prior to therapeutic ^{131}I administration): 1) *Patients <70 years of age:* If the dosimetry-determined MTA value is less than 150 mCi, then a RAI activity less than 150 mCi may be administered; 2) *Patients >70 years of age:* If the dosimetry-determined MTA value is less than the activity that was determined to be given at the time of study registration, then a lower RAI activity may be administered, even activities less than 100 mCi if the MTA is below this threshold. Dosimetry can NOT be used to justify administering therapeutic ^{131}I activities higher than what has been recommended per this protocol.

Administration of Thyrogen™ and/or therapeutic ^{131}I at a facility other than the participating site is allowed if documentation of the dates and amount/activity of drug /radioisotope administered is provided to verify adherence to protocol requirements.

Any form of oral ^{131}I (e.g., capsule or liquid) is allowed.

15.32 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

16.0 Statistical Considerations and Methodology

16.1 Study Overview

This randomized, double-blind Phase II trial will compare the response rate at 6 months after therapy with ^{131}I in combination with placebo or selumetinib for the treatment of patients with RAIA recurrent and/or metastatic thyroid cancer. Historical response rate to a single dose of RAI can be difficult to estimate from retrospective data that include heterogeneity with regards to the extent of disease treated, RAI doses administered, patient preparation, response assessments etc. Nonetheless, a retrospective analysis has demonstrated that the response rate for first-line ^{131}I therapy alone for recurrent/metastatic RAIA thyroid cancer with measurable disease is generally around 20% (Sabra et al., 2013). We estimate that patients with non-measureable disease and with the serum thyroglobulin criteria described in this protocol will have a response rate of approximately 50%. Anticipating that 40% of the patients accrued will have measureable disease and 60% with non-measureable disease only (requiring serum TG measurements to be used in response assessment), the predicted response rate for this population would be 40%. It is hoped that the combination of selumetinib and ^{131}I can increase the response rate to 65%.

This trial will also compare the best overall response rate, progression-free survival (PFS), changes in serum thyroglobulin levels and adverse event rates between the two treatment arms. In addition, we will explore the genomic and transcriptomic landscape of RAIA tumors for signatures that correlate to therapeutic benefit achieved in patients with RAI-avid recurrent and/or metastatic thyroid cancer treated with ^{131}I in combination with placebo or selumetinib.

16.2 Primary Endpoint

The primary endpoint for this study will compare the response rate with ^{131}I in combination with placebo or selumetinib for the treatment of patients with RAIA recurrent and/or metastatic thyroid cancer at the 6-month time point ("6-month time point" refers to the assessments designated to occur approximately 6 months after ^{131}I therapy in combination with placebo or selumetinib has been administered, which may be 6 months +/- 1 week from the time therapeutic RAI is administered. For patients with non-measureable disease, TG values obtained outside this window may be allowed if repeat measurements were required to ensure the this value was obtained in the context of a TSH $\leq$ 0.4.).

A patient will be classified as a responder if they have a partial or complete response at the 6-month time point when compared to the baseline, pre-study radiologic scan(s) according to the criteria outlined in Section 11.0 (confirmation of response is not required) . The proportion of patients with a response will be calculated and compared between the 2 arms using a Chi-square or Fisher's Exact test. All eligible patients who are randomized and begin treatment will be evaluable for the primary endpoint.

It is possible that patients will have clinical, radiologic, or biochemical evidence of disease progression early in the study and still demonstrate benefit from the study treatment later in the study for several reasons: 1) selumetinib alone prior to RAI may not have significant clinical efficacy, 2) Thyrogen™ stimulation can transiently increase tumor size which can be mistaken for disease progression; 3) the therapeutic effects of RAI can be delayed; and 4) evidence of progression may be evident prior to administration of RAI. Hence, patients with evidence of radiographic or clinical PD noted prior to the 6-month time point assessment may remain on study and continue to receive treatment and/or be evaluated for response at the discretion of the treating physician. The final objective response assessment at 6 months for these patients will be based upon a comparison between the 6-month radiologic scan(s) (and serum thyroglobulin,

if applicable) and the baseline, pre-study radiologic scans (and serum thyroglobulin, if applicable). However, if in the opinion of the treating physician these patients are unlikely to demonstrate benefit at the 6-month time point, the patients will be considered to have had a progression/death event, categorized as non-responders, and taken off the study.

Patients who receive additional treatment for their thyroid cancer outside of this protocol prior to the 6-month time point (except for thyroid hormone TSH suppression, palliative radiation to a non-target lesion, or therapy to prevent pathologic fractures caused by bone metastases (e.g. zoledronic acid and denosumab)) will be considered non-responders.

Final Analysis for Primary Endpoint: The primary goal is to compare ^{131}I in combination with placebo or selumetinib where the alternative hypothesis is that selumetinib and ^{131}I has an improved confirmed response rate compared to placebo plus ^{131}I. Twenty-eight evaluable patients will be enrolled to each arm, for 56 evaluable patients, total. With this sample size, we will be able to detect a significant difference between a response rate of 40% in the control group vs. 65% in the experimental group (odds ratio for response of 2.786, with 1-sided type I error = 0.15 and power = 80%). All patients who meet the eligibility criteria, sign the consent form, are randomized, and start treatment will be evaluable.

16.3 Secondary Endpoints

The following endpoints will be compared between the 2 arms: best overall response, 6- month progression-free survival, changes in serum thyroglobulin levels, and adverse event rates between the 2 treatment arms. All patients who meet the eligibility criteria, sign the consent form, are randomized, and start any treatment will be considered evaluable for the endpoints below.

Best overall response: The best overall response will be compared between the two according to the criteria outlined in Section 11.0. This comparison will be done using a chi-square test. For a patient to be classified as a response, they need a partial or complete response that is confirmed at least 4 weeks later anytime during the study.

Progression-Free Survival: Progression-free survival (PFS) is defined as the time from study entry to the first of either disease progression or death from any cause, where disease progression will be determined based on criteria outlined in Section 11.0. PFS will be estimated using the Kaplan-Meier method, where the log-rank test will be used to compare the 2 treatment arms. Evidence of progression noted from the time of registration to within 6 months after ^{131}I therapy may be disregarded as a progression event if the treating physician feels it is reasonable according to the rationale detailed in Section 16.2. The response assessment at 6 months for these patients will be based upon a comparison between the 6-month radiologic scan(s) and the baseline, pre-study radiologic scans. In addition, the 6-month PFS rate will also be compared between the arms.

Serum Thyroglobulin Levels: Changes in thyroglobulin will be assessed. The Wilcoxon Rank-Sum test will be used to compare the changes in thyroglobulin (pre-RAI and post-RAI) between the two treatment arms. (This analysis will not be possible for patients with detectable thyroglobulin antibodies.)

Adverse events: The maximum grade for each type of adverse event will be summarized using CTCAE version 4.0. The frequency and percentage of grade 3+ adverse events will be compared between the 2 treatment arms. Comparisons between arms will be made by using either the Chi-square or Fisher's Exact test.

16.4 Translational Studies

We will explore the genomic and transcriptomic landscape of RAIA tumors for signatures that correlate to therapeutic benefit achieved in patients with RAI-avid recurrent and/or metastatic thyroid cancer treated with ^{131}I in combination with placebo or selumetinib. Exploratory analysis will include correlating response to tumor genotypes. All tumors will be evaluated for common thyroid cancer gene mutations (BRAF, RAS, PIK3CA, AKT, RET/PTC, PAX8/PPARγ). Descriptive statistics and graphical techniques will be used to summarize this data by treatment arm. Given the small sample size, all these analyses will be considered hypothesis generating and exploratory.

16.5 Total Sample Size

A maximum of 56 evaluable patients (28 per arm) will be accrued onto this randomized phase II study unless the study is closed early for excessive toxicity. We anticipate accruing an additional 5% of patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, maximum accrual is 60 patients (30 per arm).

16.6 Expected Accrual and Accrual Duration

The expected accrual rate is about 3 patients per month for the ACCRU group. With this accrual rate, we expect to finish accrual within about 20 months, assuming we accrue 60 total patients.

16.7 Anticipated time to study completion

We anticipate that the study will take approximately 3 years to complete. This allows a 6 month follow-up for the final patient enrolled, along with data entry, data clean-up, and analysis.

16.8 Data & Safety Monitoring

The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The trial is monitored continually by the study team who are notified of every grade 4 and 5 event in real time. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual after any temporary suspension or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may also choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy any of the following criteria for each arm separately:

- If at any time, 6 of the initial 20 treated patients or 30% or more of all patients (i.e. when accrual is greater than 20 patients) have experienced a grade 4 non-hematologic adverse event.
- If at any time, 2 of the initial 20 treated patients or 10% or more of all patients (i.e. when accrual is greater than 20 patients) have experienced a grade 5 adverse event (non-progressive disease).
- In addition, each grade 5 event will be reviewed on a case by case basis in a real time fashion to determine whether study accrual should be suspended. We may suspend accrual after just 1 grade 5 AE, if needed, for patient safety.

16.9a Accrual Monitoring Stopping Rule

Given the expected accrual rate is around 4 patients per month, it is expected that the study will take around 25 months to fully accrue. We plan to monitor the accrual continually and if we only end up accruing 10 patients or less in the first year (after study activation), we will consider stopping the trial for slow accrual.

