SUMMARY OF CHANGES - Protocol

For Protocol Amendment to: A Phase 2 Study of Trametinib in Combination with Radioiodine (RAI) for RAS Mutant or RAS/RAF Wild-Type, RAI-Refractory Recurrent and/or Metastatic Thyroid Cancers

NCI Protocol #: 9446
Local Protocol #: 13-157

NCI Version Date: 06/17/2020
Protocol Date: 06/17/2020

#	Page(s)	Change
1.	Throughout	Editorial, formatting and grammatical changes were made throughout the protocol
2.	Throughout	NCI Version Date has been updated to 06/17/2020 throughout the protocol
3.	4	Removed the following Co-Investigator: Korey Jaben, MD
4.	29	In Section 3.1.10, Changed "/" to "or" (Prothrombin time (PT) or International normalized ratio (INR)) for clarification In Section 3.1.11, Sentence was clarified to indicate that for both men and women, contraception should be used for the duration of the study and 4 months after study completion
5.	62-63	In response to Dr. Johnson's June 5, 2020 request for amendment, the following changes to the trametinib pharmaceutical section were made: • **How Supplied:** Novartis supplies and CTEP, NCI, DCTD distributes trametinib as 0.5 mg and 2 mg (as free base) tablets. Each investigationally-labeled bottle contains 32 tablets. The tablet core contains mannitol, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate (non-animal), colloidal silicon dioxide and sodium lauryl sulfate. • 0.5 mg tablets are yellow, modified oval, biconvex and film-coated. Aqueous film coating consists of hypromellose, titanium dioxide, polyethylene glycol, iron oxide yellow. • 2 mg tablets are pink, round, biconvex and film-coated. Aqueous film coating consists of hypromellose, titanium dioxide, polyethylene glycol, polysorbate 80, iron oxide red.

#	Page(s)	Change
		• **Storage:** Store tablets at 2°C -8°C in the original bottle and dispense unopened bottles. Do not open bottles or repackage tablets or remove desiccant. Bottles should be protected from light and moisture. If a storage temperature excursion is identified, promptly return trametinib to 2°C -8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability. • **Stability:** Stability studies are ongoing. Tablets are only stable for 32 days once bottle has been opened. If multiple bottles are dispensed to a patient in the same visit, please advise the patient to open only one bottle at a time.
6.	110-112	Removed Appendix J for Drug Interactions
7.	113	Added Appendix J for Patient Clinical Trial Wallet Card

NCI Protocol #: 9446

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ClinicalTrials.gov Identifier: NCT02152995

TITLE: A Phase 2 Study of Trametinib in Combination with Radioiodine (RAI) for RAS Mutant or RAS/RAF Wild-Type, RAI-Refractory Recurrent and/or Metastatic Thyroid Cancers.

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NCI Supplied Agent: Trametinib dimethyl sulfoxide (GSK1120212B) (NSC 763093)

Commercially Available Agents: thyrotropin alpha (ThyrogenGenzyme); ^{131}I (MDS Nordion, DraxImage, or International Isotopes)

Imaging Agent: ^{124}I tracer (Sofie Biosciences (fka IBA Molecular and Zevacor), 3 D Imaging LLC, cyclotron, or NCM)

IND Sponsor: NCI

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Amended/Version #7/Version Date: 10/08/2014
Amended/Version #8/Version Date: 01/22/2015
Amended/Version #9/Version Date: 04/08/2015
Amended/Version #10/Version Date: 05/26/2015
Amended/Version #11/Version Date: 11/09/2015
Amended/Version #12/Version Date: 04/14/2016
Amended/Version #13/Version Date:11/30/2016
Amended/Version #14/Version Date: 08/10/2017
Amended/Version #15/Version Date: 03/01/2018
Amended/Version #16/Version Date: 08/20/2018
Amended/Version #17/Version Date: 02/26/2019
Amended/Version #18/Version Date: 12/05/2019
Amended/Version #19/Version Date: 06/17/2020

SCHEMA

Cohort A

Enroll patients with *RAS* MUT RAI-refractory, progressive thyroid cancer

↓

Utilize ^{124}I PET/CT lesional dosimetry to evaluate if trametinib enhances iodine incorporation sufficiently to warrant RAI therapy*

Insufficient ^{124}I PET response ↓

- Continue trametinib on **Cohort C**
- Discontinue trametinib

Sufficient ^{124}I PET response ↓

Continue trametinib and treat with RAI

↓

Tumor assessments

Cohort B

Enroll patients with *BRAF/RAS* WT RAI-refractory thyroid cancer

↓

Utilize ^{124}I PET/CT lesional dosimetry to evaluate if trametinib enhances iodine incorporation sufficiently to warrant RAI therapy*

Insufficient ^{124}I PET response ↓

- Continue trametinib on **Cohort C**
- Discontinue trametinib

Sufficient ^{124}I PET response ↓

Continue trametinib and treat with RAI

↓

Tumor assessments

NOTE: Research biopsies will be performed prior to Week 1 Day 1 and during Week 3.

Cohort C

Patients with insufficient ^{124}I PET responses (from **Cohort A** or **Cohort B)** for whom the treating physician has determined that continuing trametinib alone for the treatment of thyroid cancer is clinically reasonable

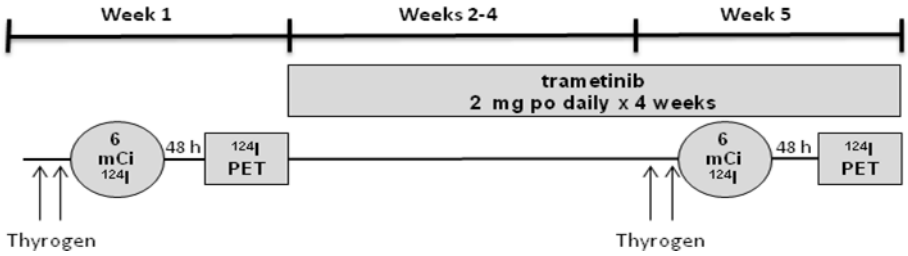
↓

Continue with protocol assessments

↓

Discontinue study when meeting criteria outlined in Section 5.5

* Schema for ^{124}I PET/CT lesional dosimetry evaluation of trametinib impact upon iodine incorporation in thyroid tumors



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1. OBJECTIVES

1.1 Primary Objectives

For Cohort A (RAS mutant (MUT) thyroid cancer patients):

1) To evaluate the effect of trametinib on enhancing radioiodine (RAI) activity by determining the proportion of patients alive at 6 months without disease progression by RECIST v1.1 criteria following treatment with RAI in co-administration with trametinib.

2) To evaluate the effect of trametinib on enhancing RAI activity by determining the objective response rate (ORR) at 6 months following treatment with radioiodine (RAI) in co-administration with trametinib.

For Cohort B (BRAF/RAS wild-type (WT) thyroid cancer):

To determine the proportion of patients following trametinib therapy with increased tumoral iodine incorporation as quantified by ^{124}I PET/CT lesional dosimetry.

1.2 Secondary Objectives

For Cohort A (RAS MUT thyroid cancer patients):

1) To determine the proportion of patients following trametinib therapy with increased tumoral iodine incorporation as quantified with ^{124}I PET/CT lesional dosimetry.

2) To evaluate the safety/tolerability of trametinib with or without RAI.

3) To evaluate changes in thyroglobulin levels in patients treated with RAI.

4) *(Exploratory)* To explore potential correlations between genomic alterations present in the tumor and/or tumoral pharmacodynamic changes induced by trametinib to clinical outcomes.

For Cohort B (BRAF/RAS WT thyroid cancer):

1) To evaluate the effect of trametinib on enhancing RAI activity by determining the ORR at 6 months following treatment with RAI in co-administration with trametinib.

2) To evaluate the effect of trametinib on enhancing RAI activity by determining the proportion of patients alive at 6 months without disease progression by RECIST v1.1 criteria following treatment with RAI in co-administration with trametinib.

3) To evaluate the safety/tolerability of trametinib with or without RAI.

4) To evaluate changes in thyroglobulin levels in patients treated with RAI.

5) *(Exploratory)* To explore potential correlations between genomic alterations present in the

tumor and/or tumoral pharmacodynamic changes induced by trametinib to clinical outcomes.

For Cohort C (select patients from Cohorts A and B with insufficient ^{124}I PET changes):

1) (*Exploratory*) Preliminary evaluation of best objective response (BOR) rate for patients treated with trametinib alone.

2) (*Exploratory*) Preliminary evaluation of the proportion of patients following treatment with trametinib alive at 6 months without disease progression by RECIST v1.1 criteria.

3) To evaluate the safety/tolerability of trametinib.

4) To evaluate changes in thyroglobulin levels in patients treated with trametinib.

5) *(Exploratory)* To explore potential correlations between genomic alterations present in the tumor and/or tumoral pharmacodynamic changes induced by trametinib to clinical outcomes.

6) *(Exploratory)* To explore the impact of continued trametinib upon RAI avidity and efficacy.

2. BACKGROUND

2.1 Study Disease

The incidence of new thyroid cancers is the fastest growing among all cancers with more than 40,000 new cases every year (Jemal et al., 2010). The majority of thyroid cancers are differentiated thyroid carcinomas of follicular origin with papillary thyroid cancer (PTC) being the most common subtype followed by follicular thyroid cancer (FTC). Metastatic disease represents the most frequent cause of thyroid cancer-related death (Mazzaferri and Kloos, 2001), and radioiodine (RAI or ^{131}I) remains a mainstay of therapy for these patients. However, resistance to RAI is a significant clinical problem. In a study of 444 patients with metastatic PTCs or FTCs, 32% of patients had undetectable RAI uptake (Durante et al., 2006). RAI status holds substantial clinical significance: the 10-year survival rate of patients with RAI-avid metastases was 56% compared to 10% for those with non-RAI avid disease (Durante et al., 2006). Despite advances in identifying targeted therapies that can induce regressions in thyroid cancer, it remains unclear how these systemic therapies alter the natural history of RAI-refractory disease. Experimental approaches for restoring RAI avidity has historically yielded disappointing results, including studies evaluating lithium carbonate and retinoic acid (Coelho et al., 2004; Liu et al., 2006). Furthermore, progress has also been stymied by the lack of techniques to precisely quantify iodine uptake.

2.2 CTEP IND Agent

Trametinib Dimethyl Sulfoxide (GSK1120212B, MEKINIST)

> The RAF-MEK-ERK pathway plays a critical role in multiple cellular functions. Activation of the pathway can result from activation/mutations of the upstream receptor tyrosine kinases (RTKs) and RAS, or upregulation/mutations in RAF and MEK. Upon

activation, RAF acts as the MAPK kinase kinase and activates MAPKK (MEK1/2), which in turn catalyze activation of the effectors ERK1/ERK2. Once activated, ERK1/2 translocate into the nucleus and phosphorylate a number of effector proteins and transcriptional factors that regulate cell proliferation, motility, differentiation, and survival.

Trametinib is one of the several MEK inhibitors in clinical development. On May 29, 2013, the U.S. Food and Drug Administration (FDA) approved trametinib for the treatment of patients with unresectable or metastatic melanoma with $BRAF^{V600E}$ or $BRAF^{V600K}$ mutations as detected by an FDA-approved test (U.S. Food and Drug Administration, 2013). On January 10, 2014, the Food and Drug Administration granted accelerated approval to trametinib and dabrafenib for use in combination to treat patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test (U.S. Food and Drug Administration, 2014).

Experience to date indicates that MEK is a valid target. In a phase 3 trial comparing trametinib with dacarbazine or paclitaxel in patients with BRAF V600E or V600K mutant metastatic melanoma, trametinib demonstrated a significantly better response rate, progression-free survival, and overall survival (Flaherty *et al.*, 2012). However, single agent activities are limited. Extensive research is underway to identify the patient selection markers and develop rational combination strategies. Preclinical studies have provided strong rationale and proof of principle for combination of MEK inhibitors with RTK inhibitors (EGFR or IGF-1R) (Gopal *et al.,* 2010; Ebi *et al.,* 2011), PI3K/AKT inhibitors (Engelman *et al.,* 2008; Hoeflich *et al.,* 2009), and mTOR inhibitors. On the other hand, the optimal dose/schedule and patient selection criteria for combination regimens have not been defined. Phase 1 results for a number of combinations have been reported, including AZD6244 + MK2206 (Tolcher *et al.,* 2011) and GDC-0973 + GDC-094 (MEK + PI3K inhibitor) (Bendell *et al.,* 2011).

The most up-to-date preclinical and clinical study information for trametinib can be found in the GSK1120212 (trametinib) Investigator's Brochure (2013).

Mechanisms of Action and Preclinical Data with Trametinib

Trametinib is a dimethyl sulfoxide (DMSO) solvate compound (ratio 1:1) with potent, allosteric and ATP non-competitive inhibition of MEK1/2 (IC_{50} of 0.7 and 0.9 nM against MEK1 and MEK2, respectively) (Gilmartin *et al.,* 2011). Trametinib inhibited MEK1/2 kinase activity and prevented RAF-dependent MEK phosphorylation (S217 for MEK1), producing prolonged pERK1/2 inhibition. Trametinib showed better potency against unphosphorylated MEK1/2 (u-MEK1/2) when compared with preactivated diphosphorylated MEK (pp-MEK), suggesting that u-MEK affords a higher affinity binding site for trametinib than does pp-MEK.

The specificity of trametinib was confirmed against a panel of 183 kinases, including MEK5 (the closet kinase homolog to MEK1/2), CRAF, BRAF, ERK1, and ERK2 (Yamaguchi *et al.,* 2011). Trametinib demonstrated equal potency against activated

MEK1- and MEK2-mediated phosphorylation of ERK (sequence identity of 85% across the whole protein and 100% in the active site for humans). Trametinib demonstrated preferential inhibition of RAF-mediated MEK1 activation (IC_{50} = 0.60 nM) over pMEK1 kinase activity (IC_{50} = 13 nM) (Investigator's Brochure, 2012a).

BRAF-mutant Colo205, A375P F11s, and HT-29 human tumor xenograft mouse models showed the most significant mean tumor growth inhibition (TGI) (80% to 87%) at 3.0 mg/kg trametinib, with multiple complete and partial tumor regressions. In the Colo205 model, tumor regression was observed even at a dose of 0.3 mg/kg (Yamaguchi *et al.,* 2011). Two KRAS-mutant xenograft models, HCT-116 and A549, also showed significant TGI (83% and 75%) but without significant tumor regressions (Gilmartin *et al.,* 2011). As predicted by cell proliferation assays, tumor xenograft lines with wild-type (wt) RAF/RAS (PC3, BxPC3, and BT474) were much less sensitive, showing only modest TGI (44-46%) with no tumor regressions.

Pharmacodynamic studies were performed in mice treated with trametinib for 14 days (Gilmartin *et al.,* 2011). In the A375P F11s xenograft model, the first dose of trametinib (3 mg/kg) significantly reduced pERK for more than 8 hours on Day 1. pERK inhibition was more sustained (over 24 hours) after the Day 7 dose, probably due to an increase in the steady-state levels of trametinib after repeated doses. The average C_{max} in blood was 1,410 nM on Day 7, with an estimated half-life ($t_{1/2}$) of 33 hours. In addition, immunohistochemistry (IHC) also confirmed inhibition of cell proliferation (reduced Ki67) and G1 cell cycle arrest (elevated p27Kip1/CDKN1B) following 4 days of treatment.

Clinical Pharmacokinetics (PK) and Activity of Trametinib

FTIH Phase 1 Trial of Trametinib Monotherapy (MEK111054)

There are 3 parts in this study. Part 1: The dose-escalation portion involves administration of trametinib (repeat doses of 0.125 mg to 4.0 mg) to patients with solid tumors or lymphoma in one of three schedules - (1) QD for 21 days followed by 7 days without drug, (2) loading dose on Day 1 or Day 1-2, followed by QD with the designated dose, or (3) QD dosing without a drug holiday. Part 2: cohort expansion at the recommended phase 2 dose (RP2D) for pancreatic cancer, melanoma, non-small cell lung cancer (NSCLC), colorectal cancer (CRC), or any BRAF mutation-positive cancer. Part 3: expansion to characterize the biologically active range of trametinib via analysis of pharmacodynamic biomarkers (biopsies or FDG-PET).

The MTD of trametinib was established as 3 mg QD, but the recommended phase 2 dose (RP2D) was chosen at 2 mg QD based on tolerability of repeated cycles (Infante *et al.,* 2010).

PK and metabolism of trametinib:

PK measurements were conducted under fasting conditions. After a single dose (Day 1), $AUC_{0\text{-}24}$ and C_{max} values were dose-proportional up to 6 mg, lower than dose proportional following 8 mg, and greater than dose proportional following the 10 mg

dose. Median T_{max} was 1.5 hours.

After repeat doses (Day 15), trametinib accumulated with a mean accumulation ratio of 6.6 at the RP2D of 2 mg QD. Between-subject variability in exposure ranged from 27-50% for C_{max} and 20-41% for AUC_{0-24} across all dosing regimens. The effective $t_{1/2}$ was approximately 4.5 days, and steady state was reached by approximately Day 15. Trametinib had a small peak:trough ratio of ~2 (Infante *et al.,* 2010). At 2 mg QD on Day 15, mean AUC_{0-24} was 376 ng•h/mL and C_{max} 23 ng/mL, and the mean trough concentrations ranged from 10.0 to18.9 ng/mL. The long half-life and small peak:trough ratio of trametinib allowed constant target inhibition within a narrow range of exposure.

Drug-drug interactions:
Trametinib is metabolized predominantly via deacetylation (non-cytochrome P450 [CYP450]-mediated) with secondary oxidation or in combination with glucuronidation biotransformation pathways (Investigator's Brochure, 2012a). The deacetylation is likely mediated by hydrolytic esterases, such as carboxylesterases, or amidases. Based on *in vitro* studies, trametinib is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2D6, and CYP3A4. Trametinib has an overall low potential for drug-drug interactions.

Pharmacodynamic effect and biomarkers:
The relationship between dose and tumor biomarkers such as pERK, Ki67, and p27, were evaluated in patients with BRAF or NRAS mutation-positive metastatic melanoma (Investigator's Brochure, 2012a). In general, increasing exposures and/or doses provided greater pharmacodynamic effects. The median change observed at a dose of 2 mg QD was 62% inhibition of pERK, 83% inhibition of Ki67, and a 175% increase in p27.

Antitumor Activity in the FTIH phase 1 trial:
In the FTIH phase 1 trial, 14 patients with BRAF-mutant melanoma received trametinib at 2 mg QD. The overall objective response rate (ORR) was 43% (6/14), including 2 complete responses (CRs) (Investigator's Brochure, 2012a). In 9 patients with BRAF wt melanoma, 2 patients achieved a partial response (PR), and 3 stable disease (SD) (Infante *et al.,* 2010). In 26 evaluable pancreatic cancer patients, there were 2 PRs (1 PR was KRAS mutation-positive) and 11 SD (2 achieved ≥20% tumor reduction) (Messersmith *et al.,* 2011). Among the 27 CRC patients (without selection of RAS or RAF mutations), 8 SD were observed.

Antitumor Activity in Melanoma

Phase 3 trial of trametinib vs. chemotherapy in advanced V600 mutant melanoma:
In a phase 3 trial, patients with unresectable stage IIIC or IV cutaneous melanoma with a BRAF V600E or V600K mutation were randomized (2:1) to trametinib (2 mg, PO, QD) or chemotherapy (dacarbazine or paclitaxel) (Flaherty *et al.*, 2012; MEKINIST, 2013). There were 322 patients in the intention-to-treat (ITT) population, of whom 273 (85%) were in the primary efficacy population (patients with $BRAF^{V600E}$-positive cancer who did not have brain metastases at baseline). Of the patients, 214 were randomized to receive trametinib, and 108 were randomized to receive chemotherapy. Investigator-

assessed efficacy data are summarized as follows:

	Trametinib (n=214)	Chemotherapy (DTIC) (n=108)
PFS		
Median, months (95% CI)	4.8 (4.3, 4.9)	1.5 (1.4, 2.7)
HR (95% CI)	0.47 (0.34, 0.65)	
P value (log-rank test)	*P*<0.0001	
Confirmed Tumor Responses		
Objective Response Rate (95% CI)	22% (17, 28)	8% (4, 15)
CR, n (%)	4 (2%)	0
PR, n (%)	43 (20%)	9 (8%)
Duration of response Median, months (95% CI)	5.5 (4.1, 5.9)	NR (3.5, NR)

CI = confidence interval; CR = complete response; HR = hazard ratio; NR = not reached; PFS = progression-free survival; PR = partial response

The 6-month OS rate was 81% in the trametinib group and 67% in the chemotherapy group. Mature data on OS are pending.

Experience with Trametinib in Metastatic Melanoma Following BRAF Inhibitor Therapy

The clinical activity of single-agent trametinib was evaluated in a single-arm, multicenter, international trial in 40 patients with BRAF V600E or V600K mutation-positive, unresectable, or metastatic melanoma who had received prior treatment with a BRAF inhibitor. All patients received trametinib at a dose of 2 mg PO QD until disease progression or unacceptable toxicity. None of the patients achieved a confirmed PR or CR.

Antitumor Activity of Trametinib in Cancer Other Than Melanoma

In a phase 1/2 monotherapy study, acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) patients were given trametinib at dose levels from 1-2 mg QD. Drug-related AEs in 45 patients were similar to that observed in patients with solid tumors, and 2 mg PO QD was selected for further investigation in this patient population. Twelve patients (23%) withdrew due to an AE, including cardiac failure (2) and infection (2). Efficacy was reported in 39 patients (Borthakur *et al.,* 2010). The best response in 13 patients with KRAS or NRAS mutations included 3 CRs (23%), 7 SD (54%), and 1 PD (progressive disease) (5%). In 26 patients with wild-type RAS or an unknown mutation, there were 2 PRs (8%).

In a multicenter phase 2 study, NSCLC patients with KRAS mutant tumors were randomized 2:1 to receive trametinib (2 mg QD) or docetaxel (75 mg/m^2 IV every 3 weeks) (Blumenschein *et al.*, 2013). A total of 134 pts were randomized to trametinib (89) or docetaxel (45); 129 patients had KRAS-mutant NSCLC. The hazard ratio for PFS was 1.14 (95% CI, 0.75-1.75; *P*=0.5197) with a median PFS of 11.7 versus 11.4 weeks for trametinib versus docetaxel. The overall response rate (ORR) was 12% for trametinib

and 12% for docetaxel.

In a double-blind, phase 2 study evaluating the combination of gemcitabine with trametinib, untreated pancreatic cancer patients were randomized to receive gemcitabine (1000 mg/m2 weekly ×7 for 8 weeks, then weekly ×3 every 4 weeks) plus either trametinib 2mg or placebo QD (Infante *et al.*, 2013). Median OS was 8.4 months with trametinib compared to 6.7 months with placebo. Median PFS was 16 weeks versus 15 weeks, and ORRs and median duration of responses were 22% and 23.9 weeks and 18% and 16.1 weeks on trametinib and placebo; the median OS and ORR in the subgroup of patients with KRAS mutations (143/160) was similar to OS and ORR for all randomized patients.

Trametinib Safety Profile

A **Comprehensive Adverse Events and Potential Risks (CAEPR)** list using NCI Common Terminology Criteria for Adverse Events (CTCAE) terms is included in Section 7.1 of the protocol.

Based on available AE data from clinical studies involving trametinib to date, the most common toxicities are rash and diarrhea. Rash and diarrhea are common, class-effect toxicities for MEK inhibitors. In addition, visual impairment and left ventricular ejection fraction (LVEF) reduction, although observed at lower frequencies, are also considered class-effect toxicities as they have been observed with trametinib as well as other MEK inhibitors.

AEs of special interest:
Rash, diarrhea, visual disorders, hepatic disorders, cardiac-related AEs, and pneumonitis are considered AEs of special interest because they are either known class effects (*i.e.*, have been observed with other MEK inhibitors) or are potentially life-threatening (Investigator's Brochure, 2013). The following sections provide integrated summaries for these AEs across different clinical trials, with emphasis on trials using trametinib as monotherapy, especially at the RP2D of 2 mg.

Refer to dose modification guidelines for the toxicities for which they are addressed in Section 6.

Rash: Rash was a common AE observed across different dose levels and in different combinations (Investigator's Brochure, 2013). At the 2 mg dose, rash was seen in 27% to 78% of patients in different trials. Of the ~370 subjects with rash AEs at the 2 mg monotherapy dose (including crossover subjects) in five studies, the majority of rash AEs were grades 1 or 2 (24% to 73%); 0% to 9% of patients experienced grade 3 rash AEs, and four patients had a grade 4 rash AE.

In a randomized phase 3 trial of trametinib vs. chemotherapy, the overall incidence of skin toxicity (including rash, dermatitis, acneiform rash, palmar-plantar erythrodysesthesia syndrome, and erythema) was 87% in patients treated with trametinib

and 13% in chemotherapy-treated patients. Severe skin toxicity occurred in 12% of patients on the trametinib arm, most commonly for secondary infections of the skin The median time to onset of skin toxicity was 15 days (range: 1 to 221 days), and median time to resolution was 48 days (range: 1 to 282 days). Dose reduction was required in 12% for skin toxicities, and permanent discontinuation of trametinib was required in 1% of patients.

Diarrhea: At the 2 mg monotherapy dose, 33% to 58% of patients in five trials had diarrhea (Investigator's Brochure, 2013). Of ~320 subjects (including crossover subjects) with diarrhea at this dose, the majority of diarrhea AEs were grade 1 or 2 in severity (33% to 56% of all study patients); 17 patients had grade 3 diarrhea, and none had grade 4 diarrhea.

Visual disorders: At the 2 mg monotherapy dose, 4% to 21% of the patients in five trials experienced visual disorders (Investigator's Brochure, 2013). Of the 85 total subjects (including crossover subjects) experiencing visual disorders at this dose level, the majority of visual disorders were grades 1 or 2 (4% to 20% of all study patients); six patients experienced grade 3 visual disorders, and one patient experienced a grade 4 visual disorder.

- *Retinal Pigment Epithelial Detachment (RPED):* Also known as chorioretinopathy, RPED is a visual impairment due to fluid accumulation under the retina and causes blurry vision. There were five cases of RPED, previously termed central serous retinopathy, reported from the integrated trametinib safety population consisting of subjects treated with trametinib 2 mg once daily from five studies (Investigator's Brochure, 2013). As of 23 June 2013, 14 cases of RPED were reported across the entire trametinib program amongst subjects treated with trametinib either as monotherapy or in combination with other anti-cancer agents (including cases from a MEK/BRAF combination study).

- *Retinal vein occlusion (RVO):* As of 23 June 2013, a total of four cases of RVO were reported across the entire trametinib program (including one case from a MEK/BRAF combination study) (Investigator's Brochure, 2013). All cases of RVO occurred in one eye only. Study drug was stopped at time of diagnosis in all cases. There was a decrease of visual acuity in two subjects with central RVO (CRVO) while the other two subjects had no meaningful decrease of visual acuity. In the two subjects with CRVO, local treatment with intravitreal injections of anti-VEGF antibodies was initiated within 2 weeks after RVO diagnosis, and visual acuity improved in one subject and restored to baseline conditions in another subject, at the time of the data cutoff. Three of these four cases were considered related to study treatment by the investigators.

Hepatic disorders: Abnormalities of liver enzymes and bilirubin have been observed with administration of trametinib (Investigator's Brochure, 2013). However, assessment of these cases was often confounded by co-morbid conditions (such as biliary obstruction), concomitant use of other potentially hepatotoxic drugs, and liver metastases. At the 2 mg monotherapy dose, 8% to 34% of patients in five trials had LFT abnormalities. Of the 96

total patients (including crossovers) with LFT changes, the majority were grade 1 or 2 in severity (4% to 20% of all study patients); 26 had grade 3 events, and 6 patients had grade 4 events.

Cardiac-related AEs: At the 2 mg monotherapy dose, 3% to 21% of the subjects in six studies had cardiac-related AEs (Investigator's Brochure, 2013). Of the 65 total subjects (including crossover subjects) experiencing cardiac-related AEs at the 2.0 mg monotherapy dose in five of the studies, the majority of cardiac-related AEs were grades 1 or 2 in severity (0% to 16% of all study subjects); 18 subjects had grade 3 cardiac-related AEs, and no subjects had Grade 4 cardiac-related AEs in any study. No subject in one study, which evaluated the effect of repeat oral dosing of trametinib 2 mg QD on cardiac repolarization in subjects with solid tumors, had cardiac-related AEs. One study subject receiving trametinib 2 mg QD had grade 5 (fatal) acute cardiac failure, with evidence of massive tumor invasion of the heart; this AE was considered not drug-related by the investigator.

In the phase 3 trial of trametinib vs. chemotherapy in patients with melanoma (MEK114267), cardiomyopathy (defined as cardiac failure, left ventricular dysfunction, or decreased LVEF) occurred in 7% (14/211) of patients treated with trametinib, and in no patients in the chemotherapy arm. Cardiomyopathy was identified within the first month of treatment in five of these 14 patients; median onset of cardiomyopathy was 63 days (range: 16 to 156 days). Cardiomyopathy resolved in 10 of these 14 (71%) patients. Cardiac monitoring should be included in trametinib protocols, to include LVEF assessment by echocardiogram or MUGA scan at baseline, one month after initiation of trametinib and then at 2- to 3-month intervals while on treatment. Refer to dose modification guidelines for cardiac AEs in the event of LVEF decline or symptomatic cardiac AEs.

Pneumonitis: At the 2 mg monotherapy dose, 0% to 4% of the subjects in five studies had pneumonitis (Investigator's Brochure, 2013). Of the nine total subjects (including crossovers) experiencing pneumonitis AEs at this dose, three subjects had grade 1 or 2 pneumonitis and six subjects had grade 3 pneumonitis.
Embryofetal toxicity: Based on its mechanism of action, trametinib can cause fetal harm when administered to a pregnant woman. Trametinib was embryotoxic and abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 0.3 times the human exposure at the recommended clinical dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Incidence of common AEs reported from a phase III trial of trametinib vs. chemotherapy in patients with advanced melanoma:

Patients with abnormal LVEF, history of acute coronary syndrome within 6 months, or current evidence of Class II or greater congestive heart failure (New York Heart Association) were excluded from this trial. Selected adverse reactions (AR) occurring in patients receiving trametinib as compared to patients in the chemotherapy arm are listed as below:

Table: Selected adverse reactions (ARs) occurring in ≥10% of patients receiving trametinib AND at a higher incidence than in the chemotherapy arm (high in the trametinib arm compared with chemotherapy by ≥5% in overall incidence or by ≥2% grade 3 or 4 AEs)

3.	**Trametinib (n=211)**		**Chemotherapy (n=99)**	
Adverse Reactions	**All Grades**	**Grades 3 and 4**	**All Grades**	**Grades 3 and 4**
Skin and subcutaneous tissue disorders				
Rash	57	8	10	0
Dermatitis acneiform	19	<1	1	0
Dry skin	11	0	0	0
Pruritis	10	2	1	0
Paronychia	10	0	1	0
Gastrointestinal disorders				
Diarrhea	43	0	16	2
Stomatitis	15	2	2	0
Abdominal pain	13	1	5	1
1.1.1 **Vascular disorders**				
Lymphedema	32	1	4	0
Hypertension	15	12	7	3
Hemorrhage	13	<1	0	0

Table: Percent-patient incidence of laboratory abnormalities occurring at a higher incidence in patients treated with trametinib versus chemotherapy (between-arm difference of ≥5% [all grades] or ≥2% [grades 3 or 4])

	Trametinib (n=211)		**Chemotherapy (n=99)**	
Preferred term	**All Grades**	**Grades 3 and 4**	**All Grades**	**Grades 3 and 4**
Increased aspartate aminotransferase (AST)	60	1.1.2	1.1.3	1.1.4
1.1.5 Increased alanine aminotransferase (ALT)	1.1.6	1.1.7	1.1.8	1.1.9
1.1.10 Hypoalbuminemia	1.1.11	1.1.12	1.1.13	1.1.14
1.1.15 Anemia	1.1.16	1.1.17	1.1.18	1.1.19
1.1.20 Increased alkaline phosphatase	1.1.21	1.1.22	1.1.23	1.1.24

Other clinically important adverse reactions observed in ≤10% of patients (n=329) treated with trametinib were: nervous system disorders (dizziness, dysgeusia), ocular disorders (blurred vision, dry eye), infections and infestations (folliculitis, rash pustular, cellulitis), cardiac disorders (bradycardia), gastrointestinal disorders (xerostomia), and musculoskeletal and connective tissue disorders (rhabdomyolysis).

Clinical Experience with the Combination of Trametinib + Dabrafenib
Preliminary data on 45 patients participating in the phase 1/2 study of dabrafenib and

trametinib, BRF113220, have been reported (Infante et al., 2011).

PK:
The plasma levels of dabrafenib were higher in combination with trametinib as compared to that with monotherapy. Geometric mean Day 15 AUC of dabrafenib in combination ranged from 3539 to 5187 ng•hr/mL, and the AUC observed in the monotherapy study was 2619 ng•hr/mL. Further data are required to understand this difference.

PK of trametinib did not appear to be affected by the addition of dabrafenib. Preliminary results showed that the geometric mean dose-normalized $AUC_{0-\tau}$ (CV%) for trametinib (dose normalized for the 2.0 mg QD dose) in combination with dabrafenib at 150 mg BID was 302 ng•hr/mL (n=17; 35%) on Day 15. Historical PK data from the trametinib FTIH study (MEK111054) indicated a mean Day 15 $AUC_{0-\tau}$ (CV%) of 360 ng•hr/mL (31%).

Safety and the RP2D for the combination of trametinib and dabrafenib
One DLT of a recurrent grade 2 neutrophilic panniculitis occurred, and pyrexia was common (51%). The RP2D was 150 mg BID dabrafenib plus 2 mg QD trametinib (both agents at the RP2D for single agent). Of the 137 patients enrolled, 32 patients were treated at the RP2D. SAEs experienced by more than one patient include: pyrexia (5%), hypotension (4%), nausea (3%), and 2% of patients had a constellation of AEs including vomiting, dehydration, or renal failure. The only grade 4 AE was a sepsis-like syndrome with fever/hypotension. Grade 3 AEs included generalized rash (n=2, 4%) and neutropenia (n=2, 4%). Skin toxicity (rash) occurred in 9 (20%) patients. Of note, the rate of SCC was 2% in this study. A single case of grade 5 hyponatremia was reported. Other common AEs are listed in the table below.

Summary of selected AEs experienced by ≥5% of patients regardless of causality in BRF113220 (treated at RP2D)

AE Term	Dose Escalation Cohort (150mg BID/2 mg QD) (n=31)
Any AE, n (%)	24 (77)
Pyrexia	10 (32)
Rash	4 (13)
Dermatitis acneiform	1 (3)
Hypotension	4 (13)

Activity
Among 77 evaluable patients with melanoma who had not received prior BRAF inhibitors, there were 43 responses (56%), including 4 CRs (5%) and 39 PRs (51%) (Weber *et al.*, 2012). Twenty-nine patients experienced SD, and three patients experienced PD. Patients were treated on four escalating dose levels of dabrafenib/trametinib (mg BID/mg QD): 75/1, 150/1, 150/1.5, 150/2. The confirmed RR for each dose level, respectively, was 67% (n=6), 64% (n=22), 48% (n=25), and 54% (n=24). Median PFS (months) for each of the first three dose levels, respectively, was 8.7, 8.3, and 5.5; PFS data are not mature for the fourth (150/2) dose level. Overall PFS was 7.4 months.

Currently, the randomized phase 2 portion (Part C) of the study of dabrafenib with or without trametinib has enrolled 162 patients as of September 1, 2011 (Investigator's Brochure, 2012b).

Clinical Experience with the Combination of Trametinib + GSK2141795 (AKT inhibitor) (TAC113886)

Twenty-three patients with advanced solid tumors received the combination using a zone-based escalation procedure enabling evaluation of multiple combination doses in parallel cohorts (Kurzrock *et al.,* 2011). While the RP2D for single agent for single agent trametinib and GSK2141795 are 2 mg/d and 75 mg/d, dose reductions were required for the combination. DLTs include grade 2 AST and ALT elevation, and grade 3 chest pain with sustained ventricular tachycardia; all DLTs were reversible with drug interruption. The most common AEs (≥10%) included nausea (26%), AST elevation (22%; grade 3/4, 9%), fatigue (22%) and rash (22%). Three MTDs were defined for variable dose ratios: 2 mg trametinib + 25 mg GSK2141795; 0.5 mg trametinib + 75 mg GSK2141795; and 1.5 mg trametinib + 50 mg GSK2141795. Three of 13 evaluable patients (unselected) had tumor shrinkage of 8% (ovarian), 16% (endometrial), and 17% (ovarian) after 8 weeks on study. The dose regimen of 1.5 mg trametinib + 50 mg GSK2141795 will be considered for further development. Additional trials to explore alternate schedules (*e.g.*, intermittent) and pharmacodynamic markers are ongoing.

2.3 Lesional dosimetry by ^{124}I PET/CT

^{131}I has been used since the late 1940s for the treatment of metastatic differentiated thyroid carcinoma (DTC). This is based on the unique ability of normal and neoplastic thyroid cells to express a protein (the sodium-iodide symporter) which can pump iodide into the cells against an electrochemical gradient. Many of the fundamental studies on the safety and efficacy of ^{131}I for metastatic DTC were carried out at MSK in the early 1950s by Benua, Sonenberg, Rawson, J. Robbins, and Yeh (Benua and Leeper, 1986). They discovered that exposure to large amounts of ^{131}I could result in toxicity to bone marrow and to the lung (Benua et al., 1962). Benua developed a method to determine the radiation dose to the bone marrow and to the lung by frequent measurements of the blood, urine, and whole body radiation levels after a standard administration of small amounts of ^{131}I. This method, termed "dosimetry", has been used for the past 50 years at MSK as a standard of care (Leeper, 1973). The dosimetry methods produces a blood maximum tolerable activity (MTA) above which significant bone marrow toxicity is likely and a pulmonary MTA for patients with diffuse lung disease, above which pulmonary fibrosis is more likely. This technique has provided important safety measures that enable us to give multiple radioiodine treatments with minimal side effects. However, dosimetry does not predict tumor response. This is due to technical limitations in precisely determining the concentration of ^{131}I in individual metastatic lesions.

The recent widespread availability of positron emission tomography (PET) enables investigators to estimate biochemical events in patients. Based on MSK studies from the 1950s, Dr. Ron Finn and colleagues have recently developed a method to generate a positron emitting isotope of iodine, ^{124}I (Pentlow et al., 1996). This enables, for the first time, to accurately determine the concentration of radioiodine in a specific lesion. This information can be transformed into the

radiation dose that is delivered to the area of isotope retention, which can be determined due to the tomographic capability of the PET instrument. In preliminary studies at MSK (Sgouros et al., 2004), we have shown that accurate whole body and lesional dosimetry can be accomplished by measuring the concentration of ^{124}I at several time points over 96 hours following a single oral administration of ^{124}I (Furhang et al., 1999). In addition to providing the MTA safety limits, this new approach can estimate the radiation dose that each lesion will receive, depending on the isotope of iodine that is administered for therapy. We have found that an extremely wide range of radiation dosages (over three log orders) exist in lesions that appear to be similar on visual inspection of a standard whole body radioiodine scintigraphic image. This concept has been confirmed by investigators in Germany and Sweden (Eschmann et al., 2002; Lubberink et al., 1999). Our data here at MSKwith ^{124}I PET in patients with metastatic thyroid cancer has established that clinical responses to RAI are observed when the lesional absorbed dose of RAI reaches ~ 2,000 cGy (rad). This treatment threshold was utilized in our recently completed pilot study: among the 8 out of 20 total patients we selected for RAI therapy, all patients experienced tumor shrinkage (5 confirmed partial responses and 3 with stable disease). At MSK, we hold the consensus view that the 2,000 cGy (rad) ^{124}I PET lesional dosimetry threshold can effectively predict clinical efficacy with RAI utilizing the 2,000 cGy (rad) threshold and is hence clinically applicable.

2.4 Rationale for utilizing MAPK pathway inhibition to enhance iodine incorporation in RAI-refractory thyroid tumors

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 iodine metabolism (Durante et al., 2007; Liu et al., 2007; Riesco-Eizaguirre et al., 2006). The $BRAF^{V600E}$ mutation decreases expression of the sodium iodide symporter (*NIS*), a protein critical for mediating iodide uptake into thyroid cells(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 suppressed *NIS* expression, which was restored with MEK inhibitor treatment (De Vita et al., 2005; Knauf et al., 2003).

Hence, genetic alterations that account for MAPK activation in about 70% of thyroid cancers can promote MEK-dependent *NIS* suppression, diminished RAI avidity, and resistance to RAI therapy.

MEK inhibition can restore iodine incorporation in an in vivo thyroid cancer model

Dr. James Fagin's group recently published studies conducted in a thyroid cancer mouse model with doxycycline (dox) inducible thyroid expression of $BRAF^{V600E}$ (Chakravarty et al., 2011). In this model, dox treatment resulted in $BRAF^{V600E}$ overexpression, MAPK activation, development of PTC, and suppression of several thyroid specific genes, including *NIS*. 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 (data not shown). We went on to test whether or not this genetic proof of concept could be recapitulated with pharmacologic inhibition of BRAF activation (**Figure 1**). $BRAF^{V600E}$ was induced with one week of dox treatment. In the following week, dox was continued in order to maintain $BRAF^{V600E}$ expression while animals were treated with the MEK inhibitor PD0325901 (PD901) or the selective oncogenic BRAF inhibitor PLX4720 (Plexxikon/Roche). ^{124}I microPET was performed to quantify iodine uptake. While expression of $BRAF^{V600E}$ suppressed thyroid RAI incorporation, inhibition of BRAF signaling with either drug increased RAI uptake over vehicle treatment (**Figure 1**). These experiments validate that inhibiting MAPK signaling with small molecule inhibitors can restore RAI uptake in thyroid tumors driven by a MAPK activating genetic alteration.