16.9b Primary Endpoint Completion Time Estimation (For clinicaltrails.gov reporting):

The primary endpoint is a comparison of the confirmed response rate between the 2 treatment arms, as discussed in detail in section 16.2. The final analysis is expected to take place around 36 months after the study begins, so we expect the primary endpoint completion time to be around 36 months after study activation.

16.9c Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin. There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Based on prior studies involving similar disease sites, we expect about 25% of patients will be classified as minorities by race and about 55% of patients to be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	6	5	11
Not Hispanic or Latino	27	22	49
Ethnic Category: Total of all subjects	33	27	60
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	2	1	3
Black or African American	6	5	11
Native Hawaiian or other Pacific Islander	1	0	1
White	24	21	45
Racial Category: Total of all subjects	33	27	60

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Tissue Biospecimen Submission

17.11 Summary Table of Tissue Biospecimens for This Protocol

Type of tissue biospecimen to submit	Mandatory or optional	When to submit	Reason for submission (background/ methodology section)	Where to find specific details for biospecimen submission
Formalin-fixed paraffin-embedded (FFPE) tissue blocks with corresponding H&E (OR (20) 5 micron- and (10) 10-micron unstained slides with corresponding H&E)	Mandatory	≤60 days after registration	Correlative studies (Section 17.3)	Section 17.2

If an institution is not able to provide the tissue, it does not cause the patient to be ineligible; however, the collection of these tissues is **strongly recommended.**

17.2 Paraffin Embedded Tissue Blocks/Slides (mandatory for research tissue)

17.21 Submit one formalin fixed paraffin-embedded (FFPE) tumor tissue block from the primary or recurrent/metastatic thyroid cancer. A corresponding H&E slide from the submitted block must be provided to permit quality assessment (QA) of tissue block.

17.22 The FFPE tissue block is preferred; however, if an institution is unable to provide a tissue block, cut 20 five-micron unstained slides and mount on charged glass slides and 10 ten-micron unstained slides mounted on uncharged slides. **Label the slides with the ACCRU patient ID number, accession number, and order of sections (i.e., 1-11). Do not use sticky labels on the slides. H&E stain the first cut slide (i.e., slide labeled 1).** For samples containing less than 7square millimeters of tumor tissue, multiple sections should be mounted onto each slide to ensure that the appropriate amount of tumor tissue is available. Ideally, each slide must have a minimum of 75% tumor tissue on the slide to be deemed adequate for study. **Do not bake or place cover slips on the slides.**

17.23 The following materials below are mandatory (unless indicated otherwise) and required for shipment:

- Paraffin embedded tissue blocks with corresponding H&E (or 30 slides per instructions in section 17.22)
- Research Tissue Specimen Submission Form
- Surgical Pathology Report (Do not redact the accession number(s))
- Operative Report-Optional

17.24 Ship all block/slide tissue specimens and accompanying materials to the following:

ACCRU Operations Office
Attn: PC Office (Study RU241306I)
[redacted]

17.3 Study Methodology and Storage Information

17.31 Submitted tissue samples will be analyzed as follows:

17.311 FFPE tumor tissue blocks/ unstained slides will be collected in search of biomarkers that may correlate to clinical responses to either ^{131}I in combination with placebo or selumetinib. To maximize the information garnered from limited archival tissues, highly sensitive array-based technologies will be used to quantify the gene expression and sequence of cancer genes.

We will isolate RNA from the tissues for interrogation with a custom-designed Nanostring platform for two purposes: a) Detection of fusion oncogenic transcripts (that cannot be detected by an exon-capture method), and b) To measure mRNA levels of three major classes of transcripts: 1) Markers of the MAPK pathway transcriptional output (e.g. Etv1, Etv4, Etv5, Spry2, Spry4, Dusp6); 2) Genes required for thyroid hormone biosynthesis (e.g. Nkx2.1, Pax8, Foxe1, Tg, Tpo, TshR, Nis, Pendrin, Dio2); and 3) Possible determinants of intrinsic resistance to therapy, including adaptive responses to MAPK pathway inhibition that have already been found to be relevant for *BRAF* MUT tumors (i.e. neuregulin mediated activation of HER3 kinase): e.g. Nrg1 (and other RTK ligands), Her2, Her3, TGFβR2). The assay will interrogate ~200 transcripts, of which only a few examples of each class are listed above.

Expression of a panel of cytokeratins, among other genes, will be used to standardize for epithelial cell content in the biopsy material.

A portion of the tumor will be processed for DNA extraction using standard laboratory protocols. Approximately 200 ng DNA isolated from archival samples will be analyzed by exon capture-based next generation sequencing of a custom panel of approximately 300 cancer gene exomes or more, which incorporates all known thyroid cancer oncogenes and tumor suppressors. Genomic DNA from the 10 ml blood draw will be used as a germline comparator to aid in identifying tumor specific alterations. According to patient consent information, remaining DNA will be stored frozen at -70ºC by BAP. As protocols are developed, they will be presented for ACCRU, IRB, and ITOG review and approval.

Given the fast-paced development of genomic and transcriptomic platforms, it is possible that by the time tissues from this study are available for analysis, more advanced DNA and RNA analytic techniques for FFPE tissues (e.g., whole exome, whole genome, RNAseq, etc.) may be available and preferred over the approach detailed above. If so, the studies discussed

above may be performed on one of these newer platforms to investigate the overall aim of identifying markers that correlate to clinical efficacy.

All analyses of the archival tumor tissue will be performed by Dr. James Fagin, Memorial Sloan-Kettering Cancer Center (New York, New York).

17.32 At the completion of the study, any unused/remaining material will be stored in the ACCRU Central Operations Office (attn: Pathology Coordinator) for future research according to the patient consent permission. Potential future research may include immunohistochemistry (IHC) analyses, DNA extraction, RNA extraction, and/or tissue microarray (TMA) construction to analyze predictive biomarkers, changes in expression pattern with therapy, and correlation with response and/or adverse events. For TMAs, the donor block remains intact except for 6 small (0.6mm) holes where the cores were taken. This process has minimal impact on the utility of the block for future clinical diagnostic needs. When a protocol is developed, it will be presented for ACCRU, IRB and ITOG review and approval. (These specimens may only be used subsequently for ITOG-approved research protocols.)

17.34 The institutional pathologist will be notified by the ACCRU Operations Office (Pathology Coordinator) if the block may be depleted.

17.35 Blocks requested to accommodate individual patient management will be returned promptly upon request.

17.4 Return of Genetic Testing Research Results

Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

If, at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sough regarding the most appropriate manner of disclosure and whether or not validation in a CLIA certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

18.0 Records and Data Collection Procedures

All data must be entered by Remote Date Entry (RDE) and completed by qualified and authorized personnel. Access the RAVE RDE system through the iMedidata portal at https://login.imedidata.com. All data on the CRF must reflect the corresponding source document. Please refer to the ACCRU website for instructions [redacted] NOTE: All reports must be de-identified and labeled with the study number, ACCRU patient ID number and initials.

18.1 Submission Timetable

Initial Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
On-Study	≤2 weeks after registration
Baseline Adverse Event	
RECIST Measurement – Baseline	
Research Blood Submission – Baseline (see Section 14.0)	
Research Tissue Submission - Baseline (see Section 17.0)[2]	
Endocrine Laboratory - Baseline	
OP and Path Reports (see Section 17.0)[1]	
End of Active Treatment/Cancel Notification Form	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy

1. Attach a copy of OP and path reports in RAVE using the Supporting Documentation Form for documentation of disease. This is in addition to the pathology material requirements for tissue submission (Section 17.0).
2. As per Section 17.0, research tissue biospecimen should be submitted ≤ 60 days after registration.

Test Schedule Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Observation
Evaluation/Treatment	X[3]	X	
Evaluation/Observation			X
Nadir/Adverse Event	X	X	X[2]
RECIST Measurement			X[1]
Endocrine Laboratory			X
RT Material		X	
End of Active Treatment/Cancel Notification		X	
Notification – Grade 4 or 5 Non-AER Reportable Events/Hospitalization	At each occurrence (see Section 10.0)		
ADR/AER	At each occurrence (see Section 10.0)		

1. Attach a copy in RAVE for documentation of response or progression on the Supporting Documentation Form.
2. Complete only at 1 month post I-131 evaluation during Observation (see Section 4.0).
3. Complete at each evaluation during Active Treatment (see Section 4.0).

Follow-up Material(s)

CRF	Event Monitoring Phase[1]				
	q. 3 months until PD for the first 12 months post-I^{131} therapy and every 6 months after that[2]	At PD	After PD q. 6 mos.	Death	New Primary
Event Monitoring[2]	X	X	X	X	At each occurrence

1. If a patient is still alive 2 years after randomization, no further follow-up is required.
2. Attach a copy in RAVE for documentation of progression on the Supporting Documentation Form.

19.0 Budget

19.1 Costs charged to patient:

Each site should review the test schedule (Section 4.0) taking into account local and regional coverage policies to determine which items are standard of care and which are research at their site. Refer to the payment synopsis for funding provided per accrual for covering study costs, as well as any additional invoiceables that may be allowed.