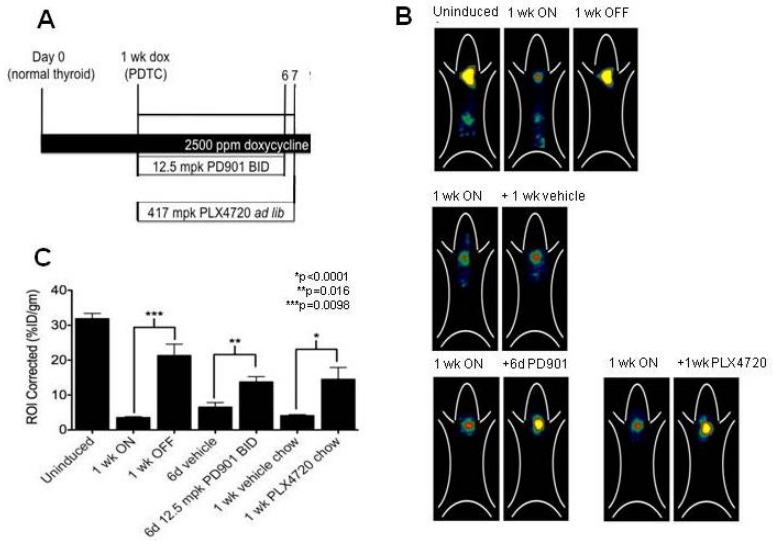

Figure 1: Pharmacologic inhibition of oncogenic BRAF signaling increases RAI uptake in a doxycycline-inducible $BRAF^{V600E}$ thyroid cancer model. A) Schematic for the experiment. *Tg-rtTA/tetO-*$BRAF^{V600E}$ mice were treated for one week with doxycycline ("1 wk ON") to induce thyroid specific $BRAF^{V600E}$ expression. Dox was either discontinued ("1 wk OFF") to halt $BRAF^{V600E}$ expression or continued to maintain $BRAF^{V600E}$ expression while drug was administered (MEK inhibitor PD0325901 (PD901) or oncogenic BRAF inhibitor PLX4720 or vehicle) for approximately 1 week. **B)** Images from ^{124}I microPET. **C)** Quantification of ^{124}I uptake measured by microPET. Thyroid uptake was quantified as % injected dose per gram of tissue (%ID/gm) in Region of Interest (ROI). mpk, mg per kg; PDTC, poorly differentiated thyroid carcinoma.

The MSK experience with MEK inhibition enhancing RAI incorporation and susceptibility

We translated these preclinical findings into an IRB-approved pilot study evaluating the impact of the AstraZeneca MEK inhibitor selumetinib upon iodine uptake in patients with RAI-

refractory thyroid cancers. A critical component of the study was the utilization of ^{124}I positron emission tomography (PET)/CT scans to precisely quantify drug-induced changes in iodine incorporation within specific lesions ("lesional dosimetry") (Pentlow et al., 1996; Sgouros et al., 2004). This provided a substantial advantage over traditional whole body radioactive iodine scintigraphy, which does not provide correlative anatomic localization for iodine uptake, is less sensitive for detecting iodine-avid metastases(Van Nostrand et al., 2010), and is only loosely quantitative (visually similar lesions can represent as much as a 3 log range of radiation dosages). With ^{124}I PET, we can also transform the ^{124}I quantification into the predicted RAI radiation dosage delivered within every individual tumor within a patient's body.

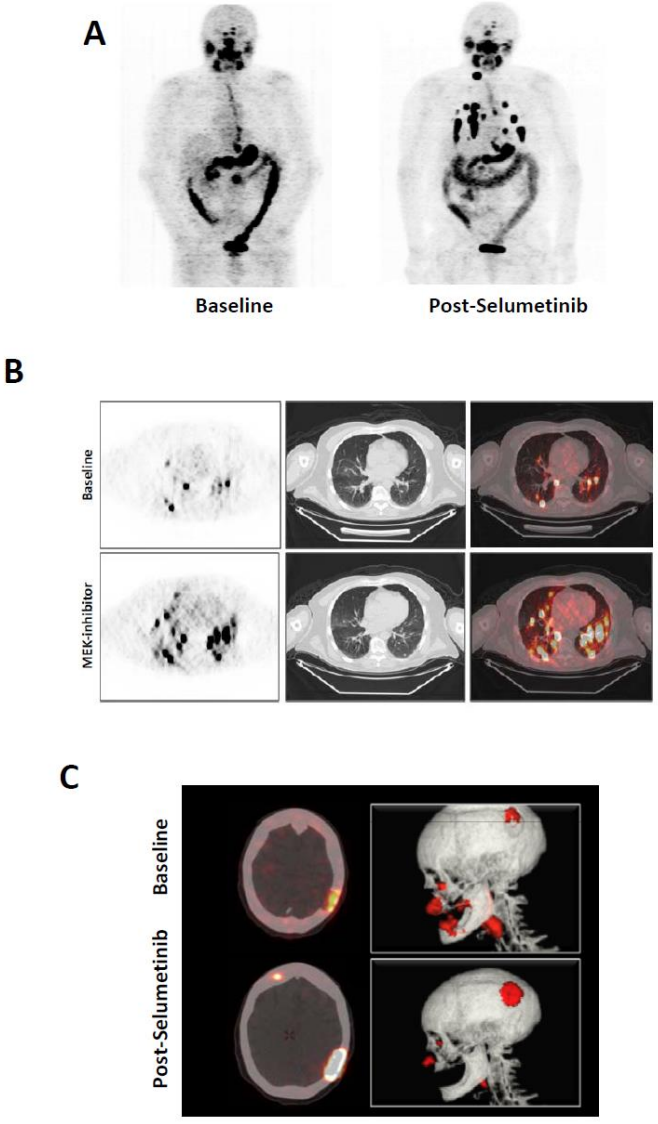

Figure 2: Clinical MEK inhibition with selumetinib enhances iodine incorporation. A) Whole body MIP images from ^{124}I PET scan demonstrates new iodine incorporation in nearly all lung and neck metastases that were previously negative at baseline in a *BRAF* MUT patient following selumetinib treatment. **B)** (from left to right) The PET, CT, and fused images from the ^{124}I PET/CT scan performed on an *NRAS* MUT patient demonstrating significantly increased and new iodine incorporation after selumetinib treatment. **C)** Fused and three-dimensional rendering of a skull metastasis with significantly increased iodine incorporation with selumetinib therapy.

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 iodine uptake, human recombinant TSH (rhTSH or Thyrogen from Genzyme) was administered prior to each ^{124}I PET, which was performed before and after 4 weeks of treatment with selumetinib. If the second ^{124}I PET scan predicted that a lesional RAI dose of $\geq$ 2,000 cGy could be achieved, RAI was administered while patients continued on selumetinib. Radiologic RECIST response and thyroglobulin levels (a thyroid tumor marker) were assessed after therapeutic RAI.

Of the 20 evaluable patients, 12 (60%) had new or increased ^{124}I incorporation after selumetinib (**Figure 2** and **Table 1**). For 8 (40%) patients, the second ^{124}I PET scan predicted that the lesional absorbed radiation dose would equal or exceed 2,000 cGy; these patients were continued on selumetinib and went on to receive therapeutic RAI. All 5 patients with *NRAS* MUT tumors enrolled onto the study exceeded this dosimetry threshold and were treated

with RAI. 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 RAI treatment. Two out of 3 *RET/PTC* and 1 out of 3 WT patients also had greater iodine incorporation on the second ^{124}I PET scan, and one of each of those genotypes went on to be treated with ^{131}I.

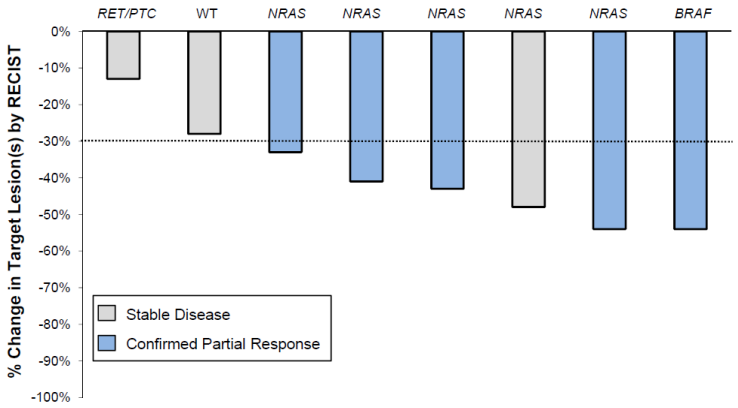

Table 1: Summary of the ^{124}I PET/CT data by tumor genotype.

Tumor Genotype	Patients with increased lesional iodine incorporation after selumetinib (fraction of total)	Patients who received RAI (fraction of total)
BRAF (9 patients)	4 (4/9)	1 (1/9)
NRAS (5 patients)	5 (5/5)	5 (5/5)
RET/PTC (3 patients)	2 (2/3)	1 (1/3)
Wild-type (3 patents)	1 (1/3)	1 (1/3)
Total (20 patients)	**12 (12/20)**	**8 (8/20)**

Figure 3: Waterfall plot of best overall response amongst the 8 patients who received RAI.

Reduction in tumor size by RECIST criteria was achieved in all patients, with 5 confirmed partial responses (cPRs) and 3 with stable disease (SD) (**Figure 3**). Substantial decreases in thyroglobulin following RAI therapy were also achieved in all 8 patients.

Rationale for evaluating trametinib in RAI-refractory thyroid cancer

The selumetinib pilot study demonstrated that MEK inhibition can enhance iodine incorporation to induce clinical responses in a subset of patients with RAI-refractory thyroid cancer. A particularly promising signal was observed in *RAS* MUT patients as all 5 enrolled in the pilot had a positive ^{124}I response with selumetinib. However, the limited number of *RAS* MUT patients treated on the study requires that further investigation be performed to better assess clinical efficacy. Cohort A of this study will be dedicated to evaluating the clinically efficacy of MEK inhibition with trametinib in combination with RAI only in patients with *RAS* MUT, RAI-refractory thyroid cancer. Cohort B will explore if MEK inhibition with trametinib can be effective for enhancing iodine incorporation in *BRAF/RAS* WT tumors, a genotype subset that

was less susceptible to selumetinib in the pilot study. In both cohorts, ^{124}PET/CT lesional dosimetry will be used to quantify changes in tumoral iodine incorporation induced by trametinib.

Trametinib was the agent selected for investigation based on emerging evidence that the clinical efficacy of MAPK pathway targeted therapies likely is related to the potency of signaling inhibition. In the phase I study of the BRAF kinase inhibitor PLX4032 for *BRAF* MUT cutaneous melanoma, only patients with tumors demonstrating near complete inhibition of ERK phosphorylation (80% or greater) experienced tumor regressions; partial pathway inhibition resulted in little or no change in tumor dimensions (Bollag et al., 2010). In a randomized phase II study of 99 melanoma patients treated with selumetinib, only 6 (5.8%) partial responses were observed, indicating that the vast majority of the estimated 46.2% of patients with *BRAF* MUT disease on the trial did not respond to selumetinib (Kirkwood et al., 2011). In comparison, the phase III trial comparing trametinib to chemotherapy for patients with BRAF *MUT* cutaneous melanoma reported an overall response rate of 22% in the trametinib group (Flaherty *et al.*, 2012). It is possible that the efficacy observed with trametinib reflects enhanced potency for inhibiting the MAPK pathway. Therefore, we hypothesize that trametinib may be as effective as selumetinib for enhancing iodine incorporation in *RAS* MUT patients, and perhaps more effective for *BRAF/RAS* WT patients.

For patients from Cohorts A and B who do not achieve sufficient increases in ^{124}I PET tumor incorporation to warrant RAI therapy, if the treating physician determines that it is clinically reasonable to continue treatment with trametinib alone, these patients will have the option of joining Cohort C which will explore the potential clinical efficacy and safety of trametinib therapy for these patients. The efficacy of MEK inhibition alone for RAI-refractory thyroid cancer has been evaluated with selumetinib in one phase II trial; that study reported only 1 partial response out of 32 evaluable patients. Only one patient with a known *NRAS* Q61R MUT tumor and 11 patients with tumors wild-type for *BRAF, NRAS,* and *HRAS* were included in that analysis. We hypothesize that more potent inhibition with trametinib will translate to greater clinical efficacy for patients with RAI-refractory thyroid cancers that are either *RAS* MUT or *BRAF/RAS* WT.

2.5 Correlative Studies Background

The impact of trametinib upon MAPK signaling and thyroid-gene expression will be evaluated in serial biopsies. The purpose of these studies will be to correlate potent MAPK pathway inhibition to changes in iodine incorporation and increase our understanding of the biologic underpinnings that may determine susceptibility/resistance to this strategy. In order to explore the impact of trametinib in different tumor genotypes, the goal will be to have a minimum of 6 patients from Cohort A and 3 patients from Cohort B undergo these two biopsies (for a total of 9 patients total). The first biopsy will be performed before Week 1 Day 1 of the study; the second biopsy will be obtained in Week 3 while the patient is on trametinib. It is preferred, but not required, that the second biopsy be performed upon the same tumor that was sampled with the first research biopsy, if safe and feasible. Both formalin fixed and flash frozen tissues will be prepared.

The fresh frozen tissue will be analyzed with protein based assays to evaluate drug-induced changes in MAPK signaling and thyroid-specific gene expression. Additionally, profiling of

cellular transcriptional output has been validated as a means of distinguishing tumor cell susceptibility to MEK inhibition (Dry et al., 2010) and the differential impact of MEK inhibition upon *BRAF* MUT versus WT tumors (Pratilas et al., 2009). Hence, a separate aliquot of the fresh frozen tumor biopsies will be used for quantification of gene transcript levels as a readout of MAPK pathway activation (Pratilas et al., 2009). In the thyroid, *DUSP5* and *PLAT* are particularly useful markers of MAPK activity, and will be explored in the samples (Chakravarty et al., 2011). Additionally, the re-expression of some key thyroid-specific genes such as *NIS* will be evaluated (Chakravarty et al., 2011).

Archival and/or frozen tissues will also be analyzed for other genomic alterations that may potentially correlate to clinical benefit with this approach.

3. PATIENT SELECTION

3.1 Inclusion Criteria

For both Cohort A and B patients:

3.1.1 Patients must have histologically or cytologically confirmed thyroid carcinoma of follicular origin (including papillary, follicular, or poorly differentiated subtypes and their respective variants). Confirmation of thyroid carcinoma will be done at MSK.

3.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥ 20 mm with conventional techniques or as ≥10 mm with spiral CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease. Tumors in previously irradiated fields may be considered measureable if there is evidence of tumor progression after radiation treatment.

3.1.3 RAI-refractory disease on structural imaging, defined as any one of the following:

a) A metastatic lesion that is not radioiodine-avid on a diagnostic radioiodine scan performed prior to enrollment in the current study, or

b) A radioiodine-avid metastatic lesion which remained stable in size or progressed despite radioiodine treatment 6 months or more prior to entry in the study. There are no size limitations for the index lesion used to satisfy this entry criterion.

c) The presence of at least one fluorodeoxyglucose (FDG) avid lesion.

3.1.4 No recent treatment for thyroid cancer as defined as:

a) No prior RAI therapy is allowed < 6 months prior to initiation of therapy on this protocol. A diagnostic study using < 10 mCi of RAI is not considered RAI therapy.

b) No external beam radiation therapy < 4 weeks prior to initiation of therapy on this protocol. (Previous treatment with radiation for any indication is allowed if

the investigator judges that the previous radiation does not significantly compromise patient safety on this protocol.)

c) No chemotherapy or targeted therapy (e.g., tyrosine kinase inhibitor) is allowed < 4 weeks prior to the initiation of therapy on this protocol.

3.1.5 Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of trametinib alone or in combination with RAI in patients < 18 years of age, children are excluded from this study.

3.1.6 ECOG performance status ≤ 2 (Karnofsky ≥60%, see Appendix A).

3.1.7 Life expectancy of greater than 3 months.

3.1.8 Able to swallow and retain orally-administered medication and does not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.

3.1.9 All prior treatment-related toxicities must be CTCAE v4.0 grade ≤ 1 (**except alopecia**). Grade 2 prior treatment related toxicities may be allowed after discussion with the Principal Investigator.

3.1.10 Patients must have normal organ and marrow function as defined below:

- Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
- Hemoglobin ≥ 9 g/dL
- Platelets ≥ 100 x 10^9/L
- Albumin ≥ 2.5 g/dL
- Total bilirubin ≤ 1.5x institutional ULN
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5x institutional ULN
- creatinine ≤ 1.5 mg/dL *OR* calculated creatinine clearance (Cockroft-Gault formula) ≥ 50 mL/min *OR* 24-hour urine creatinine clearance ≥ 50 mL/min
- Prothrombin time (PT) or International normalized ratio (INR) and partial thromboplastin time (PTT) ≤ 1.5x institutional ULN
- Left ventricular ejection fraction ≥ institutional lower limit of normal (LLN) by ECHO or MUGA

3.1.11 The effects of trametinib on the developing human fetus are unknown. Since MEK inhibitors and RAI may be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study, and 4 months after study completion. Women of child-bearing potential must have a negative pregnancy test within 2 weeks prior study registration. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform the treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of trametinib administration.

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

3.1.13 Patients must agree to undergo two separate biopsies of a malignant lesion. Biopsies do not need to be done if one of the following apply:

a) If either the site investigator or person performing the biopsy judges that no tumor is accessible for biopsy or that biopsy poses too great of a risk to the patient. (If the only tumor accessible for biopsy is also the only lesion that can be used for RECIST v1.1 response evaluation, then the patient may be exempt from biopsy after discussion with the MSK Principal Investigator.)

b) The goal will be to have a minimum of 6 patients from Cohort A and 3 patients from Cohort B attempt to have one or both of these research biopsies done (for a total of 9 patients total). Accrual may be limited only to subjects for whom tumor is accessible for biopsy and attempt at biopsy is considered safe if continued enrollment of those who are not candidates for biopsy make it impossible to reach the accrual goals for research biopsies described above. (e.g., if 19 (of 25) patients are accrued to Cohort A without any biopsies having been obtained within the cohort, then all further subjects who are registered to that cohort must qualify for attempted research biopsy in order to be enrolled into the study (i.e., subjects who would have been excluded from having biopsies done due to the above reasons would be excluded from participating in the study. These conditions also apply to Cohort B.)).

3.1.14 Availability of archival tumor tissue from the thyroid cancer primary or metastasis (A tissue block or a minimum of 30 unstained slides would be required. Patients with less archival tissue available may still be eligible for the study after discussion with the MSKPrincipal Investigator.)

For Cohort A patients only (RAS MUT patients):

3.1.15 Confirmation in a CLIA certified laboratory that one of the patient's thyroid tumors (primary tumor, recurrent tumor, or metastasis) has an *NRAS* or *KRAS* or *HRAS* mutation at G12, G13, or Q61. This group of patients will also be referred to as "*RAS* MUT".

3.1.16 Patients must have progressive disease, defined as the presence of new or growing lesion(s) on radiologic imaging within 14 months of study enrollment and/or new/worsening disease related symptoms within 14 months of study enrollment. (Progression according to RECIST v1.1 criteria is not required.)

For Cohort B patients only (BRAF/RAS WT patients):

3.1.17 Confirmation in a CLIA certified laboratory that one of the patient's thyroid tumors (primary tumor, recurrent tumor, or metastasis) does not have any of the following mutations:

a. Mutation at V600 of the *BRAF* gene

b. Mutation in *NRAS* or *KRAS* or *HRAS* at G12, G13, or Q61

These patients will be designated "*BRAF/RAS* WT".

3.2 Exclusion Criteria

3.2.1 History of another malignancy.

Exception: Patients who have been disease-free for 3 years, patients with a history of completely resected non-melanoma skin cancer, and/or patients with indolent secondary malignancies, are eligible. MSK can consult the CTEP Medical Monitor if unsure whether second malignancies meet the requirements specified above.

3.2.2 History of interstitial lung disease or pneumonitis.

3.2.3 Use of other investigational drugs within 28 days (or five half-lives, whichever is shorter; with a minimum of 14 days from the last dose) preceding the first dose of trametinib and during the study.

3.2.4 Symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression.

3.2.5 Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to trametinib, or excipients or to dimethyl sulfoxide (DMSO) or to thyrotropin alpha (Thyrogen).

3.2.6 Current use of a prohibited medication. The following medications or non-drug therapies are prohibited:

- Other anti-cancer therapy while on study. (Note: Megestrol [Megace] if used as an appetite stimulant is allowed. TSH suppressive therapy is also allowed. Palliative radiation therapy to non-target lesions is also allowed.).
- Concurrent treatment with bisphosphonates is permitted. Prophylactic use of bisphosphonates in patients without bone disease is not permitted, except for the treatment of osteoporosis.
- Because the composition, PK, and metabolism of many herbal supplements are unknown, the concurrent use of all herbal supplements is prohibited during the study (including, but not limited to, St. John's wort, kava, ephedra [ma huang], gingko biloba, dehydroepiandrosterone [DHEA], yohimbe, saw palmetto, or ginseng).

3.2.7 Patients with the following ophthalmological findings/conditions:

- Intraocular pressure >21 mmHg, or uncontrolled glaucoma (irrespective of intraocular pressure)
- Current or past history of central serious retinopathy or retinal vein occlusion

3.2.8 History or evidence of cardiovascular risk including any of the following:

- LVEF<LLN.
- A QT interval corrected for heart rate using the Bazett's formula QTcB ≥480 msec.
- History or evidence of current clinically significant uncontrolled arrhythmias (Exception: patients with controlled atrial fibrillation for >30 days prior to randomization are eligible).
- History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to randomization.
- History or evidence of current ≥ Class II congestive heart failure as defined by the New York Heart Association (NYHA) functional classification system.
- Treatment-refractory hypertension defined as a blood pressure of systolic >140

mmHg and/or diastolic >90 mmHg which cannot be controlled by anti-hypertensive therapy.
- Patients with intra-cardiac defibrillators.
- Known cardiac metastases.

3.2.9 Known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection (with the exception of chronic or cleared HBV and HCV infection, which will be allowed). Patients with Human Immunodeficiency Virus (HIV) are not eligible if on anti-retroviral medications,

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

3.2.11 Animal reproductive studies have not been conducted with trametinib. Therefore, the study drug must not be administered to pregnant women or nursing mothers. These potential risks may also apply to RAI and Thyrogen.