19.2 Tests to be research funded: Blood and tissue correlative collection and analysis.

19.3 Other budget concerns: Placebo/selumetinib provided by AstraZeneca.

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ACCRU Informed Consent Template for Cancer Treatment Trials (English Language)

***NOTES FOR LOCAL INVESTIGATORS**

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This template for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is [redacted]

- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.

- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer…What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at *https://cissecure.nci.nih.gov/ncipubs/* or call 1-800-4-CANCER (1-800-422-6237) to request a free copy.

- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

Randomized Double-Blind Phase II Study of Radioactive Iodine (RAI) in Combination with Placebo or Selumetinib for the Treatment of RAI-Avid Recurrent/Metastatic Thyroid Cancers

This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this research study because you have thyroid cancer that has spread and could potentially be treated with radioactive iodine.

Why is this research study being done?

The purpose of this research study is to find out if radioactive iodine is more effective when used in combination with the study drug, selumetinib, for the treatment of thyroid cancer that has spread.

Many thyroid cancers absorb iodine. Because of this, doctors often give radioactive iodine alone to treat thyroid cancer as part of standard practice. It is thought that the more thyroid tumors are able to absorb radioactive iodine, the more likely it is that the radioactive iodine will cause those tumors to shrink.

The goal of this study is to find out if selumetinib can help radioactive iodine work better in patients whose tumors still absorb radioactive iodine. To figure this out, treatment with radioactive iodine plus a placebo in one group of patients will be compared to treatment with radioactive iodine plus selumetinib in another group of patients. A placebo is an inactive substance that looks the same as, and is given the same way as, the active study drug being tested (selumetinib, in this case).

In this study, you will get either the radioactive iodine and a placebo, or the radioactive iodine and selumetinib. You will not get both. The effects, good and/or bad, of radioactive iodine plus placebo or radioactive iodine plus selumetinib on you and your thyroid cancer will be studied.

How many people will take part in the research study?

About 60 people will take part in this study. These people will be randomly divided into two groups of 30 people per group. One group will receive radioactive iodine plus selumetinib; the other group will receive radioactive iodine plus a placebo.

What will happen if I take part in this research study?

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Medical history and physical exam, including pulse, blood pressure, height, weight and an assessment of how well you perform activities of daily living.
- Routine blood tests. About 2 teaspoons of blood will be drawn.
- Eye exam.
- A pregnancy test done by taking a blood sample from a vein in your arm within 28 days of being registered on the study (if you are a woman of childbearing potential).
- A measurement and evaluation of your tumor by MRI and/or CT scan.
- An echocardiogram and electrocardiogram to look at your heart and heart valves to see how well they are working.
- A check to see if any of the side effects that may be caused by the study drugs are already present.

During the study

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care. They are being done more often because you are in this study.

- Physical exam, which may include pulse, blood pressure, weight and a test of how well you perform activities of daily living.
- Routine blood tests. About 2 teaspoons of blood will be drawn.
- Pregnancy test (if applicable).

You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body.

- Physical exam, which may include pulse, blood pressure, weight and a test of how well you perform activities of daily living.
- Routine blood tests. About 2 teaspoons of blood will be drawn.
- A measurement and evaluation of your tumor by MRI and/or CT scan.
- Pregnancy test (if applicable).

Research Tests

- A blood sample for research tests is required for this study. Before treatment starts, the research blood sample will be taken at the same time as the routine blood samples by drawing some blood from a vein. About 2 additional teaspoons of blood will be drawn.
- Mandatory tumor tissue submission: This study also includes research tests that will be performed on tumor tissue samples that you will provide. These samples should be tissues that were obtained from *previous* surgeries or biopsies; *no additional tumor tissue will be taken from you during this study*.

Some of the research tests done on the research blood and tissue samples are genetic tests. Because these genetic tests are not used for regular medical care, neither you nor your doctor will be told the results of the test(s). The test results will not be put in your medical record either.

There is more information about these research tests at the end of this form.

You will be "randomized" into one of the study groups described below.

Randomization means that you are put into a group by chance, as in the flip of a coin. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in either group. In the event of an emergency, your doctor may contact the sponsor to learn which group you have been placed in. This is called "unblinding".

You will take the study drug (selumetinib or placebo) in pill form, by mouth, two times every day beginning on day one of the first week, and continue taking this until 2 days after you receive the radioactive iodine (^{131}I) therapy.

After about two weeks of treatment with selumetinib or placebo, you will be asked to start a low-iodine diet for the 5 days before the process for ^{131}I therapy is started. You will continue on the low-iodine diet until one day after you receive the ^{131}I therapy. A sample diet and instructions will be provided by your study doctor.

After about three weeks of treatment with selumetinib or placebo, you will receive two injections of Thyrogen™ to help the thyroid cancer cells to take up radioactive iodine. You will not need to stop your thyroid hormone replacement, so you should not suffer from symptoms of hypothyroidism. After the Thyrogen™ injections, you will be treated with ^{131}I. If you are younger than 70 years old, you will receive about 150 mCi of ^{131}I. If you are 70 years or older, your doctor will decide what dose, from about 100 mCi to about 150 mCi, would be appropriate for you. Lower doses may be given if your doctor determines this is safer for you.

You will be asked to keep a daily record of when you take the study medication (Patient Medication Diary), and every day write down the day and time you take the medication. If you notice any side effects, you can include this information in the Comments section of the diary.

Things to avoid while participating in this study:

- Do not spend time in the sun; if you do spend time in the sun, only stay out for a short period of time and be sure to use sunscreen protection.

- Do not donate blood.
- Do not use a vitamin E supplement.
- Do not become pregnant; both males and females should *use contraception* when engaging in sexual activity while participating in this study and for up to 3 month *after* taking the last dose of study medication.
- Do not breastfeed.

Study Calendar
You will take selumetinib or placebo (75 mg by mouth) twice every day beginning on day 1 of week 1 through 2 days following ^{131}I therapy, (a total of approximately 30 days) during this study. The chart below shows what will happen to you during the treatment period and future follow-up visits as previously explained. The left-hand column shows the day in the study period and the right-hand column tells you what to do on that day.

Selumetinib or Placebo	
All Patients in Both Groups 1 and 2	
Day	**What you do**
Up to 28 days before starting study	• Medical history and physical exam, including pulse, blood pressure, height, weight and an assessment of how well you perform activities of daily living. • Routine blood tests. • Mandatory research blood sample. • Pregnancy test (if applicable). • Eye exam. • MRI and/or CT scan for tumor measurement. • Echocardiogram and electrocardiogram. • Mandatory archival tissue collection. (NOTE: Receipt of archival tumor tissue is not required for study registration and initiation of therapy.)
Week 1	• Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living. • Routine blood tests. NOTE: this does not need to be repeated if the pre-registration blood work was done within 7 days or less before starting the study drug (selumetinib or placebo). • Begin taking selumetinib or placebo twice each day on an empty stomach (1 hour before or 2 hours after a meal), approximately 12 hours apart with a glass of water. Keep taking selumetinib or placebo twice each day until the end of study, unless told to stop by your health care team. • Each day, in the Patient Medication Diary, write down when you take the study medication and any side effects you notice.

Week 2	• Continue taking selumetinib or placebo twice each day on an empty stomach (1 hour before or 2 hours after a meal), approximately 12 hours apart with a glass of water. Keep taking selumetinib or placebo twice each day until the end of study, unless told to stop by your health care team. • Each day, in the Patient Medication Diary, write down when you take the study medication and any side effects you notice.
Week 3	• Begin low iodine diet (5 days before treatment with Thyrogen™). • Medical history and physical exam, including blood pressure, weight and an assessment of how well you perform activities of daily living. • Routine blood tests. • Continue taking selumetinib or placebo twice each day on an empty stomach (1 hour before or 2 hours after a meal), approximately 12 hours apart with a glass of water. Keep taking selumetinib or placebo twice each day until the end of study, unless told to stop by your health care team. • Each day, in the Patient Medication Diary, write down when you take the study medication and any side effects you notice.
Week 4	• Pregnancy test (if applicable). • Receive two injections of Thyrogen™ over two days. • Receive radioactive iodine therapy (^{131}I therapy). • Continue taking selumetinib or placebo twice each day on an empty stomach (1 hour before or 2 hours after a meal), approximately 12 hours apart with a glass of water. Keep taking selumetinib or placebo twice each day until 2 days after you receive the radioactive iodine therapy (^{131}I therapy), unless told to stop by your health care team. • Each day, in the Patient Medication Diary, write down when you take the study medication and any side effects you notice. • Continue the low-iodine diet for 1 day after you receive the radioactive iodine therapy (^{131}I therapy).

When I am finished with treatment

When you finish treatment, you will need the following tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.

Study Calendar Following Completion of Therapy

When	What you do
One month after receiving ^{131}I	• Medical history and physical exam, including pulse, blood pressure, height, weight and an assessment of how well you perform activities of daily living. • Routine blood tests. • Assessment of side effects.
Every 3 months after receiving ^{131}I	• MRI and/or CT scan for tumor measurement. • Thyroid tests, including thyroglobulin.
12 months following ^{131}I, every 6 months up to 2 years after starting the study	• MRI and/or CT scan for tumor measurement. • Thyroid tests, including thyroglobulin.

How long will I be in the research study?

We will continue to follow you for up to 2 years from the date you were randomized on the study.