3.2.12 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with trametinib. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy.

3.2.13 Patients unable to follow a low iodine diet or requiring medication with high content in iodide (amiodarone).

3.2.14 Patients who received iodinated intravenous contrast as part of a radiographic procedure within 3 months of study registration. Those that have had iodinated intravenous contrast within this time frame may still be eligible if an urinary iodine analysis reveals that the excess iodine has been cleared after the last intravenous contrast administration.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial. (NOTE: The letter designations below do not refer to study cohort designations.)

Accrual Targets							
Ethnic Category	**Sex/Gender**						
	Females		**Males**			**Total**	
Hispanic or Latino	4	+	2		=	6	
Not Hispanic or Latino	16	+	13		=	29	
Ethnic Category: Total of all subjects	20	(A1) +	15	(B1)	=	35	(C1)
Racial Category							
American Indian or Alaskan Native	0	+	0		=	0	
Asian	2	+	1		=	3	
Black or African American	3	+	2		=	5	
Native Hawaiian or other Pacific Islander	0	+	0		=	0	
White	15	+	12		=	27	
Racial Category: Total of all subjects	20	(A2) +	15	(B2)	=	35	(C2)
	(A1 = A2)		(B1 = B2)			(C1 = C2)	

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

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

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

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

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov

4.2 General Registration Procedures

Confirm eligibility as defined in the section entitled Patient Selection.

Obtain informed consent by following procedures defined in section entitled Informed Consent Procedures.

During the registration process, registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming that the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

5. TREATMENT AND IMAGING PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy (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)).

5.1.1 Trametinib

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Trametinib	None	2 mg	Orally	Daily	28 days (4 weeks) (please see below for specifics regarding time on treatment)

- After completion of the first ^{124}I PET/CT lesional dosimetry process, all patients will start trametinib (Week 1, Day 6). Patients will remain on trametinib for about 4 weeks through the completion of the second ^{124}I PET/CT lesional dosimetry process.
- Ideally, patients will remain on trametinib continuously for a minimum of 7 days prior

to the PET/CT scan for the second lesional dosimetry (this is not a requirement). To achieve this, protocol assessments and treatments may be rescheduled (including but not limited to the second ^{124}I PET/CT lesional dosimetry, ^{131}I dosimetry/therapy, and/or repeating Thyrogen injection administration) at the discretion of the treating physician. Extending time on trametinib in this manner will not be considered a protocol violation. If the second ^{124}I PET/CT lesional dosimetry is delayed more than 4 weeks, the MSK Principal Investigator and the treating physician will determine if the patient should be continued or removed from the study. Please note that missing less than 7 dose(s) of study drug in a cycle for reasons other than toxicity issues will not be considered a violation of the protocol.

- Generally, missed doses do not need to be made up. However, making up missed doses may be considered if necessary to ensure that the patient has remained on trametinib for a minimum of 7 consecutive days as discussed above. If trametinib is missed for $\geq$ 7 days total or interruptions in trametinib dosing have occurred prior to or during whole body and blood dosimetry and ^{131}I (RAI) treatment, then having some or all of the doses made up and rescheduling the study assessments/treatments may be considered after discussion with the MSK Principal Investigator (this is not a requirement). Please note that missing less than 7 dose(s) of study drug in a cycle for reasons other than toxicity issues will not be considered a violation of the protocol.
- If lesional dosimetry with the second ^{124}I PET/CT scan reveals that a dose of $\geq$ 2,000 cGy can be delivered to at least one tumor with $\leq$ 300 mCi of RAI, then the treating physician(s) will make a clinical decision as to whether ^{131}I therapy should proceed. If ^{131}I is to be given, the patient will continue trametinib until 2 days after therapeutic RAI has been administered. If therapeutic RAI will not be given, it will be concluded that the patient's cancer is still refractory to RAI and he/she will not receive RAI. Such patients may be continued on trametinib alone if 1) the treating physician determines it to be clinically reasonable, and 2) the patient agrees to continue on trametinib. If these conditions are not met, then trametinib will be discontinued and the patient will be removed from the study.
- The impact of more than one month of trametinib therapy upon RAI uptake and/or efficiacy is unknown. Patients who do not receive ^{131}I therapy after the second ^{124}I PET/CT scan and remain on trametinib may be evaluated with a third Thyrogen-stimulated ^{124}I PET/CT scan (with the procedure detailed in Section 10.0 for Week 5) 4 weeks or more after completion of the prior ^{124}I PET/CT scan process. If the lesional dosimetry criteria for ^{131}I therapy is met on the third ^{124}I PET/CT, patients can go on to be prepared for/treated with ^{131}I and followed as detailed in Section 10.0 (in the calendar under the heading "*Study Calendar for* PATIENTS WHO RECEIVE RAI *(Week 5, Day 6 and beyond)*" (treatment with ^{131}I is not mandatory). If the third ^{124}I PET/CT scan results do not fulfill the ^{131}I treatment criteria, patients may continue on trametinib alone with the evaluations/treatments required for Cohort C.
- The effect of food on trametinib absorption is unknown. The current recommendation is to administer trametinib on an empty stomach, either 1 hr before or 2 hr after a meal; the recommendation to administer trametinib fasting may change based on emerging data.
- The patient will be requested to maintain a medication diary for each dose of medication (Appendix C). The medication diary will be returned to clinic staff at the

end of each course.

5.1.2 Diagnostic Agent thyrotropin alpha (Thyrogen;Genzyme)

Patients will undergo ^{124}I PET/CT scanning after thyrotropin alpha (Thyrogen;Genzyme Corp., Cambridge, MA) 0.9 mg IM daily injections (for two consecutive days) as previously described (Robbins et al., 2002). Thyrogen contains a highly purified recombinant form of human thyroid stimulating hormone (TSH), and is FDA approved for thyroid dosimetry.

5.1.3 Diagnostic/Therapeutic Agent ^{131}I (RAI)

^{131}I will be used for dosimetry studies and treatment of the patients whose second lesional dosimetry reveals iodine incorporation that satisfies the ^{131}I treatment threshold (see Section 5.1.4). ^{131}I has a half-life of 8 days and relatively high principal photon energy of 364 keV characterized by beta particle emissions. It will be supplied by MDS Nordion , DraxImage, or International Isotopes. It is administered orally in the form of capsules or liquid. Pregnancy is the only contraindication to radioiodine treatment. A beta-HCG pregnancy test must be performed up to 2 days prior to the administration of ^{131}I.

^{131}I therapeutic dosing will be guided by the whole body and blood dosimetry determination of the maximum tolerated activity (MTA): the ^{131}I activity administered concomitantly with trametinib is not to exceed the MTA plus 3 mCi (i.e., [^{131}I activity administered] $\leq$ [MTA + 3 mCi]).

5.1.4 Diagnostic Agent ^{124}I PET tracer

Clinical grade ^{124}I was first produced at MSK in the 1950s. It has been produced in MSK cyclotrons by bombarding tellurium targets. It is purified by novel radiochemical techniques. It has been safely used for diagnostic studies in >40 thyroid cancer patients at MSK for over 5 years. Clinical grade ^{124}I will be provided by the MSK cyclotron staff or by an outside supplier (Sofie Biosciences (fka IBA Molecular and Zevacor), 3 D Imaging LLC, or NCM) who meets MSK's minimum specifications as stated in our IND. I-124 preparation is detailed in MSK held IND # 71343. Normal organ dosimetry of ^{124}I is provided in Appendix D (Note, this is a general guideline for organ dosimetry).

^{124}I (dose, route, schedule, timing relative to imaging, special precautions or procedures, required pre-administration lab parameters): Approximately 6 mCi (range 4-7 mCi) of ^{124}I will be administered orally on Day 3 of the lesional dosimetry protocol, 2 days prior to PET/CT image acquisition (see Section 10 for the Study Calendar). A beta-HCG pregnancy test must be performed within 2 days prior to the administration of ^{124}I.

Image Acquisition/Analysis/Interpretation Details: Since ^{124}I PET/CT analysis will be performed at more than one participating site, before patients are imaged at any site a NEMA/IEC body phantom will be imaged and results analyzed under conditions similar to those to be used for patients. The phantom approximates the size and shape of a typical adult cross-section and contains six fillable spheres of diameter ranging from 10mm to 37mm surrounding a central cylindrical compartment containing non-radioactive lung equivalent material. The spheres and outer background compartment will be filled with ^{124}I of precisely known activity concentration in the ratio of 5:1. The

activity concentration will be determined from the supplier's activity measurement (recommended activity approximately 150MBq (4mCi)) and a confirming measurement in a dose calibrator at the site using an approved calibration setting, followed by careful dilution and measurement of residual activities. Following a scan of sufficient length to cover the whole phantom (two bed positions with ten minutes per bed for the phantom, patients will need more), data should be reconstructed with appropriate clinical parameters for the scanner used. These should include CT attenuation correction, scatter correction, and parameters specific to I124 – 4.18 day half life, 0.23 positron abundance, and a cascade gamma correction. SUV's and activity concentrations within each sphere, the active background, the central lung compartment, and outside the phantom should be determined using an appropriate VOI as for a patient. After applying partial volume recovery coefficients appropriate for the scanner used and for the individual sphere size, all measurements should match the activity concentrations derived from the dose calibrator measurements. Any discrepancies should be addressed. The resolution will depend on the cause and may involve modification of technique or possibly a correction factor. Raw data, a record of all measurements, procedures and parameters used, and results for the phantom study should be forwarded to MSK for review before commencing patient imaging.

The ^{124}I PET-CT scan will be performed on a PET/CT scanner at 2 days post-administration of approximately 6 mCi (range 4-7 mCi) of ^{124}I, the time at which maximal uptake of iodide by thyroid tumors generally occurs. The index lesion (i.e. metastatic thyroid tumor) will be identified by radiology co-investigators. The index lesion volume (in milliliters, ml), V_{lesion}, will be estimated by the CT study performed for attenuation correction and anatomic registration as part of the ^{124}I PET-CT scan on the PET/CT scanner. Once reconstructed, and using the commercial image-processing software provided on the PET/CT scanner's computer or a compatible, networked workstation, regions of interest (ROIs) circumscribing the index lesion on all contiguous CT slices on which the lesion appears will be drawn, yielding V_{lesion}. **Only lesions on the first ^{124}I PET-CT scan that are $\geq$ 5 mm in length in the minimum diameter will be used as the index lesion for this analysis.**

Using the PET acquisition and processing parameters routinely used for PET-CT scans at the participating sites, the reconstructed PET images will be parameterized, as usual, in terms of standard uptake value (SUV) (≡ μCi measured by PET/g of tissue / μCi administered/g of total-body mass). Using the commercial image-processing software provided on the PET/CT scanner's computer or a compatible workstation, ROIs circumscribing the index lesion on all contiguous PET slices on which the lesion appears

will be drawn, yielding the index lesion mean SUV, $\overline{SUV}_{lesion}$; alternatively, the lesion ROIs drawn on the CT scan (see above) may be superimposed on the registered PET

images to yield $\overline{SUV}_{lesion}$. From the definition of the SUV (above), the mean PET-derived ^{124}I concentration (in μCi/ml) in the index lesion not corrected for partial-

volume-averaging, $(\overline{[^{124}I\ A]}_{lesion})_{RC\text{-}uncorrected}$, will be calculated from $\overline{SUV}_{lesion}$:

$$(\overline{[^{124}I\ A]}_{lesion})_{RC\text{-}uncorrected} = \overline{SUV}_{lesion}\frac{AA}{M_{TB}} \quad (1)$$

where AA is the ^{124}I administered activity (in μCi) and M_{TB} is the patient total-body mass (in μCi).

Note that the SUVs provided by the PET scanner are *not* automatically corrected for partial-volume averaging. Using the CT-derived lesion volume, V_{lesion}, and the volume (V)-dependent recovery coefficient (ie PET-derived activity concentration (in μCi/ml)/actual activity concentration (in μCi/ml)), RC(V), previously measured for the PET/CT scanner, the PET-derived mean ^{124}I concentration (in μCi/ml) in the index lesion *not* corrected for partial-volume-averaging, $(\overline{[^{124}I\ A]}_{lesion})_{RC\text{-}uncorrected}$, will be corrected to yield the actual mean ^{124}I concentration in the index lesion, $(\overline{[^{124}I\ A]}_{lesion})_{RC\text{-}corrected}$:

$$\mathbf{(\overline{[^{124}I\ A]}_{lesion})_{RC\text{-}corrected} = \frac{(\overline{[^{124}I\ A]}_{lesion})_{RC\text{-}uncorrected}}{RC(V_{lesion})}} \quad (2)$$

The mean ^{124}I activity concentration in the index lesion per ^{124}I administered activity (in μCi/ml/mCi), $(\overline{[^{124}I\ A_{per\ mCi}]}_{lesion})_{RC\text{-}corrected}$, will then be calculated:

$$(\overline{[^{124}I\ A_{per\ mCi}]}_{lesion})_{RC\text{-}corrected} = \frac{(\overline{[^{124}I\ A]}_{lesion})_{RC\text{-}corrected}}{AA/1000} \quad (3)$$

$(\overline{[^{124}I\ A_{per\ mCi}]}_{lesion})_{RC\text{-}corrected}$ can be converted to the mean ^{131}I activity concentration in the index lesion per ^{131}I administered activity (in μCi/ml/mCi), $(\overline{[^{131}I\ A_{per\ mCi}]}_{lesion})_{RC\text{-}corrected}$, ^{131}I (and not ^{124}I) being used for therapy:

$$(\overline{[^{131}I\ A_{per\ mCi}]}_{lesion})_{RC\text{-}corrected} = (\overline{[^{124}I\ A_{per\ mCi}]}_{lesion})_{RC\text{-}corrected}\ e^{(\lambda_{I124} - \lambda_{I131})t_{imaging}} \quad (4)$$

where λ_{I124} and λ_{I131} are the physical decay constants of ^{124}I (0.00693 /h) and ^{131}I (0.00359 /h), respectively, and $t_{imaging}$ is the time post-administration of PET-CT imaging (in h).

Based on prior clinical experience, the biological half-life, T_b, of iodine in metastatic thyroid cancer lesions is typically 2 d (= 48 h). For ^{131}I, with a physical half-life T_p of

8.04 d = 193 h, the effective half-life, T_e, of ^{131}I in the index lesion is therefore:

$$T_e = \frac{T_b\, T_p}{T_b + T_p} \quad (5a)$$

$$= \frac{48\text{ h} \bullet 193\text{ h}}{48\text{ h} + 193\text{ h}} \quad (5b)$$

$$= 38.4\text{ h} \quad (5c)$$

Assuming, as usual, that the uptake of radioiodine in the index lesion (ie the 24- to 48-h uptake value) will be instantaneous and that ^{131}I lesion irradiation will be due exclusively to complete local absorption of ^{131}I beta-rays, the mean lesion absorbed dose (in rad/mCi ^{131}I), $\overline{[^{131}I\ D_{per\ mCi}]}_{lesion,}$ will be:

$$\overline{[^{131}I\ D_{per\ mCi}]}_{lesion} = 1.44\ T_e\ (\overline{[^{131}I\ A_{per\ mCi}]}_{lesion})_{RC\text{-}corrected}\ \Delta_{np} \quad (6a)$$

$$= 1.44 \bullet 38.4\text{ h}\ (\overline{[^{131}I\ A_{per\ mCi}]}_{lesion})_{RC\text{-}corrected}\ 0.405\text{ g-rad/}\mu\text{Ci-h} \quad (6b)$$

$$= 22.4\ (\overline{[^{131}I\ A_{per\ mCi}]}_{lesion})_{RC\text{-}corrected} \quad (6c)$$

where Δ_{np} = 0.405 g-rad/μCi-h is the equilibrium dose constant for non-penetrating radiations (ie beta-rays) for ^{131}I.

Finally, the ^{131}I administered activity (in mCi) required to deliver the stipulated mean absorbed dose of 2,000 rad to the index lesion, $^{131}I\ AA_{2000\ rad \rightarrow lesion}$, will be:

$$^{131}I\ AA_{2000\ rad \rightarrow lesion} = \mathbf{2{,}000\ rad/[}^{131}I\ D_{per\ mci}]lesion \quad (7)$$

If the projected $^{131}I\ AA_{2000\ rad \rightarrow lesion}$ is reasonable ($\leq$ 300 mCi), the treating physican(s) will confer and make a clinical decision as to whether ^{131}I therapy should proceed. If the decision is made to proceed to therapy, the patient will undergo the standard-of-care (ie non-investigational) "whole body and blood dosimetry" to determine the maximum tolerated activity (MTA). ^{131}I therapeutic dosing will be guided by the whole body and blood dosimetry determination of the maximum tolerated activity (MTA): the ^{131}I activity administered concomitantly with trametinib is not to exceed the MTA plus 3 mCi (i.e., [^{131}I activity administered] $\leq$ [MTA + 3 mCi]).

The foregoing analysis will have to be performed only for the second ^{124}I administration.

5.2 General Concomitant Medication and Supportive Care Guidelines

Patients will have to adhere to a low iodine diet 5 days prior to the initiation of the lesional dosimetry process and continued until the completion of that process. For those patients who

will go on to receive therapeutic ^{131}I, they will need to be continued on the low iodine diet through 1 day after ^{131}I administration. For details of the suggested low iodine diet, please see Appendix B.

5.3 Duration of Therapy

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

1. Disease progression (however, Cohort A and B patients with evidence of clinical disease progression or RECIST v1.1 radiographic progression (such as on the ^{124}I PET/CTs or other scans) prior to the 6-month evaluation of the primary/secondary endpoints may be continued on treatment and the study if the treating physician deems it clinically reasonable),

2. Intercurrent illness that prevents further administration of treatment,

3. Unacceptable adverse event(s),

4. Patient decides to withdraw from the study,

5. General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator,

6. (For Cohort A and B patients) It is determined that a patient will not receive therapeutic ^{131}I and the treating physician determines that it is not clinically reasonable to continue with trametinib therapy alone or the patient does not want to continue with trametinib therapy alone,

7. For patients who do receive therapeutic ^{131}I, trametinib will be continued until 2 days after ^{131}I is administered. Patients will remain on study for tumor assessments that will be completed approximately 6 months after ^{131}I therapy. Safety monitoring for trametinib related toxicities will be continued until 30 days after last trametinib dose.

8. All study therapy has been completed as planned.

5.4 Duration of Follow Up

Adverse events will be followed for 30 days after the last dose of trametinib. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.5 Criteria for Removal from Study

Patients will be removed from the study when criteria numbers 2-8 in Section 5.3 apply or if the following criteria apply:

- Progression of disease on Cohort C,
- Progression of disease on Cohort A or B and the patient will not be continuing to Cohort C (exceptions to this for Cohorts A and B are detailed in the Section 5.3),
- The patient is started on another therapy for his/her thyroid cancer besides what is detailed as allowed in this protocol

The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Trametinib Dose Modifications

The table below outlines the dose levels to be used for any necessary trametinib dose modifications:

Dose Level	Trametinib Dose/Schedule
0	2 mg QD
-1	1.5 mg QD
-2	1 mg QD

A maximum of two trametinib dose level reductions are allowed. If a third dose level reduction is required, treatment will be permanently discontinued. In order to ensure that patients have taken trametinib for a minimum of 7 consecutive days, missed doses may be made up (as per Section 5.1.1) and study assessments/treatments appropriately rescheduled. If trametinib is missed for ≥ 7 days or interruptions in trametinib dosing have occurred prior to whole body and blood dosimetry and ^{131}I (RAI) treatment, then having some or all of the doses made up and the study assessments/treatments appropriately rescheduled may be considered after discussion with the MSK Principal Investigator (this is not a requirement) (as per Section 5.1.1).

6.1.1 Trametinib Dose Modification for Toxicities Not Specified in Subsequent Sections

Trametinib Treatment Modification for Clinically Significant Toxicities Deemed Related to Trametinib (This section is not for specific AEs such as hypertension, rash, ejection fraction changes, pneumonitis, diarrhea, liver chemistry, QTc prolongation, or visual changes. Refer to other sections for these specific AEs).		
CTCAE v4 Grade	**Management Guideline**	**Dose Modification**
Grade 1	Monitor as clinically indicated. Provide supportive care according to institutional standards	Continue trametinib at current dose level.
Grade 2		Continue trametinib at current dose level. If intolerable, interrupting treatment may be considered only after discussion with the Principal Investigator. For patients who have trametinib held for grade 2 toxicities, trametinib may be restarted at the same dose or with one level of dose reduction.

Trametinib Treatment Modification for Clinically Significant Toxicities Deemed Related to Trametinib (This section is not for specific AEs such as hypertension, rash, ejection fraction changes, pneumonitis, diarrhea, liver chemistry, QTc prolongation, or visual changes. Refer to other sections for these specific AEs).		
CTCAE v4 Grade	**Management Guideline**	**Dose Modification**
Grade 3		• Interrupt treatment until resolution to grade 1 or baseline*. • Upon resolution to baseline or grade 1, restart with one level of dose reduction*. • If the Grade 3 toxicity recurs, interrupt trametinib. When toxicity resolves to Grade 1 or baseline, restart trametinib **reduced by another dose level**
Grade 4		Permanently discontinue trametinib.**
Trametinib should be discontinued if treatment delay is > 21 days due to toxicities. If the investigator concludes that continued trametinib will benefit a patient, the study chair (MSK PI) and CTEP Medical Monitor, may be consulted for the possibility of resuming trametinib, provided that toxicities have resolved to baseline or grade 1. *For non-life threatening Grade 3 laboratory abnormalities, trametinib may be continued at the same dose without interruption if deemed appropriate by the MSK Principal Investigator. **For Grade 4 lymphopenia, study treatment may be continued at the same dose level without interruption based upon investigator judgment.		

6.1.2 Trametinib Dose Modification for Rash

Rash is a frequent AE observed in patients receiving trametinib (Investigator's Brochure, 2012a). Recommendations for supportive care and guidelines for dose modifications for rash are based on experience with other MEK inhibitors and EGFR inhibitors (Balagula *et al.*, 2010; Lacouture *et al.*, 2011).

The institutional standards for the management of skin-related AEs can differ from these guidelines. In this case, best clinical judgment should be applied and a consultation with the MSK Principal Investigator or the CTEP Medical Monitor, through MSK, may be required.

Guidelines for Supportive Care of Rash	
Type of Care	**Action**
Prevention/Prophylaxis[a]	• Avoid unnecessary exposure to sunlight. • Apply broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥15 at least twice daily when exposed to sunlight. • Use thick, alcohol-free emollient cream (*e.g.*, glycerine and cetomacrogol cream) on dry areas of the body at least twice daily. • Use mild-strength topical steroid (hydrocortisone 1% cream) or topical antibiotic (*e.g.*, clindamycin) (should be applied at least twice daily starting on Day 1 of study treatment to areas such as face, chest, and upper back) or oral antibiotics (*e.g.*, doxycycline 100 mg BID, minocycline 100 mg BID).

Guidelines for Supportive Care of Rash	
Type of Care	**Action**
Symptomatic Care[b]	• Pruritic lesions: Cool compresses and oral antihistamine therapies. • Fissuring lesions: Monsel's solution, silver nitrate, or zinc oxide cream. • Desquamation: Thick emollients and mild soap. • Paronychia: Antiseptic bath, local potent corticosteroids in addition to antibiotics; if no improvement, consult dermatologist or surgeon. • Infected lesions: Appropriate bacterial/fungal culture-driven systemic or topical antibiotics.
[a] Rash prophylaxis is recommended for the first 6 weeks of study treatment. [b] Patients who develop rash/skin toxicities should be seen by a qualified physician and should receive evaluation for symptomatic/supportive care management.	

Trametinib Dose Modification Guidelines and Management for Rash Deemed Related to Trametinib		
Rash Severity	**Management Guideline**	**Dose Modification**
Grade 1	• Initiate prophylactic and symptomatic treatment measures.[1] • Use moderate strength topical steroid.[2]	• Continue trametinib.
Grade 2	• Initiate prophylactic and symptomatic treatment measures.[1] • Use moderate strength topical steroid.[2] • Reassess after 2 weeks.	• Continue trametinib. • If the rash is intolerable, trametinib may be interrupted until recovery to ≤ grade 1 or continued at a one dose level reduction after discussion with the MSK Principal Investigator. • If trametinib is interrupted, once rash recovers to ≤ grade 1, trametinib may be restarted at the original dose or at a one dose level reduction. • If trametinib was continued at a one dose level without treatment interruption and the rash recovers to ≤ grade 1 within 2 weeks, increasing the dose to previous dose level is permitted.
Grade ≥3	• Use moderate strength topical steroids PLUS oral methyl-prednisolone dose pack.[2] • Consult dermatologist.	• Interrupt trametinib until rash recovers to ≤ grade 1*. • **Restart with trametinib at the original dose or reduced by one dose level.**[3,4] • If no recovery to ≤ grade 2 within 4 weeks, **permanently discontinue trametinib**.
1. Rash prophylaxis is recommended for the first 6 weeks of study treatment. 2. Moderate-strength topical steroids: Hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream 3. Approval of CTEP Medical Monitor is required to restart study treatment after >4 weeks of interruption. 4. Trametinib may be escalated to previous dose level if no rash is evident 4 weeks after restarting study treatment. * If grade 3 rash develops without optimal supportive care management and is considered tolerable, the treating physician may elect to continue trametinib while initiating optimal supportive care management.		

6.1.3 Trametinib Dose Modifications for Visual Changes

Trametinib is known to be associated with visual adverse events. An ophthalmologist should be consulted if changes in vision develop. However, if the visual changes are clearly unrelated to

study treatment (e.g., allergic conjunctivitis), then monitor closely as it may be reasonable to defer ophthalmic examination. Special attention should be given to retinal findings (*e.g.*, retinal pigment epithelial detachment (RPED) or retinovascular abnormalities (*i.e.*, branch or central retinal vein occlusions [RVO]). For events of visual changes regardless of severity but for which an ophthalmic examination is conducted, a blood sample for PK analysis is encouraged when feasible, and the blood sample should be drawn as close as possible to the time of the event.

The ophthalmology exam will include best corrected visual acuity, visual field examination, tonometry, slit lamp biomicroscopic examination, and indirect fundoscopy. Optical coherence tomography is recommended at scheduled visits and if retinal abnormalities are suspected. Other types of ancillary testing including visual field examination, fundus photography, and fluorescein angiography may also be indicated as determined by clinical exam.

Guidelines regarding event management and dose reduction for visual changes considered to be related to study treatment are provided in the table below.

Management and Trametinib Dose Modification for Visual Changes and/or Ophthalmic Examination Findings		
Event CTCAE Grade	**Management Guideline**	**Dose Modification**
Grade 1*	• Consult ophthalmologist within 7 days of onset.	• If dilated fundus examination cannot be performed within 7 days of onset, hold trametinib until RPED and RVO can be excluded by retina specialist/ophthalmologist. • If RPED and RVO excluded, continue/or restart trametinib at same dose level. • If RPED suspected/diagnosed: See RPED dose modification table below (following this table); **report as SAE**. • If RVO diagnosed: **Permanently discontinue trametinib and report as SAE**.
Grade 2 and Grade 3	• Consult ophthalmologist immediately.	• Hold trametinib • If RPED or RVO excluded, restart trametinib at same dose level after visual AE is ≤ grade 1. If no recovery within 3 weeks, discontinue trametinib • If RPED diagnosed: See RPED dose modification table below; **report as SAE**. • If RVO: **Permanently discontinue trametinib and report as SAE**.
Grade 4	• Consult ophthalmologist immediately. • Report as SAE.	• Hold Trametinib • If RPED/RVO excluded, may restart trametinib at same or reduced dose after discussion with the CTEP Medical Monitor. • **If RVO or RPED, permanently discontinue trametinib**.
Abbreviations: RPED = retinal pigment epithelial detachments; RVO = retinal vein occlusion; SAE = serious adverse event *If visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), monitor closely but ophthalmic examination is not required.		

Trametinib Dose Modification for RPED	
Event **CTCAE Grade**	**Action and Dose Modification**
Grade 1 RPED (Asymptomatic; clinical or diagnostic observations only)	• Continue treatment with retinal evaluation monthly until resolution. If RPED worsens, follow instructions below.
Grade 2-3 RPED (Symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL)	• Interrupt trametinib. • Retinal evaluation monthly. • If improved to ≤ Grade 1, restart trametinib with one dose level reduction (reduced by 0.5 mg) or discontinue in patients taking trametinib 1 mg daily. • If no recovery within 4 weeks permanently discontinue trametinib

6.1.4 Trametinib Dose Modification for Diarrhea

Episodes of diarrhea have occurred in patients receiving trametinib (Investigator's Brochure, 2012a). Other frequent causes of diarrhea may include concomitant medications (*e.g.*, stool softeners, laxatives, antacids, *etc.*), infections by *C. difficile* or other pathogens, or partial bowel obstruction. Those conditions should be excluded.

Guidelines regarding management and dose modification for diarrhea considered related to trametinib are provided in the table below.

Management and Trametinib Dose Modification Guidelines for Diarrhea Deemed Related to Trametinib		
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Uncomplicated Diarrhea,[1] Grade 1 or 2	• Diet: Stop all lactose containing products; eat small meals, BRAT-diet (banana, rice, apples, toast) recommended. • Hydration: 8-10 large glasses of clear liquids per day (*e.g.*, Gatorade or broth). • Loperamide[3]: Initially 4 mg, followed by 2 mg every 4 hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea-free for 12 hours. • Diarrhea >24 hours: Loperamide 2 mg every 2 hours; maximum 16 mg/day. Consider adding oral antibiotics. • Diarrhea >48 hours: Loperamide 2 mg every 2 hours; maximum 16 mg/day. Add budesonide or other second-line therapies (otreotide, or tincture of opium) and oral antibiotics.	• Continue trametinib. • If diarrhea is grade 2 and intolerable, interrupt trametinib until diarrhea resolves to grade ≤1. • If there is an interruption in dosing, trametinib can be continued at the same dose level when treatment is restarted.

Management and Trametinib Dose Modification Guidelines for Diarrhea Deemed Related to Trametinib		
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Uncomplicated Diarrhea,[1] Grade 3 or 4 **Any Complicated Diarrhea[2]**	• Clinical evaluation mandatory. • Loperamide[3]: Initially 4 mg, followed by 2 mg every 4 hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea-free for 12 hours. • Oral antibiotics and second-line therapies if clinically indicated • Hydration: Intravenous fluids if clinically indicated. • Antibiotics (oral or intravenous) if clinically indicated. • Intervention should be continued until the subject is diarrhea-free for ≥24 hours. • Intervention may require hospitalization for subjects at risk of life-threatening complications.	• Interrupt trametinib until diarrhea resolves to ≤ grade 1. • Restart with trametinib reduced by one dose level.[4] • If 3 dose reductions of study treatment are clinically indicated, **permanently discontinue trametinib**. • If treatment delay is >21 days, discontinue trametinib.
1. **Uncomplicated diarrhea** defined by the absence of symptoms such as vomiting ≥ grade 2, pyrexia, sepsis, neutropenia ≥ grade 3, frank bleeding, and/or dehydration requiring intravenous fluid substitution (the administration of fluids alone can still be considered 'uncomplicated diarrhea' if judged by the investigator as appropriate). 2. **Complicated diarrhea** defined by the presence of symptoms such as vomiting ≥ grade 2, pyrexia, sepsis, neutropenia ≥ grade 3, frank bleeding, and/or dehydration requiring intravenous fluid substitution (the administration of fluids alone can still be considered 'uncomplicated diarrhea' if judged by the investigator as appropriate). 3. Loperamide should be made available prior to start of study treatment so loperamide administration can begin at the first signs of diarrhea. 4. Escalation of trametinib to previous dose level is allowed after consultation with the medical monitor and in the absence of another episode of complicated or severe diarrhea in the 4 weeks subsequent to dose reduction.		

6.1.5 Trametinib Dose Modification for Liver Chemistry Changes

Trametinib Dose Modification for Liver Function Test Abnormalities Deemed Related to Trametinib	
Event	**Treatment modifications and assessment/monitoring**
• ALT ≥3x ULN **but** <5x ULN **and** TB <2x ULN, **without** symptoms considered related to liver injury or hypersensitivity **and** who can be monitored weekly for 4 weeks	• **May continue study drug**. • Report as SAE if CTEP-AERS reporting criteria is met. • If **liver chemistry stopping criteria** are met any time, proceed as described below. **MONITORING:** Repeat LFT (ALT, AST, ALK, bilirubin) until they return to normal/baseline or stabilise (LFT may be every 2 weeks after 4 weeks if ALT <3x ULN and TB <2 ULN).

Trametinib Dose Modification for Liver Function Test Abnormalities Deemed Related to Trametinib	
Event	**Treatment modifications and assessment/monitoring**
<u>Criteria for discontinuing study drug</u>: When any of the liver stopping criteria below is met, discontinue trametinib **1.** ALT ≥3xULN **and** <u>bilirubin</u> ≥2x ULN or >35% direct bilirubin [1, 2] 2. ALT ≥ 3xULN **and** <u>INR</u> >1.5, if INR measured[2] (INR threshold does not apply if subject is on anticoagulant) **3.** ALT ≥5x ULN 4. ALT ≥3x ULN persists for ≥4 weeks 5. ALT ≥3x ULN **and** cannot be monitored weekly for 4 weeks 6. ALT ≥3x ULN associated with symptoms[3] (new or worsening) believed to be related to liver injury or hypersensitivity	• **Immediately discontinue study treatment**. • **Do not restart/rechallenge** unless approved by CTEP trametinib medical monitor. [• Report as SAE if: 1) CTEP-AERS reporting criteria are met, or 2) patients meet criteria 1-2. • Perform liver event **ASSESSMENT AND WORKUP (see below)**. • Monitor the subject until liver chemistries resolve, stabilize, or return to baseline (see **MONITORING** below). [**MONITORING:** <u>*In patients stopping for criteria 1-2 (with abnormal TB and INR, indicating potentially more significant liver toxicities):*</u> • Repeat liver chemistries (ALT, AST, ALK, bilirubin) and perform liver event **follow-up assessments** within **24 hours**. • Monitor subjects twice weekly until LFT return to normal/baseline or stabilize. • A specialist or hepatology consultation is recommended. <u>*In patients stopping for criteria 2-6:*</u> • Repeat LFT and perform liver event **follow up assessments** within **24-72 hrs** • Monitor subjects weekly until LFTs return to normal/baseline or stabilize. **ASSESSMENT and WORKUP:** • Viral hepatitis serology.[4] • If possible, obtain blood sample for PK analysis.[5] • CPK and LDH. • Fractionate bilirubin, if total bilirubin ≥2x ULN. • CBC with differential to assess eosinophilia. • Record clinical symptoms of liver injury, or hypersensitivity on AE CRF. • Record concomitant medications (including acetaminophen, herbal remedies, other over the counter medications). • Record alcohol use. <u>*Additional work up for patient stopping for criteria 1-2 (with abnormal TB and INR, indicating potentially more significant liver toxicities)*</u>: • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • acetaminophen adduct HPLC assay (in subjects with likely acetaminophen use in the preceding). • If there is underlying chronic hepatitis B (e.g. positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody.[6] • Liver imaging (ultrasound, MRI, CT) and /or liver biopsy.
Footnotes: 1 bilirubin fractionation should be performed if testing is available. If bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, which indicates direct bilirubin elevations and suggesting liver injury. 2. All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3x ULN **and** INR >1.5 (if INR measured) may indicate severe liver injury (possible "Hy's Law"). INR measurement is not required, and the threshold value stated will not apply to subjects receiving anticoagulants.	

Trametinib Dose Modification for Liver Function Test Abnormalities Deemed Related to Trametinib	
Event	**Treatment modifications and assessment/monitoring**
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia) 4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody 5. PK sample is desired if feasible. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. 6. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) (Le Gal *et al.*, 2005).	

6.1.6 Trametinib Dose Modification for Pneumonitis

Pneumonitis has been observed in patients receiving trametinib. To reduce the risk of pneumonitis, patients will be monitored closely for symptoms and evaluated with imaging and functional tests. Dose modification and supportive care guidelines for pneumonitis are described in the table below.

Guidelines for Trametinib Dose Modifications for Pneumonitis Deemed Related to Trametinib		
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Grade 1	• CT scan (high-resolution with lung windows) recommended. • Work-up for infection. • Monitoring of oxygenation via pulse-oximetry recommended. • Consultation with pulmonologist recommended.	Continue trametinib at current dose.
Grade 2	• CT scan (high-resolution with lung windows). • Work-up for infection. • Consult pulmonologist. • Pulmonary function tests: If < normal, repeat every 8 weeks until ≥ normal. • Bronchoscopy with biopsy and/or BAL recommended. • Symptomatic therapy including corticosteroids if clinically indicated.	• Interrupt trametinib until recovery to grade ≤1. • If AE resolved to grade ≤1 and relationship to trametinib is equivocal, restarting trametinib with one dose reduction may be considered, after discussion with the medical monitor. • If treatment delay is > 4 weeks, **permanently discontinue trametinib**.

Guidelines for Trametinib Dose Modifications for Pneumonitis Deemed Related to Trametinib		
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Grade 3	• CT scan (high-resolution with lung windows). • Work-up for infection. • Consult pulmonologist. • Pulmonary function tests-if < normal, repeat every 8 weeks until ≥ normal. • Bronchoscopy with biopsy and/or BAL if possible. • Symptomatic therapy including corticosteroids as clinically indicated.	• Interrupt trametinib until recovery to grade ≤1. • If AE resolved to grade ≤1 and relationship to trametinib is equivocal, restarting trametinib with one dose reduction may be considered, after discussion with the medical monitor. • If treatment delay is >4 weeks, **permanently discontinue trametinib**.
Grade 4	Same as grade 3.	**Permanently discontinue trametinib.**
Abbreviations: BAL = bronchoalveolar lavage; CT = computed tomography.		

6.1.7 Trametinib Dose Modification for Reduced Left Ventricular Ejection Fraction

Decreases of the left ventricular ejection fraction (LVEF) have been observed in patients receiving trametinib. Therefore, ECHO/MUGAs must be performed in regular intervals outlined in the Study Calendar. The same procedure (either ECHO or MUGA, although ECHO is preferred) should be performed at baseline and at follow-up visit(s).

Trametinib Dose Modification Guidelines and Stopping Criteria for LVEF Decrease Deemed Related to Trametinib		
Clinic	**LVEF-drop (%) or CTCAE grade**	**Action and Dose Modification**
Asymptomatic	Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN.	• Interrupt trametinib and repeat ECHO/MUGA within 2 weeks.[a] • If the LVEF **recovers** within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline): – Consult with the CTEP trametinib medical monitor and request approval for restart. – Restart treatment with trametinib at reduced dose by one dose level.[b] – Repeat ECHO/MUGA 2, 4, 8, and 12 weeks after re-start; continue in intervals of 12 weeks thereafter. • If LVEF **does not** recover within 4 weeks: – Consult with cardiologist. – **Permanently discontinue trametinib**. – Report as SAE – Repeat ECHO/MUGA after 2, 4, 8, 12, and 16 weeks or until resolution. – Consult with the CTEP trametinib medical monitor.[c]

Trametinib Dose Modification Guidelines and Stopping Criteria for LVEF Decrease Deemed Related to Trametinib		
Clinic	**LVEF-drop (%) or CTCAE grade**	**Action and Dose Modification**
Symptomatic[b]	• Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline • Grade 4: Resting LVEF ≤20%.	• **Permanently discontinue trametinib**. • **Report as SAE**. • **Consult with cardiologist**. • Repeat ECHO/MUGA after 2, 4, 8, 12, and 16 weeks or until resolution.
[a] If ECHO/MUGA does not show LVEF recovery after 2 weeks, repeat ECHO/MUGA 2 weeks later. [b] Escalation of trametinib to previous dose level can be considered if LVEF remains stable for 4 weeks after restarting of trametinib. Approval from the CTEP trametinib medical monitor is required. [c] Symptoms may include: dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.		

6.1.8 Trametinib Dose Modification for QTc Prolongation

Trametinib Withholding and Stopping Criteria for QTc Prolongation Deemed Related to Trametinib	
QTc Prolongation[a]	**Action and Dose Modification**
• QTcB ≥501 msec, or • Uncorrected QT >600 msec, or • QTcB >530 msec for subjects with bundle branch block	• Interrupt study treatment until QTcB prolongation resolves to grade 1 or baseline. • Test potassium, calcium, phosphorus, and magnesium. If abnormal, correct per routine clinical practice to within normal limits. • Review concomitant medication usage for a prolonged QTc. • Restart at current dose level.[b] • **If the event does not resolve or recurs after restarting, permanently discontinue study treatment.**
Abbreviations: msec = milliseconds; QTcB = QT interval on electrocardiogram corrected using Bazett's formula [a] Based on average QTc value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two or more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine if study treatments should be interrupted or discontinued. [b] if the QTc prolongation resolves to grade 1 or baseline, the subject may resume study treatment if the investigator and the CTEP trametinib medical monitor agree that the subject will benefit from further treatment.	

6.1.9 Trametinib Dose Modification for Hypertension

Increases in blood pressure (BP) have been observed in patients receiving trametinib. Recommendations for BP monitoring and management are provided below.

Monitoring: All BP assessments should be performed under the following optimal conditions:

- The subject has been seated with back support, ensuring that legs are uncrossed and flat on the floor.
- The subject is relaxed comfortably for at least 5 minutes.
- Restrictive clothing has been removed from the cuff area, and the right cuff size has been selected.

- The subject's arm is supported so that the middle of the cuff is at heart level.
- The subject remains quiet during the measurement.
- In subjects with an initial BP reading within the hypertensive range, a second reading should be taken at least 1 minute later, with the two readings averaged to obtain a final BP measurement. The averaged value should be recorded in the eCRF.
- Persistent hypertension is defined as an increase of systolic blood pressure (SBP) >140 mmHg and/or diastolic blood pressure (DBP) >90 mmHg in three consecutive visits with blood pressure assessments from two readings as described above. Visits to monitor increased blood pressure can be scheduled independently from the per-protocol visits outlined in the study calendar. Ideally, subsequent blood pressure assessments should be performed within 1 week.