Can I stop being in the research study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the selumetinib can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the research study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the selumetinib. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to selumetinib include those which are:

Likely risks of Selumetinib (events occurring greater than 20% of the time)

- Loose stools (Diarrhea)
- Urge to vomit (Nausea)
- Throwing up (Vomiting)
- Swelling of the extremities (arms and/or legs)
- Feeling tired (Fatigue)
- Acne/skin rash

Less likely risks of Selumetinib ***(events occurring less than or equal to 20% of the time)***

- Decrease in red blood cells, which are the oxygen carrying cells, which could make you feel tired (Anemia)
- Decrease in white blood cell (neutrophil) count and potential for increased infection risk (sepsis)
- Decrease in platelet cell count (required for blood clotting)
- Decrease in lymphocyte count (involved in immune system)
- Blurred vision
- Swelling or feeling of fullness and tightness in the abdomen (belly)
- Belly pain
- Difficulty passing stool (Constipation)
- Irritation or sores in the mouth Swelling of the face
- Fever
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver enzyme (AST/SGOT)
- Increased blood levels of phosphate
- Loss of appetite (anorexia)
- Joint pain
- Back pain
- Sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking (Dizziness)
- Headache or head pain
- Feelings of sadness, worthlessness, thoughts of suicide or death (Depression)
- Difficulty sleeping or falling asleep
- Cough
- Shortness of breath
- Hair loss
- Dry skin
- Nail changes
- Itching Skin rash with the presence of macules (flat discolored area) and papules (raised bump)
- High blood pressure (hypertension)
- Low blood potassium
- Increased levels of creatinine phosphokinase/creatinine kinase
- Skin infections (in combination with docetaxel)
- Oral stomatitis (in combination with docetaxel), (mouth blisters/sores)
- Dry mouth

Rare but serious risks of Selumetinib ***(events occurring less than 2-3% of the time)***

- Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (Systole) and heart failure

- Problems/damage with the retina portion of the eye, which can lead to blurred vision.
- Intestinal perforation (a hole in the bowel)
- Kidney injury
- Liver injury/failure
- Interstitial lung disease (in combination with docetaxel)
- Pneumonitis (in combination with docetaxel)
- Pneumonia (in combination with docetaxel)
- Febrile neutropenia (in combination with docetaxel), (Fever with dangerously low white blood cell count)
- Low albumin
- Reproductive risks: Adverse effects on offspring growth and development (including malformations, cleft palate, eye changes)

When selumetinib is used in combination with radioactive iodine, the number of patients with side effects or the strength of some side effects associated with either treatment may be increased. We do not know what these risks may be.

Early information from clinical studies in people of Asian origin, which have looked at the levels of selumetinib in the blood, suggest that people of Asian origin may experience higher blood levels of selumetinib than other people (who are not of Asian origin). Higher levels of selumetinib in the blood may cause a greater amount of side effects. Your Study Doctor will discuss whether this information has any effect on your participation in this study.

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. Women of child-bearing potential and men must agree to use adequate contraception prior to study entry, for the duration of study participation, and 6 months after completion of radioactive iodine plus either placebo or selumetinib. Adequate contraception could be either 1) hormonal/non-hormonal pill PLUS a barrier method (e.g. male condom) or 2) total abstinence.

Selumetinib/placebo capsules contain vitamin E. While taking study medication, you will be asked not to take any supplemental vitamin E because high levels of vitamin E can interrupt the body's clotting processes. If you are currently taking anticoagulant (blood clotting such as warfarin) medications, additional blood tests may be ordered to monitor your clotting ability while you are taking study medication if your physician feels it is necessary. Your physician may also adjust your anticoagulant medication dosage if necessary.

As with any medication, allergic reactions are a possibility

The risks of drawing blood include pain, bruising or rarely infection at the needle site.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the research study?

Taking part in this study may or may not make your health better. While doctors hope using selumetinib in addition to radioactive iodine therapy will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about adding selumetinib to radioactive iodine therapy as a treatment for cancer. This

information could help future cancer patients.

What other choices do I have if I do not take part in this research study?
You do not have to be in this study to receive treatment for your cancer.

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Also, your records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- Local Institutional Review Boards;
- Pharmaceutical company supporting the study (AstraZeneca);
- Your insurance company (if charges are billed to insurance);
- International Thyroid Oncology Group (ITOG);
- Academic and Community Cancer Research United (ACCRU) Coordinating Center.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of study results. You can search this Web site at any time.

Tests done at hospitals or clinics other than the study clinic

If you have blood tests or other medical tests such as scans or x-rays at a clinic or hospital other than the study clinic *[insert name of institution]*, your study doctor may need to review results of these tests as they relate to this study.

Please read the following statements and mark your choice:

I permit _____ *[investigator's name(s)]* to obtain medical information from my primary care giver _____*[primary caregiver's name(s)]* as it relates to this study. This may include information regarding any blood tests, x-rays or scans.

Will I be paid for taking part in this study?

You will not be paid for taking part in this study.

What are the costs of taking part in this research study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Tests such as physical examinations, scans, Thyrogen™, radioactive iodine, and routine blood tests that would normally be performed as part of your regular medical care will be the responsibility of you and your health plan.

You will not need to pay for any tests done only for research. This would involve the research studies done on the blood and tissue samples.

The study agent, selumetinib or placebo, will be provided free of charge while you are taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this research study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this research study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the research study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

About Using Biological Samples for Research

This study also has laboratory tests that will be performed to study small samples of blood and tissue. A blood sample will be done by drawing some blood from a vein. The blood will be taken just before treatment starts. The biopsy tissue sample will be from your original biopsy. No additional biopsies will be done to get this tissue.

The blood and tissue will be sent to ACCRU/ITOG laboratories where the tests will be done. These tests will be done in order to understand how your cancer responds to treatment. It is hoped that this will help investigators better understand your type of cancer. The results of these tests will not be sent to you or your study doctor and will not be used in planning your care. These tests are for research purposes only and you will not have to pay for them.

Please read the following statements and mark your choice:

1. I agree to provide blood samples to ACCRU/ITOG laboratories for research testing planned as part of this study:

   ☐ Yes ☐ No Please initial here: _____ Date: _____

2. I agree to provide my original biopsy tissue sample(s) to ACCRU/ITOG laboratories associated with ACCRU, for research testing planned as part of this study:

☐ Yes ☐ No Please initial here: _____ Date: _____

We would like to keep some of the blood and tissue that is left over for future research. If you agree, these samples will be kept and may be used in research to learn more about cancer and other diseases. Please read the booklet called "Providing Your Tissue For Research: What You Need To Know" to learn more about tissue research. A copy of this booklet can be found at: http://www.cancer.gov/publications/patient-education/providing-tissue.

Your blood and tissue may be helpful for research whether you do or do not have cancer. The research that may be done with your blood and tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your blood and tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep left over blood and tissue for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your blood and tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then any blood and tissue that remains will no longer be used for research.

In the future, people who do research may need to know more about your health. While ACCRU may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes blood and tissue is used for genetic research (about diseases that are passed on in families). Even if your blood and tissue are used for this kind of research, the results will not be put in your health records.

Your blood and tissue will be used only for research and will not be sold. The research done with your blood and tissue may help to develop new products in the future.

Benefits

The benefits of research using blood and tissue include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice
Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at [*insert the IRB's phone number]*.

No matter what you decide to do, it will not affect your care.

1. My blood may be kept for use in research to learn about, prevent, or treat cancer.

☐ Yes ☐ No Please initial here: _____ Date: _____

2. My blood may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

☐ Yes ☐ No Please initial here: _____ Date: _____

3. My tissue may be kept for use in research to learn about, prevent, or treat cancer.

☐ Yes ☐ No Please initial here: _____ Date: _____

4. My tissue may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

☐ Yes ☐ No Please initial here: _____ Date: _____

If you want your sample(s) destroyed at any time, write to the Secretary of the _____ Institutional Review Board _____.

ACCRU/ITOG has the right to end storage of the sample(s) without telling you.

The sample(s) will be the property of ACCRU/ITOG. Outside researchers may one day ask for a part of your sample(s) for studies now or future studies.

How do outside researchers get the sample?
Researchers from universities, hospitals, and other health organizations do research using blood and tissue. They may call ACCRU and ask for samples for their studies. ACCRU looks at the way that these studies will be done, and decides if any of the samples can be used. ACCRU sends the samples and some information about you to the researcher. ACCRU will not send your name, address, phone number, social security number, or any other identifying information to the researcher. If you allow your sample(s) to be given to outside researchers, it will be given to them with a code number. If researchers outside ACCRU use the sample(s) for future research, they will decide if you will be contacted and, if so, they would have to contact the researchers at ACCRU. Then ACCRU will contact the clinic where you registered for this study, who will contact you.

Please read the following statements and mark your choice:

I permit ACCRU/ITOG to give my sample(s) to outside researchers:

☐ Yes ☐ No Please initial here:_____ Date:_____

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Printed Participant Name: _____

Participant Signature: _____

Date: _____

Printed name of person obtaining informed consent:

_____

Signature of person obtaining informed consent:

_____

Date _____

This model informed consent form has been reviewed by the ACCRU and is the official consent document for this study. Local IRB changes to this document are allowed. Sections "What are the risks of the research study" or "What other choices do I have if I don't take part in this research study?" should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the Academic and Community Cancer Research United (ACCRU) Operations Office for approval before a patient may be registered to this study.

Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This information should be specific for each institution.

PATIENT'S MEDICATION DIARY

Today's date _____
Patient Name_____ Patient Study ID __RU241306I_____
(initials acceptable)

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 28-day cycle.
2. You will take your dose **[_____ mg (_____ 25 mg pills)]** TWICE each day **(for a total dose of _____ mg per day)** beginning on Week 1, Day 1 and continued through 2 days after therapeutic ^{131}I therapy has been administered . It is recommended to take selumetinib (or placebo) on an empty stomach (1 hour before or 2 hours after a meal), approximately 12 hours apart with a glass of water. (NOTE: Avoid excessive sun exposure and use adequate sunscreen protection if sun exposure is anticipated. Do not take vitamin E or multivitamin supplements that provide a total daily dose in excess of 100% of the recommended daily allowance for vitamin E.)
3. Record the date and the time you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
3. Bring your pill bottle and this form to your physician when you go for your next appointment.

Date	Day	Time Taken	Comments	Date	Day	Time Taken	Comments
	1				11		
	2				12		
	3				13		
	4				14		
	5				15		
	6				16		
	7				17		
	8				18		
	9				19		
	10				20		

Date	Day	Time Taken	Comments	Date	Day	Time Taken	Comments
	21				26		
	22				27		
	23				28		
	24				29		
	25				30		

Patient's Signature: _____ Date: _____

Physician's Office will complete this section:

1. Date patient started protocol treatment ____
   Date patient was removed from study
2. Patient's planned daily dose_____ ____ _____
   Total number of pills taken this month

Physician/Nurse/Data Manager's Signature _____

The Low Iodine Diet

What is Iodine?
Iodine is a mineral. It plays an important role in several processes that take place in the body. One is the production of a hormone called thyroxine, which occurs in the thyroid gland.

Where is Iodine Found?
The amount of iodine found in food varies. Much of the iodine we get comes from iodized salt and breads. Adults need 150 micrograms of iodine a day. This booklet describes a low iodine diet. This is a diet with less than 50 micrograms of iodine per day.

Why is a Low Iodine Diet Necessary?
The iodine in your diet can block the uptake of radioactive iodine by the thyroid gland. Your doctor could put you on a low iodine diet one or two weeks before you get the radioactive iodine. Stay on this diet until your test or treatment is complete. Your doctor will tell you when to begin and when to stop this diet. If you have any questions, speak with your doctor. You may also see a dietitian if necessary. If you have any questions about your diet, call (212) 639-7312 to speak to a dietitian.

What Should You Avoid?

Read all food labels to check for iodine content. Do NOT eat or use:

- Iodized salt.
- Sea salt in any form.
- Onion salt.
- Celery salt.
- Garlic salt.
- Seasoned salt.
- Kelp (seaweed).
- Any food that has:
  - Iodates
  - Iodides
  - Algin
  - Alginates
  - Carrageen
  - Agar
- Commercial breads and bakery products because they often contain iodate.
- Milk (except for 1 ounce a day), eggs, and seafood.
- Vitamins and food supplements if they have iodine. If you have any doubt, do not take them.
- Food, pills, or capsules with food dyes or that are orange, red, or brown in color. Examples include red or pink cereals or candies.
- Antiseptics, such as tincture of iodine (Betadine®) applied on a cut.
- Cough medicines (especially those with red coloring).
- Supplements such as:
  - Ensure®
  - Boost®
  - Commercial shakes
  - Nutrament®
- Restaurant and processed foods, because they are often high in iodine content.
- Soy products such as edamame, tofu, soy burgers (e.g., Boca®), etc.

- All canned foods, because the lining of the can contains iodine.

Do not stop taking any of your medicines unless your doctor tells you. If you are receiving tube feeding formula, ask your dietitian or doctor what to do. This low iodine diet does not meet the suggested daily allowance for all nutrients. You will be on it for a short time only.

Drink Plenty of Fluids
Note: Unless your doctor tells you differently, you must drink at least 8 to 10, 8-ounce cups of fluid a day. This includes the drinks in the diet guidelines and as much water as you want.

Low Iodine Diet Guidelines:

Breads and Cereals
Total number of servings per day: 6-8
(1 serving equals 1 slice of bread or 1/2 cup of cooked pasta)

Include
Plain cooked barley, oats, millet, buckwheat, bulgur wheat, quinoa; unsalted, unprocessed preservative-free boxed cereals such as puffed rice and shredded wheat; rice, plain macaroni, spaghetti, noodles; cream of rice or cream of wheat hot cereals; unsalted rice cakes, unsalted plain matzah, English muffins, plain unsalted popcorn, homemade breads prepared without commercial dough.

Avoid
All commercial breads and rolls, processed boxed cereals, salted crackers, potato chips, pretzels, bagels, bialys, Melba toast, all other crackers, egg noodles, packaged rice and pasta mixes.

Meat and Meat Substitutes
Total number of servings per day: Two–three
(1 serving equals 3 ounces of meat, fish, poultry, or 2 Tablespoons of unsalted peanut or almond butter)

Include
Fresh beef, veal, pork, lamb, chicken and turkey; unsalted peanut or almond butter; fresh-water fish such as carp, river bass, lake trout, and river perch; fresh egg white.

Avoid
Egg yolks and whole eggs, foods made with eggs; all fast foods; all canned fish such as salmon and tuna; seafood, shellfish (clams, crabs, oysters, lobsters), or any food made with fish stock; all processed meats; liver and all organ meats; all canned, dried, salted, or cured meats such as bacon, sausage, ham, frankfurters, chipped beef, luncheon meats (salami, bologna, pastrami); spicy meats such as chili, beef jerky, liverwurst; all canned or processed poultry such as turkey or chicken roll; tofu and soy products, such as soy burgers (e.g., Boca); salted peanut butter.

Milk and Milk Products
Total number of servings per day: Zero

Include
None allowed
Exception: Only 1 ounce of milk a day in your coffee or tea.

Avoid
All milk (except for one ounce daily) and milk products such as condensed or evaporated milk, cheese, yogurt, puddings, ice cream, custard; any cream such as heavy or light cream, whipped cream, sour cream; any foods made with cream or milk or cheese such as cream soup, pizza, macaroni and cheese.

Fruits
Total number of servings per day: Five
(1 serving equals 1 small piece of fruit or 3/4 cup of juice)

Include
All fresh fruit, exception: limit bananas to 1 serving per day; fresh apple sauce; all natural frozen fruits; fresh fruit juices (including bottles or cartons of fruit juice without artificial coloring or preservatives); white grape juice.

Avoid
Cranberries, all dried fruits, all canned fruits and canned fruit juices; jarred applesauce; cranberry and grape juice, canned or bottled cherries; rhubarb.

Vegetables
Total number of servings per day: Four
(1 serving equals 1/2 cup of cooked or 1 cup raw vegetable)

Include
All fresh vegetables except spinach, fresh potatoes without skin, all plain frozen vegetables without added salt, fresh or dried legumes such as lentils and peas.

Avoid
All canned vegetables and all canned vegetable juices, fresh or dried beans such as red kidney beans, lima beans, navy beans, pinto beans and cowpeas; canned legumes (such as beans, peas, and lentils); canned soups; sauerkraut, celery; commercially prepared potatoes (e.g. instant mashed potatoes); frozen vegetables with added salt; spinach.

Fat
Total number of servings per day:
Suggest four to six servings a day
(1 serving equals 1 teaspoon of butter or oil)

Include
Unsalted margarine or sweet butter (not more than 1 teaspoon of each per day), oils, vegetable shortening, plain oil and white vinegar dressing.

Avoid
Salted nuts and seeds, mayonnaise, commercial salad dressings, and lard.

Beverages
Total number of servings per day: No restrictions
One serving equals 12 ounces of a carbonated beverage or 1 cup
(8 ounces) of any of the other beverages listed

Include
Water; bottled carbonated beverages without added coloring (such as Sprite®, 7-Up®, sodium-free seltzer); brewed coffee, tea steeped from tea leaves; white tea bags; fresh lemonade or fresh orangeade.

Avoid
Mineral water containing sodium; all bottled, canned, or powdered: iced tea, lemonade, instant coffee, instant tea, instant iced-tea, fruit punch, and other powdered or commercial drinks, such as Hi-C® and Kool-Aid®; tea steeped from tea bags; soy milk and rice milk (which contain sea salt); ginger ale, Coke®, Pepsi® or any other carbonated beverages with added coloring.

Desserts and sweets
Total number of servings per day: Two
(See below for serving equivalents)

Include
Each of the following equals 1 serving:
- 1 cup Knox® clear gelatin
- 2 tablespoons (T) sugar
- 2T Honey
- 2T Maple syrup
- 2 regular size Marshmallows
- 1/2 cup Natural sorbets with no coloring or added salt

Avoid
All bakery products such as pies, cakes, pastries, danishes, muffins, donuts and cookies; graham crackers; Jell-O®, colored gelatins; chocolate and chocolate desserts; candy.

Miscellaneous
Total number of servings per day: Unlimited

Include
Pepper, spices such as cinnamon; herbs such as oregano; white vinegar, and non-iodized salt (contains trace amounts of iodine, use sparingly).