Management and Trametinib Dose Modification for Hypertension Deemed Related to Trametinib		
Event	**Management Guideline**	**Dose Modification**
Definitions used in the table: - Persistent hypertension: Hypertension detected in two separate readings during up to three subsequent visits. - Well-controlled hypertension: Blood pressure of SBP ≤140 mmHg and DBP ≤90 mmHg in two separate readings during up to three subsequent visits. - Symptomatic hypertension: Hypertension associated with symptoms (*e.g.*, headache, light-headedness, vertigo, tinnitus, episodes of fainting or other symptoms indicative of hypertension) that resolve after the blood pressure is controlled within the normal range. - Asymptomatic hypertension: SBP >140 mmHg and/or DBP >90 mmHg in the absence of the above symptoms.		
(Scenario A) • Asymptomatic and persistent SBP of ≥140 and <160 mmHg, or DBP ≥90 and <100 mmHg, or Clinically significant increase in DBP of 20 mmHg (but still below 100 mmHg).	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP. If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B).	Continue trametinib at the current dose.

Management and Trametinib Dose Modification for Hypertension Deemed Related to Trametinib		
Event	**Management Guideline**	**Dose Modification**
(Scenario B) • Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, or Failure to achieve well-controlled BP within 2 weeks in Scenario A.	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP.	• Interrupt trametinib if clinically indicated. • Once BP is well-controlled, restart trametinib **reduced by one dose level**.[a]
(Scenario C) • Symptomatic hypertension or Persistent SBP ≥160 mmHg, or DBP ≥100 mmHg, despite antihypertensive medication and dose reduction of trametinib	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP. • Referral to a specialist for further evaluation and follow-up is recommended.	• Interrupt trametinib. • Once BP is well-controlled, restart trametinib **reduced by one dose level**.[a]
(Scenario D) Refractory hypertension unresponsive to above interventions or hypertensive crisis.	Continue follow-up per protocol.	**Permanently discontinue trametinib**.
a. Escalation of trametinib to previous dose level can be considered if BPs remain well controlled for 4 weeks after restarting of trametinib. Approval from Medical Monitor is required.		

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting (via CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

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

NOTE: The highest grade currently reported is noted in parentheses next to the AE in the SPEER. Report **ONLY** AEs higher than this grade expeditiously via CTEP-AERS. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE

listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

7.1.1 CAEPRs for CTEP IND Agent

7.1.1.1 CAEPR for Trametinib

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Trametinib (GSK1120212B, NSC 763093)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1111 patients.* Below is the CAEPR for Trametinib (GSK1120212B).

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

Version 2.6, October 10, 2019[1]

Adverse Events with Possible Relationship to Trametinib (GSK1120212B) (CTCAE 5.0 Term) [n= 1111]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
CARDIAC DISORDERS			
		Heart failure	
		Left ventricular systolic dysfunction	
	Sinus bradycardia		
EYE DISORDERS			
	Blurred vision		
	Dry eye		
		Eye disorders - Other (chorioretinopathy also known as retinal pigment epithelial detachment)	
		Eye disorders - Other (retinal vein occlusion)	

Adverse Events with Possible Relationship to Trametinib (GSK1120212B) (CTCAE 5.0 Term) [n= 1111]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Eye disorders - Other (visual disorders)[2]		
		Papilledema	
	Periorbital edema		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colitis	
		Colonic perforation	
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema face		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
Generalized edema[3]			***Generalized edema[3] (Gr 2)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[4]		
INFECTIONS AND INFESTATIONS			
	Folliculitis		***Folliculitis (Gr 2)***
	Lung infection		
	Paronychia		***Paronychia (Gr 2)***
	Skin infection		***Skin infection (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	CPK increased		
	Ejection fraction decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hypoalbuminemia		
	Hypomagnesemia		***Hypomagnesemia (Gr 2)***
	Hyponatremia		***Hyponatremia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
	Pain in extremity		***Pain in extremity (Gr 2)***
		Rhabdomyolysis	

Adverse Events with Possible Relationship to Trametinib (GSK1120212B) (CTCAE 5.0 Term) [n= 1111]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
	Nail changes		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		***Pruritus (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (drug reaction with eosinophilia and systemic symptoms [DRESS])	
Skin and subcutaneous tissue disorders - Other (rash)[5]			***Skin and subcutaneous tissue disorders - Other (rash)[5] (Gr 3)***
		Stevens-Johnson syndrome[6]	
VASCULAR DISORDERS			
	Hypertension		***Hypertension (Gr 3)***
		Thromboembolic event (venous)	
	Vascular disorders - Other (hemorrhage)[7]		

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

[2]Visual disorders include visual disturbance that can be associated with conjunctival hemorrhage, corneal graft rejection, cyclitis, eye nevus, halo vision, iritis, macular edema, retinal hemorrhage, visual acuity reduced, visual impairment, and vitreous detachment.

[3]Generalized edema includes edema, lymphedema, and edema limbs.

[4]Hypersensitivity (allergic reactions) may present with symptoms such as fever, rash, increased liver function tests, and visual disturbances.

[5]Skin and subcutaneous tissue disorders - Other (rash) may include rash, rosacea, rash acneiform, erythematous rash, genital rash, rash macular, exfoliative rash, rash generalized, erythema, rash papular, seborrhoeic dermatitis, dermatitis psoriasiform, rash follicular, skin fissures, and skin chapped.

[6]Stevens-Johnson syndrome has been observed in patients treated with trametinib and dabrafenib

combination.

[7]The majority of hemorrhage events were mild. Major events, defined as symptomatic bleeding in a critical area or organ (e.g., eye, GI hemorrhage, GU hemorrhage, respiratory hemorrhage), and fatal intracranial hemorrhages have been reported.

Adverse events reported on trametinib dimethyl sulfoxide (GSK1120212B) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that trametinib dimethyl sulfoxide (GSK1120212B) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Disseminated intravascular coagulation; Febrile neutropenia; Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Myocardial infarction; Restrictive cardiomyopathy; Sinus tachycardia
EYE DISORDERS - Corneal ulcer; Eyelid function disorder; Flashing lights; Floaters; Glaucoma; Photophobia
GASTROINTESTINAL DISORDERS - Ascites; Duodenal ulcer; Esophageal necrosis; Esophageal ulcer; Esophagitis; Gastric hemorrhage[7]; Gastric ulcer; Gastritis; Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gastrointestinal fistula; Gingival pain; Hemorrhoidal hemorrhage[7]; Ileus; Obstruction gastric; Pancreatitis; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; General disorders and administration site conditions - Other (axillary pain); Localized edema; Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure; Hepatic pain; Hepatobiliary disorders - Other (hepatic encephalopathy)
INFECTIONS AND INFESTATIONS - Biliary tract infection; Catheter related infection; Device related infection; Endocarditis infective; Enterocolitis infectious; Hepatitis viral; Infections and infestations - Other (abscess limb); Infections and infestations - Other (necrotizing fasciitis); Infections and infestations - Other (oral infection); Pharyngitis; Sepsis; Upper respiratory infection; Urinary tract infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
INVESTIGATIONS - Blood bilirubin increased; Blood lactate dehydrogenase increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; GGT increased; Lipase increased; Lymphocyte count decreased; Platelet count decreased; Serum amylase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperkalemia; Hyperphosphatemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness; Muscle cramp; Musculoskeletal and connective tissue disorder - Other (compression fracture); Myalgia; Neck pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor hemorrhage[7]; Tumor pain
NERVOUS SYSTEM DISORDERS - Dysgeusia; Encephalopathy; Intracranial hemorrhage[7]; Lethargy; Nervous system disorders - Other (diplopia); Seizure; Somnolence; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Depression; Hallucinations; Insomnia; Personality change
RENAL AND URINARY DISORDERS - Acute kidney injury; Cystitis noninfective; Dysuria; Hematuria; Proteinuria; Urinary incontinence
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal fistula; Vaginal hemorrhage[7]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage[7]; Hypoxia; Laryngeal edema; Oropharyngeal pain; Pleural effusion; Pneumothorax; Productive cough; Pulmonary hypertension; Respiratory failure; Sinus disorder

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Photosensitivity; Purpura; Skin and subcutaneous tissue disorders - Other (erythema nodosum); Skin ulceration; Urticaria
VASCULAR DISORDERS - Hematoma; Hot flashes; Hypotension

Note: Trametinib (GSK1120212B) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.2 Adverse Event List for thyrotropin alpha (Thyrogen)

Potential side effects include nausea, vomiting, headache, fatigue, and flu-like symptoms. Thyrogen can also cause rapid enlargement of thyroid tumors and cause local tumor-related symptoms. For a comprehensive list of Thyrogen-related adverse events, please review the package insert.

7.1.3 Adverse Event List for ^{131}I

Early side effects (may develop immediately or during the first days after RAI treatment): In 10-20% patients, painful swelling of the remnant thyroid tissue or metastases occur. Nausea or vomiting may occur due to radiation induced gastritis. In some patients salivary complications like salivary gland pain, swelling, altered taste, epiphora, change in the taste or smell occurs. In two-thirds of patients, transient and non-clinically significant decrease in thrombocytes and leukocytes may develop.

Late side effects (may develop weeks, months or even years after radioiodine therapy): The most frequent late side effect is related to decreased salivary gland function. In approximately 5%, thrombocytopenia and leukopenia may develop. In approximately 1-2% of patients, leukemia or bone marrow aplasia may occur especially with cumulative doses of ^{131}I. Pulmonary fibrosis can develop in patients with iodine avid lung metastases in whom a delivered activity exceed the maximum tolerable activity determined by dosimetry. The females of childbearing age should avoid pregnancy for 6-12 months after RAI therapy. In males, transient elevation of follicle stimulated hormone (FSH) following ^{131}I therapy may occur. In very rare case, persistent gonadal dysfunction i.e azoospermia may occur.

7.1.4 Adverse Event List for ^{124}I

There is no anticipated side effect of low-dose (approximately 6 mCi (range 4-7 mCi)) oral ^{124}I based on data from MSK experience.

7.2 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 5.0 will be utilized for AE reporting beginning April 1, 2018 (investigators may continue

to collect and locally store AE data in CTCAE v4.0). All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

- For expedited reporting purposes only:
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

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

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (Adverse Event Expedited Reporting System), accessed via the CTEP Web site http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at (301) 897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

For protocols with CAEPRs not including a "SPEER" category, protocol-specific exceptions to the CTEP-AERs reporting table can be found in the CAEPR's "ASAEL" category instead. This protocol-specific exception is limited to Grade 1 and Grade 2 ASAEL events, *i.e.* Grade 3 through Grade 5 ASAEL-listed events are NOT exceptions to CTEP-AERS reporting

7.3.2 Expedited Reporting Guidelines

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

Note: A death on study requires both routine and expedited reporting regardless of

causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions." 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.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

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

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

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

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

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

Expedited AE reporting timelines are defined as:

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

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

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

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

Effective Date: May 5, 2011

7.3.3 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

The reporting window for expedited adverse events begins on Week 1 Day 1.Any serious adverse event occurring prior to Week 1 Day 1 is excluded from CTEP-AERs reporting.

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through CTEP-AERS must <u>also</u> be reported in routine study data submissions.**

7.5 Secondary Malignancy

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

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

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

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

7.6 Second Malignancy

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

7.7 Serious Adverse Event (SAE) Reporting for MSK Patients Only

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSK)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
  - An explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
  - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

Hospitalization or prolonged hospitalization for scheduled therapy (eg. I-131 therapy) of the target disease of the study will not require adverse event reporting.

8. PHARMACEUTICAL AND/OR IMAGING AGENT INFORMATION

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

8.1 CTEP IND Agent(s)

8.1.1 Trametinib dimethyl sulfoxide (GSK1120212B) (NSC 763093) Commercially labeled.

Chemical Name (IUPAC): equimolecular combination of acetamide, N-[3-[3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-3,4,6,7-tetrahydro6,8-dimethyl- 2,4,7-trioxopyrido[4,3-

d]pyrimidin-1(2H)-yl]phenyl] with 1,1'-sulfinylbis[methane]

Other Names: trametinib, GSK1120212, JTP-74057, JTP-78296, JTP-75303, Mekinist

CAS Registry Number: 1187431-43-1

Classification: MEK inhibitor

Molecular Formula: $C_{26}H_{23}FIN_5O_4 \cdot C_2H_6OS$ **M.W.:** 693.53

Approximate Solubility: Trametinib dimethyl sulfoxide is almost insoluble in water (<0.0001 mg/mL at 25° C)

Mode of Action: Trametinib dimethyl sulfoxide is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2. Tumor cells commonly have hyperactivated extracellular signal-related kinase (ERK) pathways in which MEK is a critical component. Trametinib dimethyl sulfoxide inhibits activation of MEK by RAF kinases and MEK kinases.

Description: Trametinib dimethyl sulfoxide is a white to almost white powder.

- **How Supplied:** Novartis supplies and CTEP, NCI, DCTD distributes trametinib as 0.5 mg and 2 mg (as free base) tablets. Each investigationally-labeled bottle contains 32 tablets.

  The tablet core contains mannitol, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate (non-animal), colloidal silicon dioxide and sodium lauryl sulfate.

  - 0.5 mg tablets are yellow, modified oval, biconvex and film-coated. Aqueous film coating consists of hypromellose, titanium dioxide, polyethylene glycol, iron oxide yellow.
  - 2 mg tablets are pink, round, biconvex and film-coated. Aqueous film coating consists of hypromellose, titanium dioxide, polyethylene glycol, polysorbate 80, iron oxide red.

- **Storage:** Store tablets at 2°C -8°C in the original bottle and dispense unopened bottles. Do not open bottles or repackage tablets or remove desiccant. Bottles should be protected from light and moisture.

  If a storage temperature excursion is identified, promptly return trametinib to 2°C - 8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

- **Stability:** Stability studies are ongoing. Tablets are only stable for 32 days once bottle has been opened. If multiple bottles are dispensed to a patient in the same visit, please advise the patient to open only one bottle at a time.

Route of Administration: Oral. Take by mouth on an empty stomach, either 1 hour before or 2 hours after a meal. If a dose of trametinib is missed, the dose can be taken if it is more than 12 hours until the next scheduled dose.

Potential Drug Interactions: *In vitro* studies suggest that trametinib dimethyl sulfoxide is not a substrate of CYP enzymes or of human BCRP, MRP2, OATP1B1, OATP1B3, OATP2B1, OCT1 or MATE1 transporters. Trametinib elimination by deacetylation to metabolite M5 is dependent on carboxylesterases (CES1b, CES1c and CES2). M5 is eliminated by CYP3A4 and other pathways, presenting the clinically relevant, albeit low, potential for drug-drug interaction. Trametinib is a substrate for P-gp and BSEP, but this is not expected to be clinically relevant due to trametinib's high permeability.

Trametinib dimethyl sulfoxide is an *in vitro* inhibitor of CYP 2C8, and is anticipated to have overall low potential for drug interactions as a perpetrator. It is also a weak CYP3A4 inducer and expected to have little clinical effect on sensitive substrates. Trametinib is not an inhibitor of CYP 1A2, 2A6, 2B6, 2C9, 2C19, 2D6 and 3A4 and not an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2 MRP2 and MATE1.

Patient Care Implications: Advise women study participants of reproductive potential to use effective contraception while receiving study treatment and for 4 months after the last dose of trametinib. Refer to the protocol document for specific guidance.

8.1.2 Agent Ordering and Agent Accountability

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

Agent may be requested electronically to PMB. Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and

4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

8.1.2.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from PMB using the appropriate Investigational Agent (Drug) (DARF). available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

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

8.2 Other Investigational Agent(s)

8.2.1 Sodium iodide-124

Molecular Formula: Na ^{124}I

Molecular Weight: 147 g/mol

Half-Life: 4.18 days

Formation Reaction: ^{124}TE (p,n) ^{124}I

Supplier: Sofie Biosciences (fka IBA Molecular and Zevacor), 3 D Imaging LLC, MSK cyclotron staff, or NCM

Solution preparation: The solution for oral administration is formulated by adding approximately 5 mCi of sodium iodide-124 suspended in a solution 0.1 N sodium phosphate buffer to 3-5 mL of 0.2% disodium EDTA in water for injection. An aliquot of the sodium iodide-124 solution is added to an oral solution formulation consisting of 2 mg/mL disodium EDTA in purified water, USP. A total of 3-5 mL of oral solution is prepared. The sodium iodide-124 is diluted with not more than 5 mL of oral solution contained within a sterile glass vial fitted with a septum and aluminum crimp sealing ring. The finished product is measured. One unit should contain 6 mCi (range 4-7 mCi) per dose.

Storage requirements/Stability: Sodium iodide-124 has a half-life of 4.2 days. Sodium iodide bulk material will be chemically processed for iodine-124 recovery within 72 hours of the end of bombardment. The formulated sodium iodide solution will be used within 8 hours of formulation.

Route of administration: Administered orally.

8.3 Commercial Agent(s)

8.3.1 Thyrotropin alpha (Thyrogen)

Product description: Thyrogen® (thyrotropin alfa for injection) (Genzyme)is a highly purified recombinant form of human thyroid stimulating hormone (TSH), a glycoprotein which is produced by recombinant DNA technology. Thyrotropin alfa is synthesized in a genetically modified Chinese hamster ovary cell line.

Thyrotropin alfa is a heterodimeric glycoprotein comprised of two non-covalently linked subunits, an alpha subunit of 92 amino acid residues containing two N-linked glycosylation sites and a beta subunit of 118 residues containing one N-linked glycosylation site. The amino acid sequence of thyrotropin alfa is identical to that of human pituitary thyroid stimulating hormone. Both thyrotropin alfa and naturally occurring human pituitary thyroid stimulating hormone are synthesized as a mixture of glycosylation variants. Unlike pituitary TSH, which is secreted as a mixture of sialylated and sulfated forms, thyrotropin alfa is sialylated but not sulfated. The biological activity of thyrotropin alfa is determined by a cell-based bioassay. In this assay, cells expressing a functional TSH receptor and a cAMP-responsive element coupled to a heterologous reporter gene, luciferase, enable the measurement of rhTSH activity by measuring the luciferase response. The specific activity of thyrotropin alfa is determined relative to an internal Genzyme reference standard that was calibrated against the World Health Organization (WHO) human TSH reference standard.

Thyrogen is supplied as a sterile, non-pyrogenic, white to off-white lyophilized product, intended for intramuscular (IM) administration after reconstitution with Sterile Water for Injection, USP. Each vial of Thyrogen contains 1.1 mg thyrotropin alfa, 36 mg Mannitol,5.1 mg Sodium Phosphate, and 2.4 mg Sodium Chloride.

After reconstitution with 1.2 mL of Sterile Water for Injection, USP, the thyrotropin alfa concentration is 0.9 mg/mL. The pH of the reconstituted solution is approximately 7.0.

Solution preparation: Please refer to the package insert for standard preparation instructions.

Route of administration: Thyrogen is administered as an intramuscular injection after reconstitution with Sterile Water for Injection, USP.

8.3.2 ^{131}I

Product description: ^{131}I will be used for dosimetry studies and treatment of the patients whose second lesional dosimetry reveals iodine incorporation that satisfies the ^{131}I treatment threshold (see Section 5.1.3). ^{131}I has a half-life of 8 days and relatively high principal photon energy of 364 keV characterized by beta particle emissions. It is supplied by MDS Nordion, DraxImage, or International Isotopes. It is administered orally in the form of capsules or liquid. Pregnancy is the only contraindication to radioiodine treatment. A beta-HCG pregnancy test must be performed up to 2 days prior to the administration of ^{131}I.

Route of administration: Oral

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies

9.1.1 *Genomic studies for enrolled patients: (To be performed by Dr. James Fagin's MSK Human Oncology and Pathogenesis Program, HOPP laboratory)* Beyond the *RAS* and *BRAF* mutation testing that will be done in a CLIA lab for eligibility assessment, further genetic characterization may be performed upon submitted tissues. Specifically, testing for *RET* and *PAX8-PPARG* rearrangements would be of interest for the *BRAF/RAS* WT patients. The genomic technology utilized to analyze these and other genetic alterations will be determined by platform and funding availability. Potential approaches may include next generation sequencing platforms to analyze select genes/exons or whole exome/whole genome sequencing. Comparisons of DNA between tumor and normal tissue (from a 10 mL research blood draw) may be performed as appropriate, thus generating germline sequencing data. This will be limited to participants enrolled at MSK only. There is no intention to analyze the germline data beyond utilizing it as a normal control for the tumor tissue analysis, and generally germline data will not be communicated to the patient.

The following procedure will be followed by MSK investigators for the unique situation in which a potentially actionable incidental finding has been discovered in the course of research conducted on samples collected under this protocol:

In the event an investigator's research identifies a finding that he or she believes should be communicated to the subject (and/or family designee), the investigator shall communicate this to the IRB. The finding will be reviewed by a group convened by the IRB (and appointed in consultation with the Physician-In-Chief) to determine whether the incidental finding should be discussed with the subject. In the event that group convened by the IRB determines that the finding should be discussed with the subject, and the subject has consented to be re-contacted, then the treating/consenting physician shall be contacted by the -IRB representative and asked to refer the subject to the Clinical Genetics Service for further discussion of the research finding.

After appropriate counseling and consent, the Clinical Genetics Service will request permission to confirm the result in a New York DOH-approved laboratory prior to communication of the specific result. If the patient is not available (e.g. deceased), then the surrogate designated on the consent will be contacted and the above will occur.

Whole exome or genome sequencing data will be deidentified; samples will be labelled with patient study IDs to preserve links to clinical data. The deidentified genomic data will be stored to a protected server that is specifically set aside for clinical trial data.

The IRB and Clinical Genetics Service, as per above flow chart, will be notified when a participant's samples uncover a potentially reportable incidental finding(s). The following information must be provided to IRB representative and Clinical Genetics:

- Participant Name/MRN #
- Type of Biospecimen (tissue, blood, etc)
- Incidental Finding
- Project # (HBUC/Waiver or Protocol #) that this analysis occurred under
- Collection Protocol #

Clinical Genetics Service Contact: rtmgapirb@mskcc.org

9.1.1.1 Collection of Specimen(s)

Archival tumor tissue (unstained slides or tissue blocks) will be collected for this analysis. (Tissues from research biopsies as described in Section 9.2.1.1 can also be used for this analysis.)

For the research blood specimen, approximately 10 mL of blood will be collected in a tube with EDTA (usually lavender top) any time after the informed consent has been signed. These blood samples can then be stored at 2-8ºC for up to 3 days; for longer term storage, the tubes must be stored at -80ºC.

9.1.1.2 Handling of Specimens(s)

Genomic alterations will be assessed. The approach(es) for detecting *RET* and *PAX8-PPARG* rearrangements and other genetic alterations will be determined by the availability of assays and funding at the time of analysis.

9.1.1.3 Shipping of Specimen(s)

For each sample indicate the unique subject ID number, anatomic location of biopsy, and the date of the specimen.

Archival paraffin blocks of formalin-fixed biopsy specimens should be placed in a padded envelope. Paraffin blocks should be wrapped in a plastic bag before placement in the envelope and mailed to the address specified in 9.1.1.4. The blood samples must be shipped by Overnight Delivery (specifically, Federal Express or UPS), packed in sufficient dry ice (at least 10 pounds) to ensure that they remain frozen for at least two days. Label the outside of the container with "Biohazard," "Frozen Biopsy Samples, Freeze upon Arrival." Shipment should ONLY be scheduled for early in the week (Mondays, Tuesdays or Wednesdays) to ensure that the samples do not wait over a weekend for delivery. Samples will be shipped in batches and must be in accordance with the guidelines set forth by the International Air Transport Association (IATA) for shipment of diagnostic specimen via air. Samples must be sorted by subject ID number so that all samples from a given subject are readily accessible. A notification regarding shipment must be sent via e-mail to Dr. Alan L. Ho (hoa@mskcc.org).

9.2 Laboratory Correlative Studies

9.2.1 *Quantifying changes in MAPK and alternate signaling pathways in response to trametinib*

9.2.1.1 Collection of Specimen(s)

Pre-treatment biopsies will be performed prior to Week 1 Day 1 and on-treatment biopsies will be performed in Week 3. It is preferred, but not required, that the second biopsy be performed upon the same tumor that was sampled with the first research biopsy, if safe and feasible. Patients may be exempt from biopsy if either the investigator or person performing the biopsy judges that no tumor is accessible for biopsy or that biopsy poses too great of a risk to the patient (if the only tumor accessible for biopsy is also the only lesion that can be used for

RECIST v1.1 response evaluation, then the patient may be exempt from biopsy after discussion with the MSK Principal Investigator). Radiologic guidance (CT, MRI or ultrasound guided) approaches and obtaining multiple cores to ensure sufficient biopsy material (at least 3 cores preferred) are allowed as long as it is considered reasonably safe for the patient.

Tissue will be divided for formalin fixation and flash freezing in liquid nitrogen as directed by the Principal Investigator. Fixation will be done per institutional guidelines. For flash frozen samples, the biopsy sample will be placed into a cryovial, which will be submerged in a liquid nitrogen bath until the tissue is frozen. If tissue is limited, the local Principal Investigator may decide only to create flash frozen samples.

9.2.1.2 Handling of Specimens(s)

The fresh frozen or fixed tissue will be analyzed with protein based assay(s) and/or gene transcriptional assay(s) to evaluate drug induced changes in MAPK signaling. Abrogation of negative feedback pathways with small molecule targeted therapies leading to activation of alternate signaling pathways to mediate drug resistance have been well described. Candidate signaling pathways that may be activated in response to trametinib-mediated MEK inhibition will also be interrogated.

Profiling of cellular transcriptional output has been validated as a means of distinguishing tumor cell susceptibility to MEK inhibition (Dry et al., 2010) and the differential impact of MEK inhibition upon *BRAF* MUT versus WT tumors (Pratilas et al., 2009). In the thyroid, *DUSP*s are particularly useful markers of MAPK activity, and may be explored in the samples (Chakravarty et al., 2011). Additionally, the re-expression of some key thyroid-specific genes such as *NIS* will be evaluated (Chakravarty et al., 2011).

The approach(es) utilized will be determined by the availability of assay(s) and funding at the time of analysis. This analysis could also be performed on the submitted archival tissue in addition to, or in lieu of, analysis of tissues obtained from research biopsies.

9.2.1.3 Shipping of Specimen(s)

For each sample indicate the unique subject ID number, anatomic location of biopsy, and the date of the specimen.

The frozen samples must be shipped by Overnight Delivery (specifically, Federal Express or UPS), packed in sufficient dry ice (at least 10 pounds) to ensure that they remain frozen for at least two days. Label the outside of the container with "Biohazard," "Frozen Biopsy Samples, Freeze upon Arrival." Shipment should ONLY be scheduled for early in the week (Mondays, Tuesdays or Wednesdays) to ensure that the samples do not wait over a weekend for delivery. Samples will be shipped in batches and must be in accordance with the guidelines set forth by the International Air Transport Association (IATA) for shipment of diagnostic specimen via air. Samples must be sorted by subject ID number so that all samples from a given subject are readily accessible. A notification regarding shipment must be sent via e-mail to Dr. Alan L. Ho (hoa@mskcc.org).

9.3 Special Studies

Not Applicable

10. STUDY CALENDAR

Pre-Study and Weeks 1-5 study calendar for all patients:

NOTE FOR THE ^{124}I PET/CT LESIONAL DOSIMETRY: Changes in the scheduling of the tests and/or assessments below, including the first or second ^{124}I PET/CT lesional dosimetry process, may be considered in the event of holidays, scheduling conflicts, unanticipated delays (e.g. delays in ^{124}I shipment, weather, etc…) or interruptions in trametinib therapy after discussion with the Principal Investigator. (NOTE: Week and day number designations may change if there are interruptions in study treatments/assessments.)

	Pre-Study[f]	Wk 1						Wk 2	Wk 3	Wk 4	Wk 5				
		D1	D2	D3	D4	D5	D6 & D7				D1	D2	D3	D4	D5
Trametinib[a]							X	X	X	X	X	X	X	X	X
Adherence to low iodine diet[b]	X[b]	X	X	X	X	X				X[b]	X	X	X	X	X
Thyrogen[c]		X	X								X	X			
^{124}I administration (approximately 6 mCi)[d]				X									X		
^{124}I PET/CT						X									X
beta-HCG[g]	X[g]	X[j]									X[j]				
Tumor Genotyping	X[e]														
Informed consent	X														
Demographics	X														
Medical history	X														
Concurrent meds	X	X----------													X
Physical exam	X					X[k]			X						X[k]
Vital signs	X					X[k]			X						X[k]
Height	X														
Weight	X					X[k]			X						X[k]
Performance status	X					X[k]			X						X[k]
CBC w/diff, plts	X	X[k]							X		X[k]				
chemistry[h]	X	X[k]							X		X[k]				
PT/aPTT (include INR)	X														
EKG	X														
Echocardiogram or MUGA[m]	X														
Ophthalmology exam[n]	X														
Adverse event evaluation		X----------													X
Radiologic evaluation (CT(s) and/or MRI(s)) for tumor measurements NO IODINATED CONTRAST IS ALLOWED	X														
TSH, free T4, thyroglobulin, thyroglobulin antibody[l]		X		X		X			X		X		X		X
Research blood sample[o]	X														
Research biopsy[i]	X								X						

a: Trametinib is to be started on Week 1, Day 6 at 2 mg orally daily. If the second lesional dosimetry with ^{124}I PET/CT indicates that RAI should be given, trametinib will be continued until 2 days after RAI has been administered. If the lesional dosimetry with ^{124}I PET/CT indicates that RAI should not be given, trametinib may or may not be discontinued (see the appropriate table below). Ideally, patients will remain on trametinib continuously for a minimum of 7 days prior to the performance of the PET/CT for the second lesional dosimetry (scheduled here in Week 5), (this is not a requirement). To achieve this, the second lesional dosimetry may be rescheduled at the discretion of the treating physician. If the second lesional dosimetry is delayed more than 4 weeks, the MSK Principal Investigator and the treating physician will determine if the patient should be continued or removed from the study. If trametinib is missed for $\geq$ 7 days total or interruptions in trametinib dosing have occurred prior to or during whole body and blood dosimetry and ^{131}I (RAI) treatment, then having some or all of the doses made up and rescheduling the study assessments/treatments may be considered after discussion with the Principal Investigator (this is not a requirement).

b: Patients should adhere to a low iodine diet for 5 days prior to the initiation of the lesional dosimetry process (considered in the first day of the 5 day process) until its completion (the fifth day when the PET/CT is performed). Patients who go on to whole body and blood dosimetry and ^{131}I treatment will be continued on the low iodine diet through 1 day after ^{131}I is given. Please see Appendix B for details of the low iodine diet.

c: 0.9 mg Thyrogen will be administered intramuscularly on Days 1 and 2 of Weeks 1 and Week 5.
d: Approximately 6 mCi (range 4-7 mCi) of ^{124}I administered orally.
e: Tumor genotyping can be conducted on the primary tumor, recurrent tumor, or a metastasis. Results can be obtained any time before patient is registered to the study.
f: All Pre-Study evaluations must be done ≤28 days prior to Week 1 Day 1 unless otherwise specified.
g: pregnancy test (for women of childbearing potential). Pre-study beta-HCG levels need to be drawn within 2 weeks prior study registration.
h: chemistry includes albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
i: The first research biopsy will be performed prior to initiation of Week 1 Day 1. The second biopsy will be performed in Week 3 of the study. It is preferred, but not required, that the second biopsy be performed upon the same tumor that was sampled with the first research biopsy, if safe and feasible. Patients may be exempt from biopsy if either the investigator or person performing the biopsy judges that no tumor is accessible for biopsy or that biopsy poses too great of a risk to the patient (if the only tumor accessible for biopsy is also the only lesion that can be used for RECIST v1.1 response evaluation, then the patient may be exempt from biopsy after discussion with the MSK Principal Investigator). Radiologic guidance (CT, MRI or ultrasound guided) approaches and obtaining multiple cores to ensure sufficient biopsy material (at least 3 cores preferred) are allowed as long as it is considered reasonably safe for the patient.
j: beta-hcg (for women of childbearing potential) must be done within 2 days prior to administering ^{124}I.
k: The days designated for these evaluations/tests are only suggestions. These can be scheduled for any time during the week for which they are scheduled.
l: TSH, free T4, thyroglobulin, and thyroglobulin antibody will be drawn on Day 1 of weeks 1 and 5 (preferably prior to administration of Thyrogen on that day) Only TSH will be drawn on Day 3 during Weeks 1 and 5. TSH and Thyroglobulin total and antibody will be drawn on Days 5 of Weeks 1 and 5 (i.e., the weeks that the ^{124}I PET/CT are to be performed). TSH and Free T4 will be drawn for the Week 3 assessment (thyroglobulin and thyroglobulin antibodies are not required to be drawn during this week).
m: The same modality (echocardiogram or MUGA) should be used at baseline and at follow-up.
n: Ophthalmology exams should be obtained at baseline, and if clinically indicated, during study. Ophthalmology exam should include Ocular Coherence Tomography, fundoscopy, tonometry, visual field examination, and corrected visual acuity assessments.
o: For the research blood specimen, approximately 10 mL of blood will be collected in a tube with EDTA (usually lavender top) any time after the informed consent has been signed.

Study Calendar for PATIENTS WHO RECEIVE RAI *(Week 5, Day 6 and beyond)*

If the second lesional dosimetry with trametinib reveals sufficient tumoral iodine incorporation to deliver a dose of ≥ 2,000 cGy with ≤ 300 mCi of RAI, then the patient will continue on trametinib and a low iodine diet (as decided by the treating physician(s)). The schedule of treatments and assessments for these patients are detailed below (NOTE: Week and day number designations may change if there are interruptions in study treatments/assessments):

	Wk 5 **D6 & D7**	**Wks 6 & 7**	**5 weeks (+/- 2 weeks) after RAI therapy**	**About 3 or 4 months after RAI**	**About 6 months after RAI (+/- 1 week)**
Trametinib[a]	X	X			
Adherence to low iodine diet[a]	X	X			
Whole body and blood dosimetry and ^{131}I (RAI) treatment with Thyrogen stimulation (per standard of care)[a]		X			
Concurrent meds	X----------X				
Physical exam			X		
Vital signs			X		
Weight			X		
Performance status			X		
CBC w/diff, plts			X		
chemistry[b]			X		
TSH, free T4, thyroglobulin, thyroglobulin antibody			X	X	X
beta-HCG		X[c]			
Echocardiogram or MUGA[e]			X[e]		
Adverse event evaluation	X----------X (Monitored for 30 days following the last dose of trametinib.)				
Radiologic evaluation (CT(s) and/or MRI(s)) for tumor measurements NO IODINATED CONTRAST IS ALLOWED	X[d]			X[d]	X[d]

a: Patients will be continued on trametinib and a low iodine diet. Whole body and blood dosimetry and thyrogen-stimulated ^{131}I (RAI) treatment is to be completed no later than in Week 7 (unless changes/interruptions of study drug administration and/or study assessments had to be enacted such that whole body and blood dosimetry and therapeutic RAI has to be completed after Week 7)(this dosimetry will be conducted as per institutional guidelines). Trametinib will be continued through 2 days after therapeutic ^{131}I administration. The low iodine diet will be continued through 1 day after ^{131}I treatment. ^{131}I therapeutic dosing will be guided by the dosimetric determination of the maximum tolerated activity (MTA): the ^{131}I activity administered concomitantly with trametinib is not to exceed the MTA plus 3 mCi (i.e., [^{131}I activity administered] ≤ [MTA + 3 mCi]). **Delays in performing the whole body and blood dosimetry and RAI treatment due to holidays, scheduling conflicts, or interruptions in trametinib therapy may be allowed after discussion with the MSK Principal Investigator.**

b: chemistry includes albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

c: beta-hcg (for women of childbearing potential). To be completed within 2 days prior to administration of RAI.

d: CT(s) WITHOUT CONTRAST and/or MRI(s) to reassess disease is/are to be done after completion of the second ^{124}I PET/CT scan and before the administration of RAI. Scans will be repeated about 3 to 4 months after RAI and about 6 months (+/- 1 week) after RAI; it is requested that attempts be made to have scans performed as close to 6 months from the time RAI (^{131}I) was administered if possible to best assess the 6-month PFS endpoint. If an additional scan is required to confirm a complete or partial response after the 6 month scan, an additional radiologic evaluation should be completed within 1 to 3 months after the last scan. Schedule of the radiographic assessments may be altered if there are disruptions of the planned assessment/treatment schedule after discussion with the Principal Investigator. Failure to complete the scans after RAI will not be considered protocol violations with the exception of those scheduled for 6 months following RAI.

e: Followup echocardiogram or MUGA should be performed within 1 month after discontinuing trametinib. The same modality used at baseline should be performed for this followup.

Study Calendar for PATIENTS WHO DO NOT RECEIVE RAI *(Week 5, Day 6 and beyond)*

For both COHORT A (*RAS* MUT) and B (*BRAF/RAS* WT) patients: If analysis of the second lesional dosimetry suggests that therapeutic RAI will not be given, it will be concluded that the patient's cancer is still refractory to RAI and RAI will not be administered. Such patients may be continued on trametinib alone (in Cohort C) if 1) the treating physician determines it to be clinically reasonable, and 2) the patient agrees to continue on trametinib **If these conditions are not met, then trametinib will be discontinued and the patient removed from the study; for these patients, the "Off Study" requirements detailed in the table below will be performed within 30 days of trametinib discontinuation.**
(NOTE: After completion of the designated evaluations/treatments through Week 5 detailed in the "*Pre-Study and Weeks 1-5 study calendar for all patients*" above, the subsequent week will be considered Cycle 2, Week 1 of treatment (what would have been considered Week 6 in the study calendars above). Week and day number designations may change if there are interruptions in study treatments/assessments:

	Cycle 2 Wk 1	**Cycle 2 Wk 2**	**Cycle 2 Wk 3**	**Cycle 2 Wk 4**	**Cycle 3+ Wk 1**	**Off Study[c]**
Trametinib	X	X	X	X	X	
Concurrent meds	X----------X					
Physical exam			X		X[b]	X
Vital signs			X		X[b]	X
Weight			X		X[b]	X
Performance status			X		X[b]	X
CBC w/diff, plts			X		X[b]	X
chemistry[a]			X		X[b]	X
TSH, free T4, thyroglobulin, thyroglobulin antibody					X (to be checked about every 2 cycles)[b]	
Echocardiogram or MUGA	Approximately every 3 cycles starting with Cycle 4. Use the same methodology for baseline and follow up.					
Adverse event evaluation	X----------X					X
Tumor measurements	CT and/or MRI will be performed every 8 weeks (+/- 1 week) (or approximately every 2 cycles) with the first scan assessment on trametinib treatment to be performed during Cycle 2, Week 4 or Cycle 3, Week 1. After 10 months on treatment with trametinib, scans will be performed every 12 weeks (+/- 1 week)(or approximately every 3 cycles). If early, unplanned CT and/or MRI scan(s) is/are performed which can serve as an assessment of response prior to the protocol-mandated radiologic scans, the next set of protocol-mandated scans may be rescheduled to occur in 8 weeks (+/- 1 week) or 12 weeks (+/- 1 weeks) (according to the criteria described above) from the time of the last assessment (this is not mandatory). Documentation (radiologic) must be provided for patients removed from study for progressive disease. Objective responses should be confirmed with a second assessment performed at least 4 weeks later.					

a: chemistry includes albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
b: After the completion of Cycle 2, these tests and evaluations will be done once each cycle, preferably on week 1 of each cycle if possible. The exceptions are blood tests for TSH, free T4, thyroglobulin, and thyroglobulin antibody which are to be checked every 8 weeks +/- 1 week (about every 2 cycles).
c: These off study assessment will be performed within 30 days of discontinuing trametinib.

Trametinib toxicities will be monitored only for 30 days following the last dose of trametinib.

The impact of more than one month of trametinib therapy upon RAI uptake and/or efficiacy is unknown. Patients who do not receive ^{131}I therapy after the second ^{124}I PET/CT scan and remain on trametinib may be evaluated with a third Thyrogen-stimulated ^{124}I PET/CT scan (with the procedure detailed in Section 10.0 for Week 5) 4 weeks or more after completion of the prior ^{124}I PET/CT scan process. If the lesional dosimetry criteria for ^{131}I therapy is met on the third ^{124}I PET/CT, patients can go on to be prepared for/treated with ^{131}I and followed as detailed in Section 10.0 (in the calendar under the heading "*Study Calendar for* PATIENTS WHO RECEIVE RAI *(Week 5, Day 6 and beyond)*" (treatment with ^{131}I is not mandatory). If the third ^{124}I PET/CT scan results do not fulfill the ^{131}I treatment criteria, patients may continue on trametinib alone with the evaluations/treatments required for Cohort C.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response as per the Study Calendars in Section 10. In addition to a baseline scan if necessary, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

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) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with trametinib.

Evaluable for objective response. Please see Section 13 for guidelines regarding evaluable for response.

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

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor

measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

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

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'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.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

11.1.3 Methods for Evaluation of Measurable Disease

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

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

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

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

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. ALL CTs SHOULD BE PERFORMED WITHOUT IODINATED CONTRAST.

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

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast),

then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.
Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). 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: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). 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, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases

where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2 Evaluation of Non-Target Lesions

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

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

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

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

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

11.1.4.3 Evaluation of Best Overall Response

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

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR

Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

- See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

NOTE: On this study, patients with clinical or radiographic 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 or radiographic 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. If a new target or non-target lesion is identified on any radiologic study (including the ^{124}I PET/CT scan) prior to the administration of therapeutic ^{131}I,the first radiologic study prior to ^{131}I that produces a RECIST measurement of the new lesion will be used as the baseline comparator for subsequent evaluations, including assessment of the 6-month response assessment.

11.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment (initiation of trametinib) to time of progression or death, whichever occurs first.

11.2 Antitumor Effect – Hematologic Tumors

Not applicable.

11.3 Other Response Parameters

Not applicable.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

Note: If your study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS.

Weekly meetings will occur to monitor patient accrual. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the

study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of once per year, more frequently if indicated.

Potential genotype/phenotype data may be sent to the NIH repository (or any other public database by participating investigators. If data is to be sent to the NIH, local investigators will follow the MSK IRB/PB GWAS SOP-503 to ensure compliance with the data submission. Investigators will not include identifying information such as the patient's name, date of birth, etc with the submission to NIH and the data will be coded for transmission, as specificed by the applicable policies. The data will be maintained under the controlled access portion of the NIH database.

12.1.2 Responsibility for Data Submission

N/A –Single Institution Study

12.2 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

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

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

   a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial

by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

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

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

Cohort A (RAS MUT): Two co-primary objectives are defined for this cohort: proportion of patients alive, progression-free at 6 months following treatment with trametinib and RAI; and objective response rate (ORR, complete response or partial response) at 6 months following treatment with trametinib and RAI. "6 months" (also described below as the "six-month time point") refers to assessments performed approximately 6 months after the co-administration of RAI with trametinib. (All radiologic assessments performed will be compared back to the baseline scans performed prior to trametinib and RAI therapy.) If either one of these objectives is met, the treatment would be considered worthy of further testing in this disease.