Avoid
All salted foods such as salted nuts, Chinese food, soy sauce, catsup, Worcestershire sauce, chili sauce, all commercial sauces, tomato sauce, all gravies, olives, pickles, relish, bouillon cubes, soup bases, iodized salt, sea salt, onion salt, garlic salt, celery salt, seasoned salt, kelp (seaweed); molasses; any food containing food coloring, iodates, iodides, iodate dough conditioners or stabilizers, algin, alginate, carrageens, agar, or nori (seaweed); all sushi; red wine vinegar, balsamic vinegar (with caramel coloring); all additives, preservatives, or artificial colorings.

Sample Menu for a Low Iodine Diet

BREAKFAST
1 Fruit 1⁄2 cup orange juice
3 Breads 1⁄2 cup oatmeal (no milk)
1 plain unsalted matzah
1 Meat 1 egg white omelet
Misc. 2 teaspoons sugar

1 Beverage 1 cup brewed coffee

MID MORNING SNACK
1 Fruit 2 Rice cakes
1 teaspoon unsalted butter
1 cup water

LUNCH
1 Meat 3 oz fresh turkey breast
2 Fats 2 tsp oil
2 Breads 2 slices homemade white bread
1 Vegetable 1 cup Romaine lettuce
1 Beverage 1 cup fresh lemonade

MID AFTERNOON SNACK
1 Fruit 1 fresh apple
1 Meat 2 tablespoons unsalted peanut butter
DINNER
1 Meat 3 oz roast beef
2 Breads 1 baked potato (no skin)
2 Vegetables 1 cup fresh broccoli
2 Fats 2 tsp oil (used in cooking)
1 Fruit 1 orange
1 Beverage 1 cup white tea

BEDTIME SNACK
1 Fruit 1 small pear
1 Beverage 1 cup tea made from fresh tea leaves

1275 York Avenue, New York, New York 10065
Revised 2002, 2004, 2006, 2008

Guidance For Management and Investigation of Selumetinib Related Adverse Events

The following are recommended, not mandatory, assessments and/or interventions for potential selumetinib-related adverse events.

1. **Recommendations for diarrhea management**
   Diarrhea may occur during treatment with selumetinib (AZD6244) and action should be taken as soon as symptoms develop. The recommendations for diarrhea management in are based on guidelines from the American Society of Clinical Oncology (J Clin Oncol 2004; 22:2918-26). These guidelines recommend that treatment-induced diarrhea should be carefully monitored and treated aggressively to ensure that severe complications are avoided and that treatment is not delayed.

   Patients should be made aware that they are likely to experience diarrhea and be encouraged to record the number of stools and report possible associated symptoms

   Patients should be given loperamide (in accordance with local regulation and local practice) to take home with them and be advised to start immediately after the first episode of unformed stool.

   Patients should be given dietary advice in case of diarrhea (e.g. BRAT [bananas, rice, apple sauce, toast, plain pasta] diet; readily digestible food; avoidance of lactose-containing products, fried, fatty or spicy food) and increase fluid intake (8–10 glasses of clear fluids daily, including water and fluids containing salt and sugar, such as sports drinks and clear broth).

   Patients should seek advice early, from their physician or study nurse, if

   - Persistent Grade 1 or 2 diarrhea (see 2.2) or
   - Grade 3 or 4 diarrhea
   - Diarrhea becomes complicated by associated vomiting or inability to take oral fluids; marked abdominal distension or cramping; bloody stools, fever or symptoms of hypotension.

Table 1 CTCAE (version 4) grading for diarrhea

CTCAE Grade	Patients without colostomies	Patients with colostomies
Grade 1	Increase in number of stools per day (<4)	Mild increase in loose watery colostomy output compared with pre-treatment
Grade 2	Increase in number of stools per day (4-6) or nocturnal episodes	Moderate increase in loose watery colostomy output compared with pre-treatment, not interfering with normal activity
Grade 3	Increase of more than 7 stools per day or incontinence or needing support for dehydration.	Severe increase in loose watery colostomy output compared with pre-treatment and interfering with normal activity
Grade 4	Life-threatening consequences (eg, hemodynamic collapse)	

Initial management of uncomplicated Grade 1 or 2 diarrhea
Patients should **immediately** start loperamide after the first episode of diarrhea (4 mg initially) and continue loperamide (2 mg every 4 hours or after each unformed stool) until they have been free from diarrhea for at least 12 hrs

If **after 12 hours of loperamide treatment** the diarrhea is not improving or resolved, the patient should be instructed to contact the center and to increase to high dose loperamide (2 mg every 2 hours, or 4 mg every 4 hours at night) and continue to take loperamide until they have been free from diarrhea for at least 12 hrs. Additional treatment may be considered according to local practice.

Management of persistent (>24h) Grade 1 or 2 diarrhea despite loperamide at high dose
The patient should be seen by the physician or study nurse for full evaluation and the following should be considered:

- Rehydration and electrolytes replacement as appropriate
- Infectious causes and etiologies such as Clostridium difficile or viral gastroenteritis;
- Antibiotics if appropriate (for example an oral fluroquinolone for 7 days) particularly if the patient is neutropenic ($<1 \times 10^9$/L) or has a fever;
- Discontinuation of loperamide and start of octreotide (Sandostatin);

It may also be appropriate to consider:

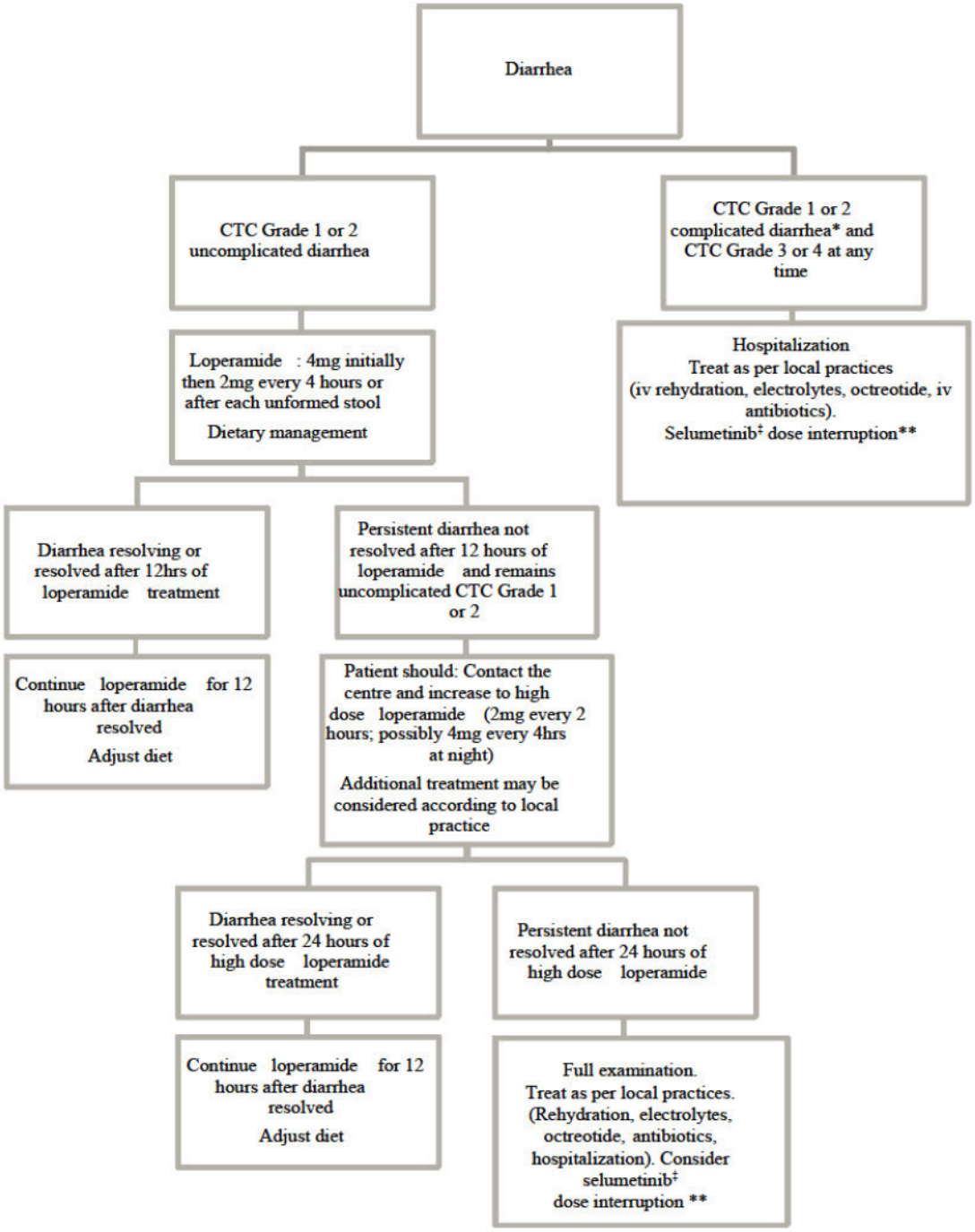
- Addition of other second-line anti-diarrheal agents according to local practice
- Selumetinib (or matching placebo) interruption until resolution of the diarrhea
- Hospitalization

In studies involving combination of selumetinib (or matching placebo) with other anti-cancer treatment, interruption or delay of the combination agent may be considered according to manufacturer's guidance or local practice.

Management of any grade uncontrolled or complicated diarrhea, or Grade 3-4 diarrhea
Hospitalization and full evaluation,
Intravenous fluids, electrolytes and antibiotics if needed (e.g. fluoroquinolone)
Interrupt selumetinib (or matching placebo) until diarrhea and associated symptoms resolve
Start octreotide (Sandostatin).

In studies involving combination of selumetinib (or matching placebo) with other anti-cancer treatment, interruption or delay of the combination agent may be considered according to manufacturer's guidance or local practice.

Figure 1. Guidance for the management of patients with diarrhea



*Diarrhea becomes complicated by associated vomiting or inability to take oral fluids; marked abdominal distension or cramping; bloody stools, fever or symptoms of hypotension
****Consider interruption or delay of combination anticancer agent if applicable**
‡ selumetinib or matching placebo
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2. Guidance for the Management of Patients with Rash

Recommendations to start on day 1 of treatment with selumetinib‡ and for the duration of treatment

- Use skin moisturizer (thick, alcohol-free) at bedtime
- Avoid excessive exposure to sunlight
- Use sunglasses/sunscreen (PABA-free, SPF ≥15; UVA and UVB protection) as needed
- Use of topical retinoids or benzoyl peroxide is not recommended

CTC Grade 1 rashes

Mild or moderate strength topical steroid

and/or topical antibiotic

CTC Grade 2 rashes

Moderate strength topical steroid

and oral antibiotic

CTC grade ≥3 rashes
CTC grade 2 rashes considered by the patient to be intolerable

Moderate strength topical steroid

and oral antibiotic
(consider broad spectrum/gram negative cover if infection suspected)

Consider referral to a dermatologist: manage rash per recommendation

Interrupt selumetinib‡ until rash improves to grade 2 or less

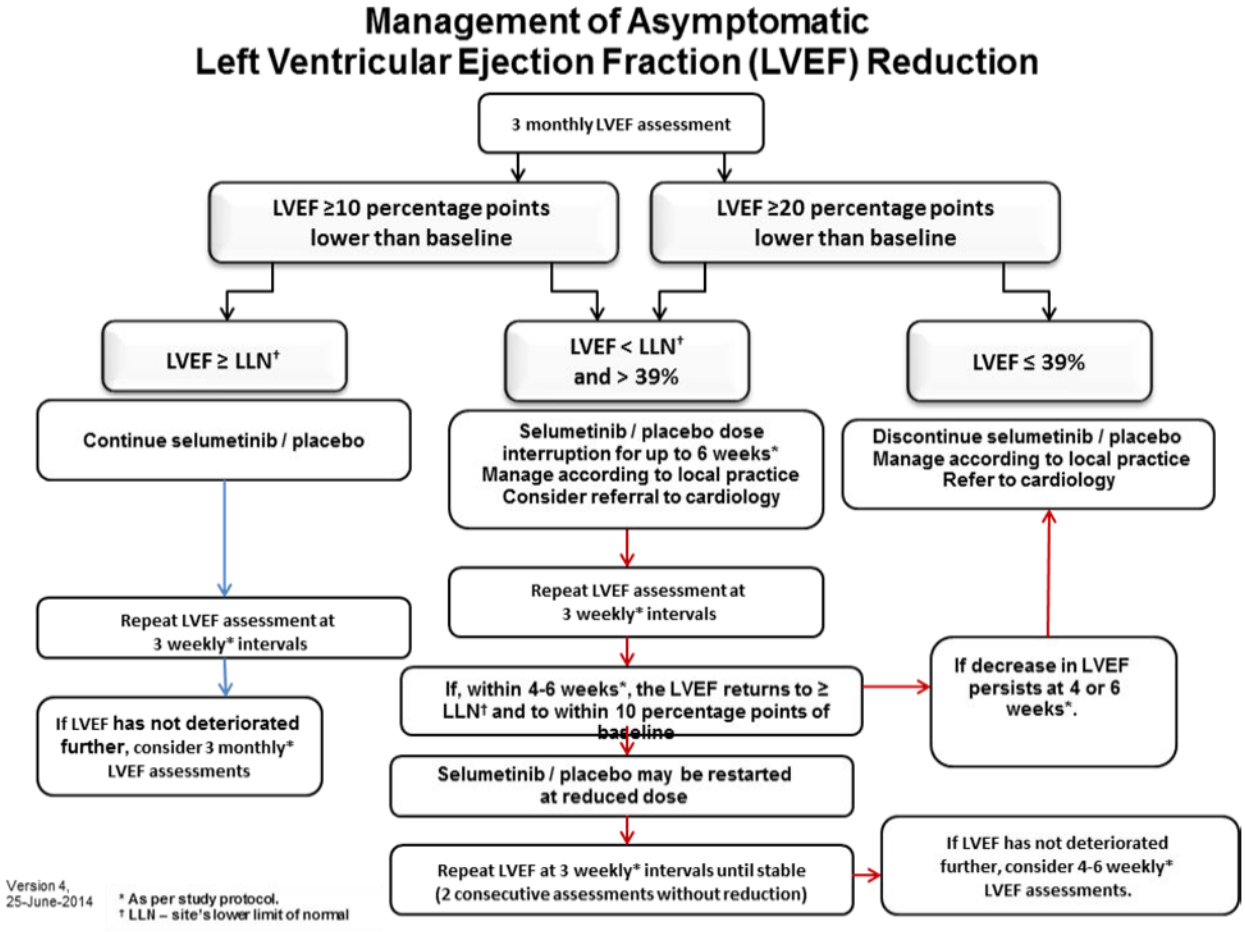
Selumetinib‡ may be restarted at original dose or reduced at the discretion of the investigator

Table 1: Example topical steroids and antibiotics (use according to local guidelines)

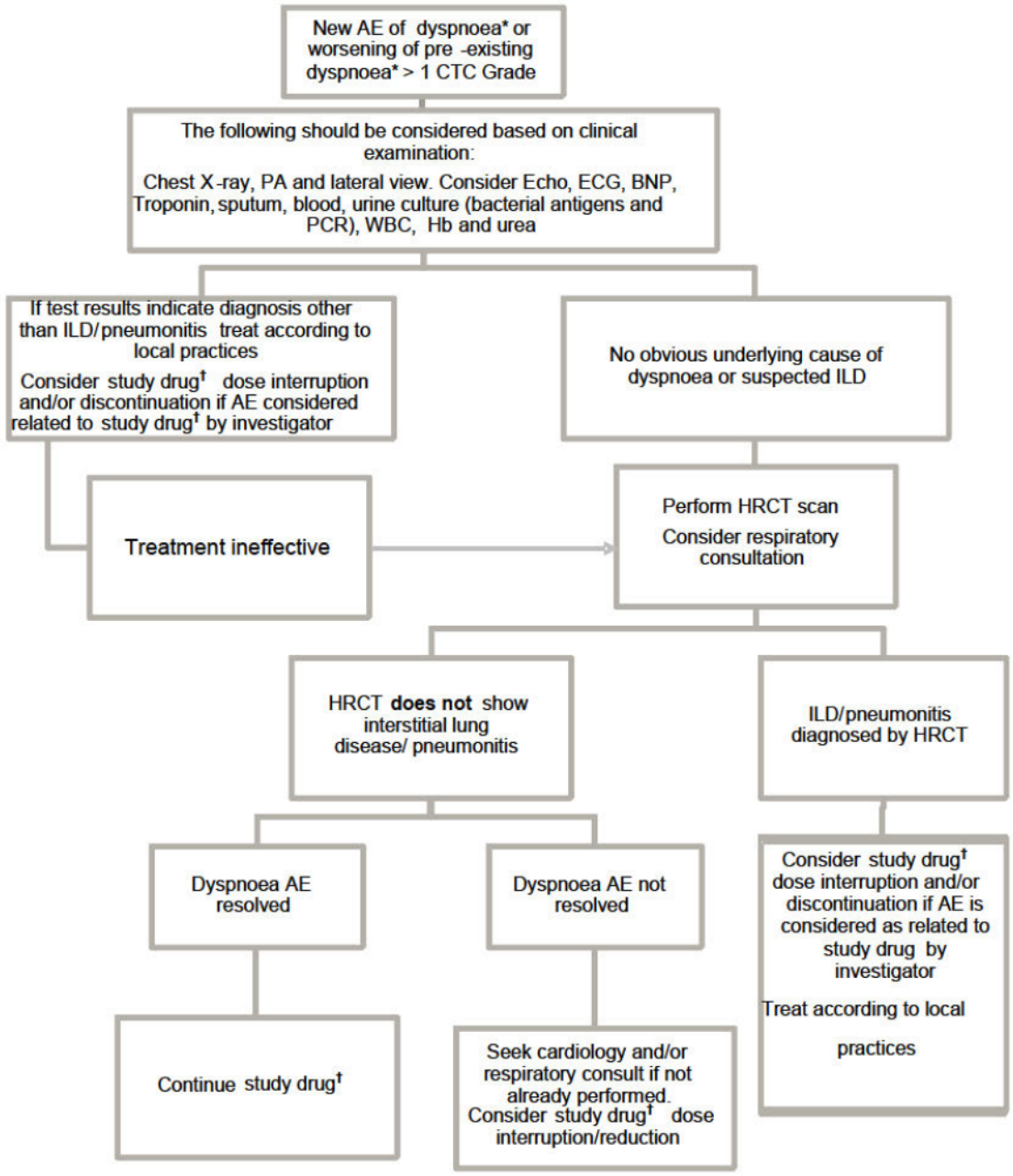
Topical steroids moderate strength	Triamcinolone acetonide 0.025% Fluticasone proprionate 0.05%	Desonide 0.05% Aclometasone 0.05%
Topical antibiotics	Clindamycin 1 - 2% Metronidazole 1%	Erythromycin 1% - 2% Silver sulphadiazine 1%
Oral antibiotics	Doxycycline 100 mg bd 500 mg bd	Minocycline 100 mg bd Oxytetracycline

‡ selumetinib or matching placebo

3. Guidance for management of patients with an asymptomatic reduction in LVEF (provided by AstraZeneca)



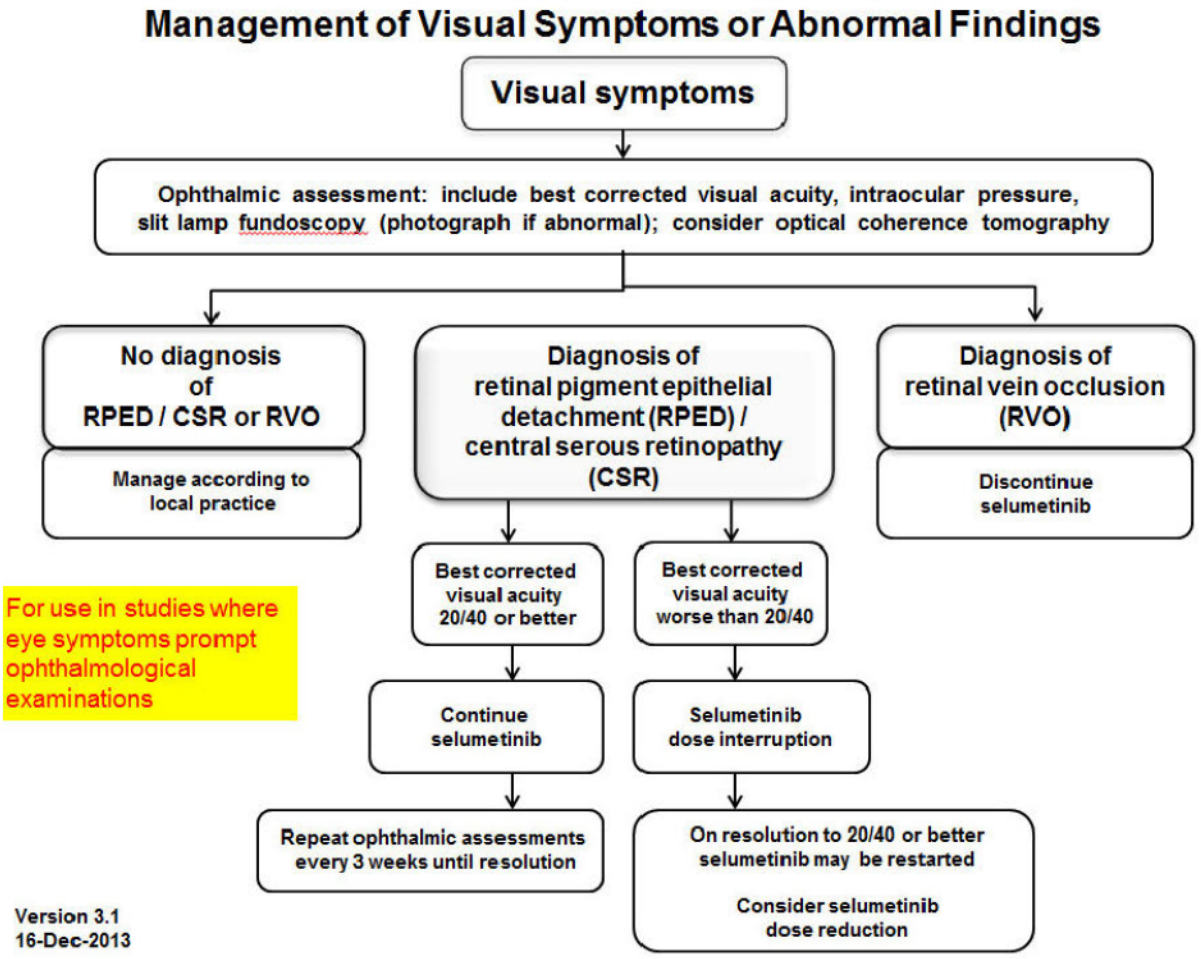
4. Guidance for investigation of patients with new/worsening dyspnea (provided by Astra Zeneca) (*not considered related to disease under study)



BNP: Brain Natriuretic
CTC: National Cancer Institute common toxicology
Echo: Echocardiography
Hb: Haemoglobin
HRCT: High resolution computerised

ILD: Interstitial Lung
PA: posteroanterior
PCR: Polymerase chain
WBC: White blood cells
Version: Final 3.0 23-Jul-2013

5. Guidance for management of patients with visual symptoms (provided by Astra Zeneca)



6. Recommendations of Oral Care (provided by Astra Zeneca)

Oral Care Recommendations for Patients treated with Selumetinib:
Patients should be encouraged to take responsibility for their own oral care wherever possible. This may require frequent encouragement and education. The general recommendations of Rubenstein et al (2004) are to maintain a clean and pain-free mouth which reduces patient discomfort and helps prevent infection and promote dietary intake. Evidence from the literature regarding implementation and efficacy of oral protocols and patient education, suggest that patients who are taught oral care protocols perform oral care more diligently, take more responsibility for their care and may show an improvement in oral symptoms.

Prevention, early diagnosis and management of stomatitis may reduce the need for dose interruption and / or reductions of the study medications due to severe stomatitis and so allow the patient to continue on the study drugs. It is strongly recommended that patients receive advice regarding daily oral health care regimes, both before and during treatment.

Mouthwashes:
Patients with a healthy mouth may use nonalcoholic mouthwash several times (4 to 6 times daily, or according to the instructions) daily (e.g. after each meal) during the study.

Saline mouthwashes (Sodium chloride 0.9%) should be preferred in cases of stomatitis, and should be used at a different time to tooth brushing (e.g. after tea).

Use of a mouthwash immediately after selumetinib intake is recommended.

The tongue can be gently brushed (if not sore) with a soft toothbrush.

Patients with, or at risk of, stomatitis should not use commercial / over-the-counter mouthwashes because of the alcohol content and astringency. Chlorhexidine mouthwashes are not recommended for the treatment of established stomatitis.

The mouth should be regularly inspected by the patient and healthcare professionals.

Smoking should be strongly discouraged; patients should be offered help with smoking cessation if necessary in the form of nicotine replacement therapy or referral to smoking cessation services.

A high alcohol intake should be discouraged and patients advised to avoid painful stimuli such as spicy foods, hot food and drink.

Dental care:

Dentate patients:

- Patients who are free from dental problems may be at less risk of stomatitis
- Teeth should be brushed twice daily with a fluoride toothpaste and soft toothbrush, in the morning before breakfast and last thing in the evening before bed, about 30 minutes after eating. Toothbrush should be replaced regularly, at least every 3 months. Patients with stomatitis should change their toothbrush every 4 - 6 weeks.
- Use of soft toothbrush is recommended
- Dental floss should be used once daily (caution in patients with coagulopathies including a low platelet count)

Edentulous patients:

- Dentures should be left out whilst at rest
- Dentures should be cleaned thoroughly twice daily (before and after soaking overnight) and after every meal using a soft toothbrush and denture cleaner water
- Dentures should be soaked overnight in a mild denture-soaking solution.

In the event of sore mouth or stomatitis:

- Consider treating stomatitis at an early stage (CTCAE grade 1) or as soon as the patient complains of a sore mouth.
- Consider using oral topical analgesic anesthesia with or without topical steroids, antiviral and/or antifungal medications depending on the patient's clinical condition and the local standard medical practice.

Recommended dental care

- **Brush teeth twice daily using a fluoride toothpaste and soft toothbrush**
  - **in the morning, before breakfast**
  - **before bedtime, at least 30 mins after evening meal**
  - **the tongue can be gently brushed, if not sore**
- **Use dental floss once daily (caution in patients with coagulopathies)**
- **Use non-alcoholic mouthwash (in patients with a healthy mouth)**
  - **immediately after selumetinib/placebo intake**
  - **several times daily or according to the instructions**
- **Clean dentures thoroughly using a soft toothbrush and a mild denture-soaking solution**
  - **in the morning, after overnight soaking**
  - **after every meal**
  - **before soaking overnight**
- **Dentures should be left out while resting**

Management of stomatitis

- **Consider treatment at CTC Grade 1 or as soon as the patient experiences sore mouth**
- **Saline (0.9% sodium chloride) mouthwash recommended**
  - **use at times other than after toothbrushing**
- **Chlorhexidine mouthwashes and over-the-counter mouthwashes are not recommended**
- **The following may be considered depending on the patient's clinical condition and local medical practice**
  - **oral topical analgesic anaesthesia**
  - **topical steroids**
  - **antiviral and/or antifungal medication**

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