All patients enrolled in the trial who are treated with trametinib through the completion of the second ^{124}I PET scan will be included in determination of these primary endpoints. Patients who are taken off study prior to completion of the second ^{124}I PET scan may be replaced. Patients who are deemed to qualify for treatment with ^{131}I based on the second ^{124}I PET scan, but do not receive it, will be considered to have had a progression/death event and categorized as non-responders. After having received therapeutic ^{131}I, patients who, for any reason, do not have the 6-month evaluation, will be considered to have had a progression/death event and categorized as non-responders. Patients for whom it is determined that the second ^{124}I PET/CT demonstrates insufficient iodine incorporation to warrant treatment with RAI (^{131}I) still have RAI-refractory disease; they will not receive RAI treatment and will be considered to have had a progression/death event and be categorized as non-responders.

It is possible patients will have clinical or RECIST v1.1 radiologic evidence of disease progression prior to the 6-month time point evaluation. These patients may still obtain clinical benefit on the study at the 6-month time point for several reasons: 1) trametinib 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 disease progression prior to the 6-month time point evaluation may remain on study at the discretion of the treating physician. The final objective response and disease progression assessments 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. The one exception is if a new target or non-target lesion is identified on any radiologic study (including the ^{124}I PET/CT scan) prior to the administration of therapeutic ^{131}I,the first radiologic study prior to ^{131}I that produces a RECIST measurement of the new lesion will be used as the baseline comparator for subsequent evaluations, including assessment of the 6-month response assessment. 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 classified as progression/death event /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 to have had a progression/death event and

be categorized as non-responders.

(NOTE: For assessment of ORR, as long as one of the 2 scans required for confirmed PR or confirmed CR designations is performed for the 6 month evaluation, then that patient will be counted as having had a confirmed PR or CR. The other scan required for confirmed PR or CR designation can be obtained on a scan prior to or following the 6 month time point assessment (as long as the two assessments are separated by 4 weeks)).
An exact binomial stage design will be used to discriminate between true 6-month progression/death rates of 20% vs. 50%, and between true ORR rates at 6 months of 5% and 25%. Twenty-five patients will be enrolled. If at least 9 patients are alive, free of progression and have not received additional non-protocol related therapy for thyroid cancer at the 6-month time point, or at least 4 RECIST responses (CR + PR) are observed among the 25 patients at the 6 month time point, this regimen would be considered worthy of further testing in this disease.

This design yields 94% power to detect a true 6-month time point progression/death rate of at least 50%, and 90% power to detect a ORR rate of at least 25%. It yields a 0.05 probability of a positive progression/death result if the true 6-month time point progression/death rate is no more than 20%, and a 0.04 probability of a positive ORR at the 6-month time point result if the true ORR is no more than 5%. Therefore, assuming that progression/death and ORR are independent, the overall type 1 error is <0.1. The type 1 error decreases very slightly if progression/death rate and ORR are positively correlated.

The analysis of progression or death will capture the potential benefit of disease control without continuous treatment that the study strategy provides (as opposed to indefinite, continuous chemotherapy). The pilot study evaluating selumetinib enhancement of RAI therapy had similar eligibility requirements to those in this study, except that the pilot did not require radiographic evidence of disease progression prior to enrollment as this study does. Still, an unplanned, retrospective analysis of 16 patients on the pilot selumetinib study revealed that 15 had evidence of tumor progression on imaging up to one year prior to enrollment, suggesting that the disease for this patient population generally has a propensity to progress. In a phase II study evaluating gefitinib for RAI-refractory thyroid cancer patients (disease progression prior to enrollment was not required) in which some minor reductions in tumor size but no RECIST responses were observed, the median progression-free survival was only 3.9 months (Pennell et al., 2008), corresponding to a 6-month PFS of 34% (under exponential distribution assumption). Because our study requires progression of disease at enrollment, we expect a higher progression rate, therefore assumed a 20% 6-month PFS (null hypothesis). Since all the RAI-refractory patients on the pilot selumetinib study with enhanced RAI incorporation had durable partial responses or stable disease up to 6 months following RAI, we are targeting 50% of patients to be progression-free at the 6 month time point with treatment on this study. For ORR, the assumption that only 5% of these patients would have a RECIST response with RAI alone at the 6-month time point is based upon the premise that we are enrolling a population deemed refractory to RAI alone according to clinical criteria.

Cohort B (BRAF/RAS WT): The primary objective for this arm will be to explore if treatment with trametinib can increase iodine incorporation in thyroid cancer metastases to a predicted lesional absorbed radiation dose equal to or exceeding 2,000 cGy with the administration of ≤

300 mCi RAI. We will consider the treatment worthy of further investigation if at least 3 of the 10 patients enrolled meet this criterion (what we call here "response"). If the true response rate in the population is less than 10%, the probability of seeing 3 or more responses in 10 patients is 7% or less. Therefore, we can be reasonably certain that 3 or more responses are indicative of real drug activity. All patients enrolled in the trial who receive at least one dose of trametinib will be included in determination of these endpoints. Patients who are taken off study prior to receiving one dose of trametinib may be replaced.

13.2 Sample Size/Accrual Rate

The planned sample size for Cohort A is 25 patients and for Cohort B 10 patients. We anticipate accruing 1-2 patients per month in both Cohorts A and B.

13.3 Stratification Factors

The study will consist of two cohorts: Cohort A (*RAS* MUT patients) and Cohort B (*BRAF/RAS* WT patients).

13.4 Analysis of Secondary Endpoints

Cohort A (RAS MUT patients): One secondary endpoint will be to determine if treatment with trametinib can adequately increase iodine incorporation in thyroid cancer metastases to a threshold sufficient to warrant ^{131}I treatment in patients with RAI-refractory thyroid cancer. "Adequate increase" is defined as increasing iodine incorporation in thyroid cancer metastases to a predicted lesional absorbed radiation dose equal to or exceeding 2,000 cGy with the administration of $\leq$ 300 mCi RAI. Proportion of patients with an adequate increase will be reported, along with the corresponding exact 95% confidence interval.

In another secondary analysis, the goal will be to determine whether treatment with trametinib and RAI is accompanied by decrease in thyroglobulin. For that purpose, we will perform a Wilcoxon signed rank test for paired samples to compare the thyroglobulin level before and after RAI treatment in the subset of patients treated with RAI.

Assessing the safety/tolerability of trametinib in combination with RAI will be investigated as a secondary endpoint. All patients will be evaluable for toxicity from the time of their first treatment with trametinib. Toxicities will be assessed through the NCI Common Terminology Criteria for Adverse Events version 4.0, individually reported and summarized. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018 but investigators may continue to collect and locally store AE data in CTCAE v4.0. Monitoring for trametinib-related toxicities will be continued until 30 days after the last dose of drug therapy.

Cohort B (BRAF/RAS WT patients): Secondary objectives will be determining the ORR (per RECIST v1.1 criteria) at the 6-month time point and the proportion of patients following at the 6-month time point alive without disease progression by RECIST v1.1 criteria (evaluation of these objectives will be conducted according to all the specific criteria described above in Section 13.1 for Cohort A, including the allowance for patients to remain on study even with evidence of clinical or RECIST v1.1 radiologic disease progression prior to the 6-month time

point assessments).

In another secondary analysis, the goal will be to determine whether treatment with trametinib and RAI is accompanied by decrease in thyroglobulin. For that purpose, we will perform a Wilcoxon signed rank test for paired samples to compare the thyroglobulin level before and after RAI treatment in the subset of patients treated with RAI.

Assessing the safety/tolerability of trametinib in combination with RAI will be investigated as a secondary endpoint. All patients will be evaluable for toxicity from the time of their first treatment with trametinib. Toxicities will be assessed through the NCI Common Terminology Criteria for Adverse Events version 4.0, individually reported and summarized. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018 but investigators may continue to collect and locally store AE data in CTCAE v4.0. Monitoring for trametinib-related toxicities will be continued until 30 days after the last dose of drug therapy.

Cohort C (select patients from Cohorts A and B with insufficient ^{124}I PET changes): If analysis of the second lesional dosimetry suggests that therapeutic RAI will not be given, it will be concluded that the patient's cancer is still refractory to RAI and he/she will not receive RAI. Such patients may be continued on trametinib alone in Cohort C if 1) the treating physician determines it to be clinically reasonable, and 2) the patient agrees to continue on trametinib. The efficacy of MEK inhibition alone for RAI-refractory thyroid cancer has been evaluated with selumetinib in one phase II trial; that study reported only 1 partial response out of 32 evaluable patients. The study included only one patient with a *NRAS* Q61R MUT tumor and 11 patients with tumors wild-type for *BRAF, NRAS,* and *HRAS*. We hypothesize that more potent inhibition with trametinib will translate to greater clinical efficacy for patients with RAI-refractory thyroid cancers that are either *RAS* MUT or *BRAF/RAS* WT.

We estimate that approximately 10 patients in total from Cohorts A and B will be enrolled in Cohort C. Amongst these patients, we will estimate the proportion of patients following at the 6-month time point alive without disease progression by RECIST v1.1 criteria, the best objective response (BOR) along with the corresponding exact 95% confidence intervals, and the safety/tolerability of trametinib.

Changes in thyroglobulin will also be assessed while on treatment with trametinib; a Wilcoxon signed rank test for paired samples to compare the thyroglobulin level before and after RAI treatment in the subset of patients treated with RAI.
Exploratory Objectives: We will also be performing correlative studies on serial research biopsies in a minimum of 6 *RAS* MUT and 3 *BRAF/RAS* WT patients and archival tumor tissue in order to evaluate the impact of trametinib upon 1) expression and phosphorylation of MAPK signaling pathway proteins, 2) expression and phosphorylation of negative feedback loops connected to the MAPK pathway (such as her3), 3) quantitative levels of mRNA transcripts for MAPK regulated and thyroid-specific gene products, and 4) the presence of other genetic alterations (the studies and assays completed will be dependent upon the existing technology at the time of analysis as well as the funding that is available). These analyses will be descriptive and exploratory given the limited number of samples examined.
The impact of trametinib therapy upon RAI uptake and/or efficiacy beyond one month is

unknown. Patients who do not receive ^{131}I after the second ^{124}I PET/CT and remain on trametinib (those on Cohort C) may be evaluated with a third ^{124}I PET/CT scan. These patients will have the same Cohort A and B primary/secondary endpoints evaluated in an exploratory manner. For patients who go on to be treated with ^{131}I, that data will not be included in the statistical analyses for Cohorts A and B, but kept separate for this exploratory analysis. The BOR data collected with trametinib therapy alone (prior to ^{131}I therapy) from these patients will still be used for Cohort C analysis.

13.5 For phase 2 protocols only: Reporting and Exclusions

13.5.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with trametinib.

13.5.2 Evaluation of Response

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

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

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

14. PROTECTION OF HUMAN SUBJECTS

14.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure

of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

It is also stated in the consent formthat research data (e.g. genomic sequence) may be placed into databases monitored by the National Institutes of Health, and may be made accessible to investigators approved by the U.S. government. The requirements for submission of the genotype/phenotype data into the NIH GWAS Repository (or any other public database) will be followed as per MSK IRB GWAS SOP-503.

15. INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

Future Contact: Participants will be provided with results of the clinical assay tests, but will not be told the results from the research assays. With their permission, the participant and/or family

members may be contacted in the future to ask if they are interested in learning about the potential findings of inherited risks for cancer (and other types of diseases) that may have been an outcome of the research assay testing of their samples. Requirements for reporting incidental findings are located in Section 9.1.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

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

APPENDIX B: LOW IODINE DIET

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, riverbass, 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

APPENDIX C: PILL DIARY

MSK IRB 13-157: A Phase 2 Study of Trametinib in Combination with Radioiodine (RAI) for RAS Mutant or RAS/RAF Wild-Type, RAI-Refractory Recurrent and/or Metastatic Thyroid Cancers

Patient Name: _____ MRN:_____
Cycle Number: ____(cycle length = 28 days)

To be completed by MD/RN:
Total Daily Dose of Trametinib: _____

Study Medication Instructions:

- Take trametinib once daily, either 1 hour before or 2 hours after a meal
- Please fill out each dose on this diary
- Bring your study medication and diary to your next visit

Date	Was Dose Taken?	At What Time?	Total Number of Pills Taken
EXAMPLE: 11/3/2016 Day 1	☒Yes ☐No	08:52 **AM**/PM	1 pill 2 mg
___/___/___ Day 1	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___ Day 2	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___ Day 3	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___ Day 4	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___ Day 5	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___ Day 6	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___ Day 7	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___ Day 8	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___ Day 9	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___ Day 10	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___ Day 11	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___ Day 12	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___ Day 13	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___ Day 14	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___	☐Yes ☐No	___:___ AM/PM	___ mg

Day 15			
___/___/___ Day 16	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___ Day 17	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___ Day 18	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___ Day 19	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___ Day 20	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___ Day 21	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___ Day 22	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___ Day 23	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___ Day 24	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___ Day 25	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___ Day 26	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___ Day 27	☐Yes ☐No	___:___ AM/PM	___ mg
___/___/___ Day 28	☐Yes ☐No	___:___ AM/PM	___ mg

Patient Signature: _____ Date: ___/___/___

MD/RN Signature:_____ Date: ___/___/___

Comments:

APPENDIX D: **^{124}I NORMAL ORGAN RADIATION DOSIMETRY**

(Note: this is a general guideline)

^{124}I-Iodide Normal Organ Radiation Dosimetry

	Absorbed Doses			
			1 ^{124}I-Iodide PET-CT scan	2 ^{124}I-Iodide PET-CT scans
	^{124}I-Iodide[1]		0.9 rad[2] + 6 mCi ^{124}I-Iodide	2*0.9 rad[2] + 6 mCi ^{124}I-Iodide
Target Organ	rad/mCi	rad/6 mCi	rad	rad
Adrenals	0.21	1.3	2.2	4.3
Brain	0.57	3.4	4.3	8.6
Bone Surfaces	0.42	2.5	3.4	6.8
Breasts	0.23	1.4	2.3	4.6
Gall Bladder Wall	0.26	1.6	2.5	4.9
Heart Wall	0.37	2.2	3.1	6.2
Kidneys	0.20	1.2	2.1	4.2
Large Intestine - Lower Wall	0.37	2.2	3.1	6.2
Large Intestine - Upper Wall	0.29	1.7	2.6	5.3
Lens of Eye[3]	0.41	2.5	3.4	6.7
Liver	0.36	2.2	3.1	6.1
Lungs	0.36	2.2	3.1	6.1
Muscle	0.41	2.5	3.4	6.7
Pancreas	0.32	1.9	2.8	5.6
Red Marrow	0.42	2.5	3.4	6.8
Small Intestine	1.0	1.0	1.9	3.8
Stomach Wall	1.7	1.7	2.6	5.2
Testes	0.24	1.4	2.3	4.7
Thyroid[4]	N/A	N/A	N/A	N/A
Total Body[5]	0.41	2.5	3.4	6.7
Urinary Bladder Wall				
2-hr Voiding Interval	0.37	2.2	3.1	6.2

1 Hays M *et al*. MIRD Dose estimate Report No 5. J Nucl Med **15**: 857-860, 1975. Assumes 25% 24-h thyrod uptake.

2 Wu et al. Eur J Nucl Med Mol Imaging 31:38-43, 2004.

3 Lens-of-Eye absorbed dose equated with the muscle absorbed dpse

4 In post-thyroidectomy and post-ablation thyroid cancer patients, there is NO functional thyoird to irradiate. For the ~0% "thyroid" uptake for such patients, the normal-organ doses are likely LOWER than those presented.

5 Total-Body absorbed dose equated with the Muscle absorbed dose

APPENDIX E: DOSIMETRIC RADIOIODIDE SCINTIGRAPHY (AKA 'FULL DOSIMETRY') (I-131 as Sodium Iodide)

Equipment Required

A Whole body scanning gamma camera with dual detectors and High Energy General Purpose (I-131) collimators; calibrated for use with I-131using a 20% window centered at 364 keV.

B. SPECT/CT as needed post therapy.

C. Well scintillation counter capable of counting I-131 blood samples.

D. I-131 standard for well counter, activity approximately 0.5 microcuries, accurately known.

E. I-131 standard for gamma camera, activity approximately 300 microcuries, accurately known.

Radiopharmaceutical, Dose, & Technique of Administration

- Radiopharmaceutical: I-131 as sodium iodide
- Dose: I-131 for full dosimetry: ≤5.0 mCi
- Technique of administration: Oral

Patient Preparation

A. Pregnancy: I-131 is **contraindicated** in pregnant women. In women who are of childbearing age, **pregnancy testing must be performed before the use of I-131 as dictated by the protocol.**

B. Breast feeding:
1. Elective studies using I-131 in lactating women should be postponed for at least 2 weeks, to decrease the radiation dose to the breast.
2. Breast feeding should be discontinued, following the administration of I-131.

C. Patients are instructed to continue their Levoxyl/Synthroid. They do not have to be fasting and can have a light breakfast before the scheduled appointment for dosimetry.

APPENDIX F: RESEARCH LAB DRAW FORM

NCI Protocol #: 9446
Local Protocol #: 13-157

Protocol Title: A Phase 2 Study of Trametinib in Combination with Radioiodine (RAI) for RAS Mutant or RAS/RAF Wild-Type, RAI-Refractory Recurrent and/or Metastatic Thyroid Cancers

	Principal Investigator: Alan Ho, MD, PhD	**Solid Tumor Head and Neck**
Research blood for Protocol 13-157. ***Please place in -80 freezer***	***Time(s) Samples Brought To Storage: _____*** ***Dr. James Fagin's lab, Z519***	

	Date of Informed Consent:	**Date Drawn:**	**Time Drawn:**

Sample drawn by:_____

10 milliliters of blood will be collected in one Purple Top EDTA tube.

Please contact the Research Study Assistant below immediately once the blood is drawn.

Research Study Assistant:
Phone:
Pager:

APPENDIX G: RESEARCH BIOPSY SAMPLE FORM

NCI Protocol #: 9446
Local Protocol #: 13-157

Protocol Title: A Phase 2 Study of Trametinib in Combination with Radioiodine (RAI) for RAS Mutant or RAS/RAF Wild-Type, RAI-Refractory Recurrent and/or Metastatic Thyroid Cancers

	Principal Investigator: Alan Ho, MD, PhD	**Solid Tumor Head and Neck**
Sample Type:	***Time(s) Samples Brought To Storage:*** _____ ***Dr. James Fagin's lab, Z519***	

Date of Informed Consent:	**Type of Biopsy:**	**Date of Biopsy:**

Research Study Assistant:
Phone:
Pager:

APPENDIX H: RESEARCH SLIDES FORM

NCI Protocol #: 9446
Local Protocol #: 13-157

Protocol Title: A Phase 2 Study of Trametinib in Combination with Radioiodine (RAI) for RAS Mutant or RAS/RAF Wild-Type, RAI-Refractory Recurrent and/or Metastatic Thyroid Cancers

	Principal Investigator: Alan Ho, MD, PhD	**Solid Tumor Head and Neck**
Sample Type: ***Date dropped off:***	***Time(s) Samples Brought To Storage:*** _____ ***Dr. James Fagin's lab, Z519***	

Research Study Assistant:
Phone:
Pager:

APPENDIX I: PATIENT CALENDAR HANDOUT

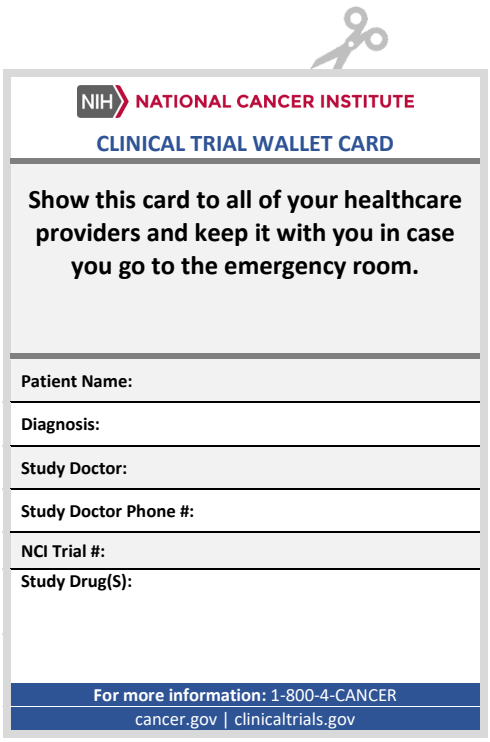
Protocol Title: A Phase 2 Study of Trametinib in Combination with Radioiodine (RAI) for RAS Mutant or RAS/RAF Wild-Type, RAI-Refractory Recurrent and/or Metastatic Thyroid Cancers

NOTE: **ALL** lab appointments must be done first during Week 1 and Week 5

Please contact your MD's office with any scheduling questions or concerns.

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Week 1: Day 1 Lab Nuclear Medicine Follow-up with Primary MD on regular clinic day(s)	**Day 2** Nuclear Medicine	**Day 3** Lab Nuclear Medicine	**Day 4** Off-Day	**Day 5** Lab Nuclear Medicine	**Day 6** Begin study drug
Off week, drug only →					
Week 3: Lab* Follow-up with Primary MD on regular clinic day(s) * anytime this week					
Off week, drug only →					
Week 5: Day 1 Lab Nuclear Medicine	**Day 2** Nuclear Medicine	**Day 3** Lab Nuclear Medicine	**Day 4** Off-Day	**Day 5** Lab Nuclear Medicine Week 5 Day 5 MD visit	

Appendix J: **PATIENT CLINICAL TRIAL WALLET CARD**



NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S):

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov