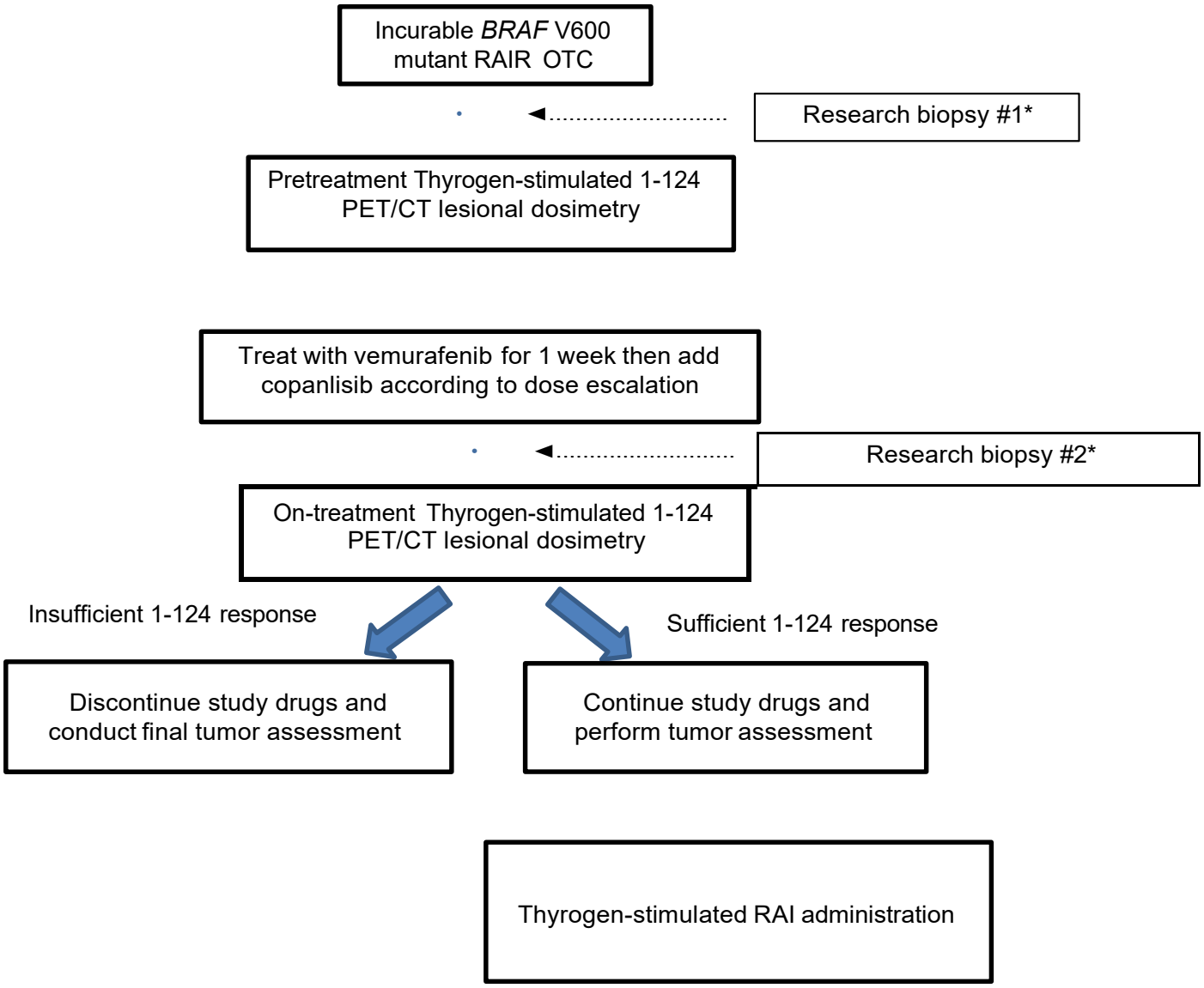
MSK PROTOCOL COVER SHEET

A Phase Ib Trial of Vemurafenib Plus Copanlisib to Enhance Radioiodine Avidity in Radioiodine-RefractoryThyroid Cancers

Alan Ho, MD, PhD/ Medicine/Head & Neck Oncology

Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA



When the MTD is reached, 4 additional patients will be enrolled at the MTD in an expansion cohort.

Target enrollment: 6-32 patients

Disease monitoring:
1 month: Thyroglobulin
3-4 months: Tumor imaging plus thyroglobulin
6 months: Tumor imaging plus thyroglobulin

This is a single-cohort phase Ib study, with a 3+3 dose-escalation design, to establish the maximum tolerated dose (MTD) of combined MAPK and PI3K pathway inhibition with vemurafenib (BRAF inhibitor) and copanlisib (pan-PI3K inhibitor) in patients with advanced radioiodine-refractory (RAIR) *BRAFV600* mutant thyroid carcinoma. Once the MTD for the combination is established, 4 additional patients will be enrolled in an expansion cohort at the identified MTD (to ensure that a total of 10 patients are treated at the MTD).

The goal of this study is to determine a safe dosage of vemurafenib plus copanlisib that effectively redifferentiates RAIR tumors such that they become susceptible to radioiodine (RAI) therapy and

enhances retention. Following pretreatment 1-124 PET/CT assessment, vemurafenib alone will be given for about 1 week followed by the combination of vemurafenib plus copanlisib. During this period, patients will be assessed with 1-124 PET/CT to establish whether they meet the dosimetry requirements to warrant treatment with RAI (1-131). Patients who meet the dosimetry requirements will be treated with 1-131. Those who do not will have study drug discontinued and removed from study.

The primary objective of this study is to establish the MTD for vemurafenib plus copanlisib. Secondary objectives include assessing the proportion of patients who meet the criteria for 1-131 therapy, evaluating the effect of vemurafenib plus copanlisib on RAI uptake and retention on serial **1-**124 PET/CT scans, and determining the overall response rate (ORR; per RECIST v1.1 [response evaluation criteria in solid tumors version 1.1]) and progression-free survival (PFS) at 6 months after combination vemurafenib plus copanlisib and 1-131 therapy.

Pre- and on-treatment biopsies will be performed to assess changes in tumoral gene expression; these findings will be correlated with changes observed in RAI uptake quantified on 1-124 PET scans.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary objective:

- To identify the MTD of vemurafenib plus copanlisib for patients with *BRAF* mutant RAIR thyroid cancer.

Secondary objectives:

- To determine the proportion of patients with *BRAF* mutant RAIR thyroid cancer treated with vemurafenib and copanlisib at the MTD who meet the criteria for 1-131 treatment as determined by 1-124 PET/CT lesional dosimetry.

- To determine the proportion of patients with BRAFmutant RAIR thyroid cancer treated with vemurafenib and copanlisib (all dose levels) who meet the criteria for 1-131 treatment as determined by 1-124 PET/CT lesional dosimetry.

- To quantify the effect of vemurafenib and copanlisib on RAI uptake and retention using serial 1-124 PET/CT scans.

- To evaluate whether the combination of vemurafenib and copanlisib enhances 1-131 activity, by determining the ORR (per RECIST v1.1) at 6 months after treatment with vemurafenib plus copanlis ib and 1-131.

- To evaluate whether the combination of vemurafenib and copanlisib enhances 1-131 activity, by determining progression-free survival (PFS) at 6 months (per RECIST v1.1) after treatment with vemurafenib plus copanlisib and 1-131.

Exploratory objectives:

- To evaluate tumoral gene expression changes associated with vemurafenib plus copanlisib in serial research biopsy specimens.

- To examine genomic alterations in tumors from patients in whom vemurafenib plus copanlisib does and does not enhance RAI uptake and retention, by use of research biopsy specimens or archival tissue.

- To evaluate time to next thyroid cancer treatment, tumor changes after study therapy, serum thyroglobulin changes and survival.

3.0 BACKGROUND AND RATIONALE

3.1 RAIR differentiated thyroid cancers (DTCs)

The majority of thyroid cancers are differentiated carcinomas of follicular origin, with papillary thyroid cancer {PTC) the most common, followed by follicular thyroid cancer. rvletastatic disease represents the most frequent cause of thyroid cancer-related death,[1] and RAI (1-131) remains a mainstay of therapy. RAI is selectively concentrated in thyroid tumors, making it an effective therapy, with manageable side effects. However, many patients with metastatic tumors do not have, or lose, the ability to trap iodine; this is designated as RAIR disease. RAIR metastatic DTCs are incurable, with a 10-year overall survival of only 10%.[1]

Standard therapy for RAIR DTCs includes the multitargeted tyrosine kinase inhibitors {TKls) lenvatinib and sorafenib.[2,3] SELECT, a randomized phase Ill trial evaluating lenvatinib (Eisai) compared with placebo, met its primary PFS endpoint (median PFS, 18.3 months [lenvatinib] versus 3.6 months [placebo]; hazard ratio, 0.23 [95% CI, 0.14-0.31]; p<0.0001), leading to FDA approval.[2] Unfortunately, toxicity remains a significant issue, with a 76% rate of grade 3 treatment-related toxicity in the lenvatinib group, compared with 9.9% in the placebo group. Treatment that can restore the capacity of RAIR tumors to trap and respond to a single administration of 1-131 ("redifferentiation") without the need for maintenance drug therapy could replace or defer the need for TKls. Last, a survival benefit of TKls in patients with RAIR thyroid cancer has yet to be demonstrated.

3.2 Inhibition of aberrant mitogen-activated protein kinase (MAPK) signaling partially redifferentiates RAIR thyroid cancers and restores RAI avidity

Approximately 70% of PTCs possess mutually exclusive oncogenic mutations in the rv1APK pathway,[4] the most common of which is *BRAFv^{600E},* which has been shown to be a factor of poor prognosis.[5] Constitutive rv1APK pathway activation promotes RAI refractoriness by suppressing the expression of genes that mediate iodide uptake and thyroid hormone biosynthesis, such as the Na+n- symporter, thyroid peroxidase, and thyroglobulin.[6,7] Using genetically engineered mouse models of BRAFmutant thyroid cancer, we previously demonstrated that f'v1APK pathway inhibition restores the expression of these genes to enhance tumor RAI avidity.[6,7]

We subsequently translated this concept to the clinic, demonstrating in a proof-of-concept study that the allosteric MEK 1/2 inhibitor selumetinib (AstraZeneca) can restore RAI avidity and efficacy in patients with RAIR disease **(Figure 1).**[8] A critical feature of this study was the use of 1-124 PET/CT scans to precisely quantify drug-induced changes in iodine incorporation within specific lesions ("lesional dosimetry").[19,20] This technique provides 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,[21] and is only loosely quantitative (visually similar lesions can represent as much as a 3-log range of radiation dosages). Using 1-124 PET, we can transform the 1-124 quantification into the predicted 1-131 radiation dosage delivered within every individual tumor within a patient's body. Each of the 20 evaluable patients in the study had RAIR disease, defined as having one of the following criteria: (1) non-RAI-avid lesion/s on

diagnostic whole-body radioactive iodine scintigraphy, (2) RAI-avid lesion/s that did not respond to RAI therapy, or (3) fluorodeoxyglucose (FDG)-avid lesion/s on PET scan. Eligible patients with RAIR disease underwent 1-124 PET/CT scans after stimulation with recombinant thyroid-stimulating hormone (TSH), before and after receiving a 4-week course of selumetinib (75 mg BID twice a day). If the second 1-124 PET scan predicted that a lesional RAI dose of 2,000 cGy could be achieved, 1-131 was administered while patients continued to receive selumetinib. Of the 20 evaluable patients, 12 (60%) had new or increased 1-124 incorporation after selumetinib **(Figure 1A-C).** For 8 patients (40%), the second 1-124 PET scan predicted that the lesional absorbed radiation dose would exceed 2,000 cGy; these patients continued to receive selumetinib and went on to receive therapeutic RAI. Reduction in tumor size, by RECIST, was achieved in all patients, with 5 confirmed partial responses; 3 patients had stable disease **(Figure 1D).** Substantial decreases in serum thyroglobulin (Tg) following RAI therapy were achieved in all 8 patients. These results were reported in the *New England Journal of Medicine.*[18]

However, in the selumetinib study, only 1 of 9 patients with *BRAFv*$^{600}_{E}$ responded to MEK 1/2 inhibitor treatment.[8] We hypothesized that to improve outcomes in the BRAFmutant group would require more-potent inhibition of MAPK signaling than what could be achieved with MEK inhibition alone. Vemurafenib is an ATP-competitive BRAF inhibitor that abrogates monomeric *BRAFv*$^{6}_{ooE}$ signaling and paradoxically activates BRAF wild-type dimers in normal cells,[22] resulting in a wide therapeutic

A

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

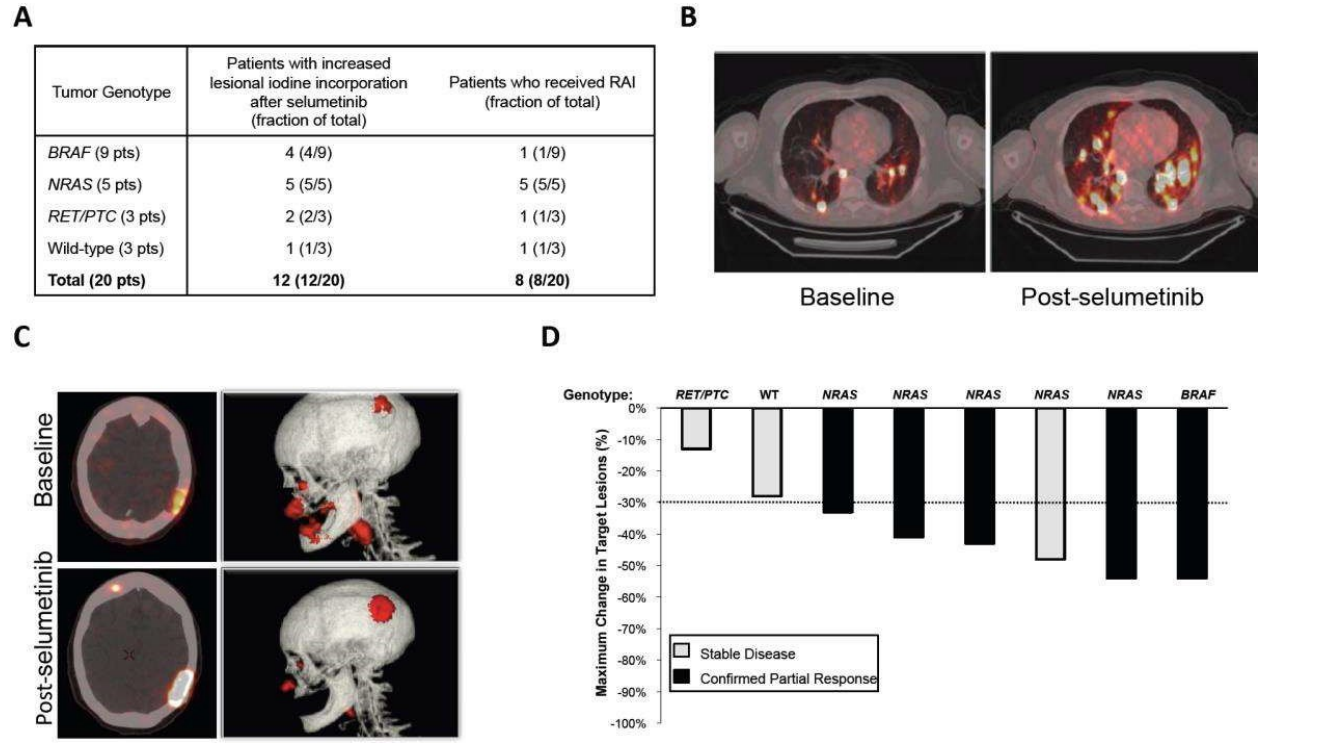


Figure 1. *Se/umetinib restores iodine incorporation in RAIR thyroid cancers.* **A)** Summaryof the 1-124 PET/CT data. **B)** Fused 1-124 PET/CT images showing new/increased iodine incorporation after selumetinib *(NRAS* mutant patient). **C)** Fused and 3-D rendering of a skull metastasis showing new/increased iodine incorporation (another *NRAS* mutant patient). **D)** Waterfall plot of the maxim um change in target lesions(%) (relative to a prestudy scan) for the 8 patients who received 1-131.

Figure 1. *Selumetinib restores iodine incorporation in RAIR thyroid cancers.* **A)** Summaryof the 1-124 PET/CT data. **B)** Fused 1-124 PET/CT images showing new/increased iodine incorporation after selumetinib *(NRAS* mutant patient). **C)** Fused and 3-D rendering of a skull metastasis showing new/increased iodine incorporation (another *NRAS* mutant patient). **D)** Waterfall plot of the maxim um change in targetlesions (%) (relative to a prestudy scan) for the 8 patients who received 1-131.

window that facilitates robust MAPK inhibition in the tumor cells. We subsequently studied vemurafenib in a 10-patient pilot study of *BRAF* mutant RAIR OTC. Six of the 10 patients had increased iodine avidity, as quantified on 1-124 PET/CT-4 of whom met the criteria for treatment with

1-131.[9] At 6 months, 2 of these patients had partial responses and 2 had stable disease. Transcriptional analysis of sequential biopsy specimens from 3 patients showed that successful inhibition of the 1\/IAPK pathway with vemurafenib led to induction of thyroid-specific gene expression, which we predicted would mediate RAI uptake.[10] These exciting results, derived from patient samples, validated the biologic principles first demonstrated in our mouse models.

3.3 Preclinical data supporting the use of combined MAPK and PI3K pathway inhibition to enhance RAI uptake and retention

The effectiveness of 1-131 is governed by the degree to which thyroid tumors can absorb (uptake) ***and*** retain (retention) RAI. In our BRAFmutant mouse models, we observed that, although 1\/IAPK inhibition enhanced RAI uptake, deficient iodide retention was not changed. Exposure to BRAF inhibition led to increased AKT phosphorylation, suggesting that activated PI3K signaling contributes to the suppression of genes involved in iodide retention. Using our *BRAF* mutant thyroid cancer mouse model, we investigated the effect of the pan class I PI3K inhibitor GDC-0941 (Genentech) in combination with the BRAF/MEK inhibitor CH5126766 (Chugai) on iodide uptake and retention. After 8 days of therapy, both iodide uptake and retention were enhanced with combination therapy, with retention enhanced to levels approximating what is observed in normal thyroid glands **(Figure 2A)**. On histopathologic examination, the combination resulted in a significant reorganization of tumor cytologic architecture, including the creation of large colloid-filled follicles. These are thyroid hormone-producing mechanical subunits in normal thyroid glands that take up elemental iodide and catalyze its covalent bonding to the protein thyroglobulin (a process known as "iodine organification") **(Figure 2B).** The physiologic and histopathologic changes observed in this thyroid cancer mouse model correlated with dramatic restoration of expression of dual oxidase 1 and 2 *(DUOX1, DUOX2),* thyroid-specific genes that catalyze a critical step in iodine organification and that are key mediators of iodine retention. In animals treated with 1-131 concurrently with combination targeted drug therapy, higher levels of

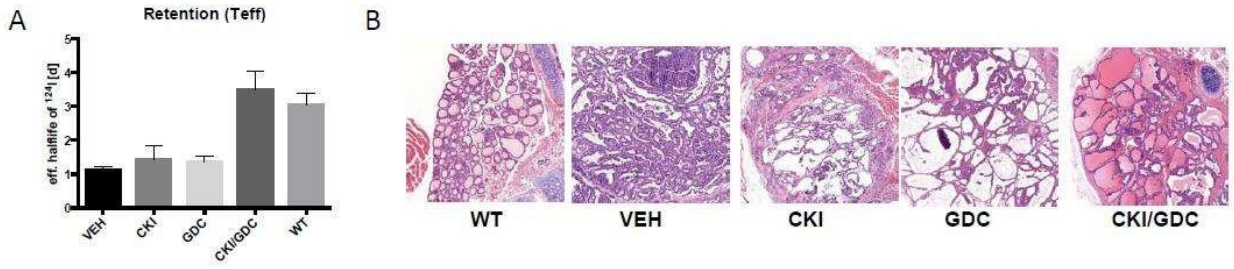


Figure 2. *MAPK and PI3K pathway inhibition enhances RA/ retention and redifferentiates thyroid tumors to form follicular structures in a TPO-Cre/LSL-BRAFv^{600E} mouse model.* **A)** After 1 week of therapy with the indicated drug, effective tumoral half-life of RAI is calculated on serial measurements made with 1-124 microPETscans. **8)** Histologyof normal thyroid (WT) and vehicle or drug-treated tumors examined after 5 days of treatment. *Veh,* vehicle; *CK/, I* CH5126766 BRAF/MEK inhibitor; *GOG,* GDC-0941 (pan class I PI3K inhibitor).

RAI-bound thyroglobulin, which is a surrogate marker for greater RAI retention, were observed within the tumors. Taken together, these results strongly suggest that adding pan-PI3K inhibition to 1\/IAPK pathway targeting restores both RAI uptake and retention by promoting the creation of normal thyroid follicles that facilitate iodine organification within the tumor, translating to a greater concentration and residence time of the 1-131 radiation dose to the tumor, which would be predicted to result in greater antitumor efficacy.

3.4 BRAF inhibition in DTC

BRAFv^{600E} mutant thyroid cancers are associated with a more aggressive course and increased cancer-related mortality, compared with *non-BRAF* mutant PTCs.[11,12] Targeting BRAF in these

patients has been shown to have clinically meaningful activity. In a phase II study of vemurafenib in patients with BRAFV600E mutant PTC, the response rate was 39% in the untreated cohort and 27% in the cohort previously exposed to multitargeted VEGF TKIs.[13]

Whereas the addition of MEK inhibition has been shown to improve outcomes in other cancers, such as BRAFmutant melanoma[14,15] and anaplastic thyroid carcinoma,[16]the same has not yet been demonstrated for *BRAF* mutant PTC. In a randomized phase II trial of dabrafenib versus dabrafenib plus trametinib in patients with *BRAF* mutant PTC, objective response rates were largely similar (45% with dabrafenib, 38% with dabrafenib plus trametinib).[17] In addition, median PFS was not statistically different (11.4 months for dabrafenib versus 15.1 months for dabrafenib plus trametinib), nor was median duration of response (15.7 months for dabrafenib versus 13.3 months for dabrafenib plus trametinib).17

Given the lack of compelling clinical data supporting enhanced efficacy of combined BRAF/MEK inhibition and the potential for increased toxicity when drugs inhibiting both pathways are administered, the present study is limited to targeting BRAF alone with vemurafenib plus copanlisib. Furthermore, the data from our 10-person pilot study of vemurafenib for redifferentiation of *BRAF* mutant RAIR thyroid cancer will serve as a useful comparator to evaluate the contribution of copanlisib for this purpose.

3.5 Clinical experience with combined MAPK and PI3K inhibition

Previous studies attempting to combine MAPK and PI3K pathway inhibitors reported variable tolerability, including 2 trials that failed to identify an MTD with a continuous dosing schedule (MEK inhibitor trametinib plus AKT inhibitor afuresertib[24] and vemurafenib plus pan-PI3K inhibitor BKM120[25]) and 1 that successfully established an MTD but still identified issues with long-term tolerability (trametinib plus pan-PI3K inhibitor buparlisib[26]). A phase I trial combining vemurafenib with the pan-PI3K inhibitor PX-866 successfully identified an MTD for the combination (vemurafenib 720 mg BID plus PX-866 8 mg daily).[27] The most common all-grade treatment-related adverse events observed included gastrointestinal toxicities (nausea, diarrhea, vomiting), arthralgia, fatigue, and skin adverse events (rash and photosensitivity). Evaluation of 4 dose levels identified 2 dose-limiting toxicities (DLTs): grade 3 rash and grade 3 pancreatitis. Other grade .::3 treatment-related adverse-events included lipase elevation and liver function test abnormalities (AST/ALT elevation). The additional advantage of developing a MAPK plus PI3K pathway inhibitor combination for tumor redifferentiation is that only a limited, discrete period of drug therapy would need to be applied (~16 days without dose interruptions), increasing the likelihood of identifying therapeutic doses that are effective and tolerable.

Vemurafenib is FDA approved for the treatment of unresectable or metastatic melanoma with *BRAF* V600E mutation and for Erdheim-Chester disease with *BRAFV600* mutation. Vemurafenib is also National Comprehensive Cancer Network (NCCN) Compendium-approved for BRAF-positive OTC. Copanlisib is FDA approved for the treatment of patients with relapsed follicular lymphoma who have had at least 2 prior systemic therapies.

We will likely be able to establish a safe and effective dose/schedule for combination vemurafenib and copanlisib administered for only slightly more than 2 weeks in total (~16 days). *We hypothesize that vemurafenib (BRAF inhibitor) plus copan/isib (P/3K inhibitor) can be safely administered to restore RA/ uptake and retention, thus vvarranting therapy Vvith 1-131, in patients Vvith RAIR thyroid cancer.*

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a phase Ib trial that will follow a 3+3 dose-escalation design, as detailed in **Section 9.2.** The primary objective of this study is to determine the MTD of vemurafenib plus copanlisib. When the MTD is reached, 4 additional patients will be enrolled at the MTD. Patients for whom vemurafenib plus copanlisib enhances RAI avidity (as measured on serial 1-124 PET/CT scans) beyond the lesional dosimetry threshold specified in the protocol will receive Thyrogen-stimulated 1-131 therapy.

Secondary objectives include determining the proportion of patients in whom the combination of vemurafenib plus copanlisib increases tumoral iodine incorporation (calculated for patients treated at the MTD *and* all dose levels). Tumor uptake and retention of iodine will be evaluated. For patients treated with 1-131, the efficacy of the therapy will be evaluated by assessing the ORR (by RECIST v1.1) and the proportion of patients alive and without disease progression at 6 months after treatment with vemurafenib plus copanlisib and 1-131.

As an exploratory objective, we will perform sequential pre- and on-treatment biopsies to analyze the changes in tumoral gene expression induced by vemurafenib plus copanlisib, as well as the putative associations of genetic alterations in the tumor that may portend successful redifferentiation with the experimental combination. We will also collect data about time for patients to initiate new thyroid cancer treatment and radiographic progression after study treatment.

4.2 Intervention

Eligible patients with *BRAF* mutant RAIR thyroid cancer will undergo recombinant human TSH (Thyrogen; Genzyme Corporation, Cambridge, MA)-stimulated 1-124 PET/CT lesion dosimetry (total of 4 1-124 PET/CT scans will be performed during this process) to quantify baseline RAI avidity in index metastatic lesion(s).

Patients will then receive vemurafenib alone for approximately 7 days, followed by the addition of copanlisib at the designated dose levels (see **Table 9-1**). A second on-treatment Thyrogen-stimulated 1-124 PET/CT lesional dosimetry analysis will be performed to assess for changes in 1-124 uptake and retention. If lesional dosimetry with the second 1-124 PET/CT scan (at ~48 h {~2 days) after delivery of 1-124) reveals that a dose of .::2000 cGy can be delivered to at least 1 tumor with :s;300 mCi of 1-131, then the Principal Investigator (PI) and treating physician(s) will decide whether 1-131 therapy should proceed for that patient. For eligible patients, therapeutic 1-131 will be administered concurrently with vemurafenib and copanlisib. The study medication will then be discontinued, and tumor assessments will be conducted by serial radiologic scan(s) and serum thyroglobulin tests (scans will be performed at baseline, before 1-131, 3-4 months after 1-131, and 6 months after 1-131). For patients whose tumors do not demonstrate sufficient iodine incorporation, the study medication will be discontinued, a final imaging assessment will be performed, and the patient will be removed from the study. Without dose interruption, this schedule would involve treating patients with vemurafenib for approximately 20 days; copanlisib will be administered once a week, for a total of 2 doses.

If there is evidence of disease progression before completing treatment with vemurafenib and copanlisib, study treatment with these drugs and 1-131 will be allowed to continue if the treating physician deems that such a decision is clinically justifiable.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Therapeutic agent copanlisib

The PI3K/AKT/mammalian target of the rapamycin (mTOR) pathway is one of the most prominent pathways that promote cellular survival and is constitutively activated in many types of cancers.[21] Class I PI3K is downstream of most cancer-associated tyrosine kinase growth factor receptors (such as epidermal growth factor receptor/human epidermal growth factor receptor, insulin-like growth factor 1 receptor, platelet-derived growth factor receptor, vascular endothelial growth factor, and c-KIT or mesenchymal epithelial transition factor).

Four of these PI3K isoforms (PI3Ka, PI3Kf3, PI3Ky, and PI3Ko) are categorized as class I enzymes because they can use phosphatidylinositol-4,5-bisphosphate (PI-4,5-P2) as a substrate to generate phosphatidylinositol-3,4,5-trisphosphate (PIP3). Elevated PIP3 in cellular membranes drives several hallmarks of the cancer phenotype: cell proliferation, survival, metabolic reprogramming, and migration. PI3Ka and f3 are ubiquitous; PI3Ky and o are expressed mostly in hematopoietic tissues.

As expected from its pharmacological properties, copanlisib, a small molecule pan-class 1 PI3K inhibitor with predominant activity against PI3Ka and PI3Ko isoforms, demonstrated antitumor activity in preclinical models, characterized by activating genetic aberrations of the PI3K pathway.

Copanlisib exhibits a potent kinase inhibitory effect on all 4 isoforms, with biochemical ICso (the half maximal inhibitor concentration) values of 0.5 nM, 0.7 nM, 3.7 nM, and 6.4 nM for PI3Ka, PI3Ko, PI3Kf3, and PI3Ky, respectively. Copanlisib also potently regulates nuclear localization of the forkhead family members, resulting in the induction of transcriptional programs that lead to rapid cell death by apoptosis. For additional background information, please refer to the Investigator's Brochure.

Copanlisib is supplied as a lyophilized preparation in a 6-ml injection vial. The total amount of copanlisib (BAY 80-6946) per vial is 60 mg. The solution for intravenous (IV) infusion is obtained after reconstitution of the lyophilisate with 0.9% sodium chloride solution.

Please refer to the Pharmacy Instructions for detailed instructions for the reconstitution of the lyophilisate and for further dilution of the reconstituted solution.

Copanlisib is administered in a normal saline solution IV during the course of 1 h. No IV glucose preparations should be administered on the days of infusion.

For continuous use (as in follicular lymphoma), dosing is weekly for the first 3 weeks of a 28-day cycle (on days 1, 8, and 15), followed by a 1-week break (i.e., no infusion on day 22).

Copanlisib will be supplied by Bayer (Bayer AG; Leverkusen, Germany).

5.2 Therapeutic agent vemurafenib

Vemurafenib is a low-molecular-weight orally available inhibitor of the activated form of the BRAF serine-threonine kinase enzyme, which is commonly found in thyroid cancer. Vemurafenib selectively inhibits oncogenic BRAF kinase. The rationale for identifying such a compound was first provided in 2002, when the high prevalence of activating mutations in the *BRAF* gene was identified in a variety of cancers. The high level of selectivity of vemurafenib has been demonstrated in

biochemical, cell-based, and *in vivo* assays. The dose of vemurafenib, 960 mg BID, was identified in the phase I dose-finding study PLX 06-02 and is established as the recommended dosage for phase II and III trials. Commercial supply of vemurafenib will be used for this trial.

5.3 Diagnostic agentthyrotropin a (Thyrogen; Genzyme)

Patients will undergo 1-124 PET/CT scanning after 2 consecutive daily injections of thyrotropin a (Thyrogen; Genzyme, Cambridge, rv1A, USA) at 0.9 mg intramuscularly, as previously described.[37] Thyrogen contains a highly purified recombinant form of human TSH and is FDA approved for thyroid dosimetry.

5.4 Therapeutic agent 1-131 (RAI)

Oral 1-131 (RAI) will be used for treatment of patients whose second lesional dosimetry 1-124 PET/CT scan reveals iodine incorporation that satisfies the threshold for RAI (1-131) treatment. 1-131 has a half-life of 8 days and a relatively high principal photon energy of 364 keV, characterized by beta particle emissions. It is administered orally in the form of capsules or liquid. Pregnancy is the only contraindication to 1-131 treatment. A serum beta-HCG pregnancy test must be performed up to 2 days before the administration of 1-131 (for woman of child-bearing potential). Commercial supply of 1-131 will be used for this trial.

5.5 Diagnostic agent 1-124 PET tracer

Clinical-grade 1-124 was first produced at 1\/lemorial Sloan Kettering Cancer Center (MSK) in the 1950s. It has been produced in MSK cyclotrons by bombarding tellurium targets. It is purified using novel radiochemical techniques. For this study, clinical-grade 1-124 will be provided by outside suppliers (e.g. Sofie Biosciences [Dulles, VA, USA; formerly known as IBA 1\/blecular North America and Zevacor Pharma]; 3D Imaging [Little Rock, AR, USA]) who meet MSK's minimum specifications as stated in the MSK-held investigational new drug (IND; IND# 71343). 1-124 will be given orally as a capsule or liquid. The normal organ dosimetry of 1-124 is provided in **Appendix A**

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Histologically or cytologically confirmed thyroid carcinoma of follicular origin (including papillary, follicular, and poorly differentiated subtypes and their respective variants).

- A tumor sample (primary, recurrent, or metastatic tumors) possessing a *BRAFV600* mutation, as confirmed in a CUA-certified laboratory or using an FDA-approved assay.

- 1\/leasurable disease by RECIST v1.1 (tumors in previously irradiated fields may be considered measurable if there is evidence of tumor progression after radiation treatment)

- RAIR disease, as defined by any one of the following:
    - A metastatic lesion that is not RAI-avid on a diagnostic radioiodine scan

  - An RAI-avid lesion that remained stable in size or progressed despite RAI treatment before entry in this study (there are no size limitations for the index lesion used to satisfy this entry criterion)
  - The presence of at least 1 FOG-avid lesion

- No receipt of treatment for thyroid cancer, defined as:
  - No 1-131 therapy <6 months before initiation of the protocol (time of initiation of the protocol is defined as the first day of drug therapy with vemurafenib and copanlisib); diagnostic activities of 1-131 (0-10m Ci) are allowed within 6 months of initiating the protocol
  - No external beam radiation therapy <4 weeks before initiation of the protocol
  - No chemotherapy or targeted therapy including TKIs <4 weeks (or <5 half-lives of the drug) before the initiation of this protocol

- Age 18 years

- ECOG performance status S2 or Karnofsky Performance Score (KPS) 70%

- Tissue from the primary tumor or metastases available for correlative studies. Either a paraffin block or at least 20 unstained slides are acceptable (30 unstained slides is ideal); if <20 unstained slides are available, and a paraffin block is not available, the patient may be able to participate at the discretion of the investigator

- Able to swallow and retain an orally administered pill without any clinically significant gastrointestinal abnormalities that may alter absorption, such as malabsorption syndrome or major resection of the stomach or bowels

- Agree to undergo 2 research biopsies of (a) malignant lesion(s). Tumor tissue obtained before study consent or treatment can also be submitted in lieu of performance of the first pretreatment biopsy if the Principal Investigator deems it to be of sufficient quantity/quality/timeliness (tumor tissue obtained more than 3 years from time of study consent would not be eligible). Patients may be exempt from biopsy if (1) the investigator or person performing the biopsy judges that no tumor is accessible for biopsy, (2) the investigator or person performing the biopsy feels that the biopsy poses too great of a risk to the patient, or (3) the patient's platelet count is <100,000/mcl or the patient cannot be safely removed from anticoagulation therapy (if the anticoagulation therapy needs to be temporarily held for the biopsy procedure). If the investigator deems a second research biopsy to be high risk, the patient may be exempt from the second biopsy.

- Screening laboratory values meeting the following criteria:
  - WBC 2000/µL
  - Neutrophils 1500/µL
  - Platelets 100 x 10^3/µL
  - Hemoglobin >9.0 g/dl
  - Lipase s1.5 x ULN
  - AST/ALT ::,;3 x ULN

- Total bilirubin 1.5 x ULN (except subjects with Gilbert syndrome, who can have total bilirubin <3.0 mg/dl)
- Serum creatinine 1.5 x ULN or creatinine clearance (CrCI) .:::40 mUmin (if using the Cockcroft-Gault formula below):

$$\textit{Female}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dl}}$$

$$\textit{Male}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dl}}$$

6.2 Subject Exclusion Criteria

- Untreated metastatic brain or leptomeningeal tumors (metastatic brain or leptomeningeal tumors treated with radiation and/or surgery are allowed)
- Prior malignancy if diagnosed and treated within 2 years of trial drug initiation (with the exception of nonmelanoma skin cancers or Stage I cancers treated with curative intent). Patients may be included if they have completed therapy for a prior malignancy >2 years before drug initiation and currently have no evidence of disease
- Inability to follow a low-iodine diet or requiring a medication with a high content of iodide (amiodarone)
- Current congestive heart failure class >2, as defined by the New York Heart Association functional classification system
- Myocardial infarction <6 months before the initiation of protocol
- Unstable angina (angina symptoms at rest) or new-onset angina (begun within the last 3 months)
- Uncontrolled hypertension (blood pressure >150/90, despite optimal medical management)
- Uncontrolled type I or II diabetes mellitus, as judged by the investigator, or Hgb A1C of >8.5
- Arterial or venous thrombotic event or embolic event, such as a cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism, within 3 months before the start of study medication
- Nonhealing wound, ulcer, or bone fracture (tumor-related nonhealing wounds are allowed)
- Active, clinically serious infections CTCAE v5.0 grade >2
- History of concurrent condition of interstitial lung disease and/or severely impaired lung function

- Known history of HIV infection (all patients must be screened for HIV up to 28 days before start of study)

- Seizure disorder requiring medication

- Therapy with a prohibited concomitant medication **(Section 9.5)** that cannot be temporarily held (at least 2 weeks before initiation of vemurafenib plus copanlisib until 1 week after the last dose) or replaced with a nonprohibited concomitant medication

- Systemic corticosteroid therapy at a daily dose >15 mg prednisone or equivalent (previous corticosteroid therapy must be stopped or reduced to the allowed dose at least 7 days before study registration)

- Cytomegalovirus (CMV) PCR-positive at baseline

- Evidence or history of a bleeding diathesis or any hemorrhage or bleeding CTCAE v5.0 grade 3 within 4 weeks before the start of study protocol

- HBV or HCV infection. All patients must be screened for HBV and HCV up to 28 days before the start of study medication using the routine hepatitis virus laboratorial panel. Patients positive for HBsAg or HBcAb will be eligible if they are negative for HBV-DNA (these patients should receive prophylactic HBV antiviral therapy). Patients positive for anti-HCV antibody will be eligible if they are negative for HCV-RNA

- Known hypersensitivity to any of the test drugs, test drug classes, or excipients in the formulation

- Substance abuse or medical, psychological, or social conditions that may interfere with the patient's participation in the study or evaluation of the study results

- Patients who are pregnant

- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception during dosing and for 6 months after the last administration of study treatment. Highly effective contraception methods include:

    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least 6 weeks before taking study treatment. In cases of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone-level assessment (FSH level in the postmenopausal range) is this acceptable

- Male sterilization (at least 6 months before screening). The vasectomized male partner should be the sole partner for that patient
- Use of oral, injected, or implanted hormonal methods of contraception or placement of an intrauterine device or intrauterine system or other forms of hormonal contraception that have comparable efficacy (failure rate <1%)-for example, hormone vaginal ring or transdermal hormone contraception. **Note:** In cases of use of oral contraception, women should have been stable, on the same pill for a minimum of 3 months before taking study treatment
- Women are considered postmenopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least 6 weeks ago. In cases of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone-level assessment is she considered not of child-bearing potential.

- Sexually active men, **unless** they use a condom during intercourse while on treatment and for 6 months after stopping treatment with study drugs (men should not father a child in this period). A condom is required to be used by vasectomized men as well during intercourse to prevent delivery of the drug via semen.

7.0 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team. Patient recruitment most likely will occur in the medical oncology and endocrinology clinics of the Head and Neck Disease management team. If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study. Investigators will discuss the study and review/sign the informed consent documents with the patient.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review.

8.0 PRETREATMENT EVALUATION

<u>To be performed any time before the start of study medication</u>:

- Collection of ~10 ml of blood, preferably in a lavender-top tube (with EDTA)

- Research tumor biopsy: The first of 2 research biopsies will be performed any time before administration of vemurafenib and copanlisib. Any tumor site is allowed, but metastatic tumors are preferred, and every attempt should be made when performing both biopsies to obtain tissue from the same tumor. Tumor tissue obtained before study consent or treatment can also be submitted in lieu of performance of the first pretreatment biopsy if the Principal Investigator deems it to be of sufficient quantity/quality/timeliness. See **Section 6.1** for exemption clauses regarding biopsy.

Within 30 days of starting study, the following tests must be done:

- Signed informed consent form
- History and physical examination
- Vital signs (blood pressure, pulse), including weight
- Performance status (ECOG or Karnofsky Performance score)
- Radiologic studies (CT [without iodinated contrast] or MRI scan) for disease assessment
- Record of concomitant medications
- Comprehensive metabolic panel, including albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT (AST), SGPT (ALT), and sodium
- Complete blood count
- Thyroid function studies (TSH level, thyroglobulin, thyroglobulin antibody, and free T4)
- *BRAF* mutation testing of the primary tumor, recurrent tumor, or metastasis if not done previously (results obtained any time before study registration can be used for patient enrollment)
- EKG (or ECG)
- Echocardiogram (ECHO)
- Dermatologic exam
- Request for archival tumor tissue (if tissue is not already available at MSK; receipt of tissue is not required for study enrollment or initiation)
- Lipase
- Crvt\/ PCR
- HIV serologies
- HBV serologies
- HGV serologies
- Hgb A1C

To be performed within 7 days of starting study:

- Serum beta-HCG (pregnancy test) in women of child-bearing potential

9.0 TREATMENT/INTERVENTION PLAN

9.1 Schedule of events (for all patients initiating treatment)

The week and day designations below may be subject to change if disruption in the evaluation or treatment schedule occurs. If there is a disruption to the schedule of events (including but not limited to a dose hold, inability to schedule appointments or procedures, or failure to comply with a low-iodine diet), making up or rescheduling some or all of the study assessments or treatments may be considered after discussion with the Principal Investigator (this is not a requirement).

- As detailed in the calendars included in **Section 10,** protocol procedures are subdivided into 3 consecutive study periods: (1) the pretreatment 1-124 PET/CT lesional dosimetry process (the days/scheduling during this period are designated as "Daypre-tx [Dpre-tx]"); followed by (2) on-treatment procedures during study drug treatment (designated as **"Daytx [Dtx]"),** which is the MTD period; and ending with (3) posttreatment assessments. The protocol procedures listed above will be taking place simultaneously with the dose escalation.

- After providing signed informed consent, patients will be required to perform a pretreatment biopsy (before starting vemurafenib and copanlisib), unless the patient is exempt as defined in **Section 6.1.**

1) Pretreatment Thyrogen-stimulated 1-124 PET/CT lesional dosimetry {Dore-tx|

Thyrogen-stimulated 1-124 PET/CT lesional dosimetry will be performed to establish baseline iodine avidity (for details of 1-124 PET/CT acquisition, analysis, and interpretation, please see **Appendix B).**

- Patients will adhere to a low-iodine diet **(Appendix C)** beginning preferably 7 days before the initiation of the lesional dosimetry process (but minimally 5 days prior).
- Blood draw(s) for TSH, free T4, thyroglobulin, and thyroglobulin antibody will be collected on Dpre-tx **1** (before Thyrogen injection) and Dpre-tx **3.** TSH, thyroglobulin, and thyroglobulin antibody will be collected on Dpre-tx **5.**
- Thyrogen injections (0.9 mg) will be administered intramuscularly on Dpre-ix **1** and **2.**
- 1-124 (approximately 6 mCi (4-7 mCi)) will be administered orally on Dpre-tx **3.**
- 1-124 PET/CT will be performed on Dpre-ix **4 (~24 h),** Dpre-tx **5 (~48 h),** Dpre-ix **6 (~72 h), and** Dpre-ix **8 (~120 h)** (hour designations are approximations of the interval from the time that the 1-124 is orally administered, not specific hours at which the scans must be done). The low iodine diet can be discontinued after the last 1-124 PET/CT scan. **Note:** If no iodine uptake is detected on the PET/CT scan done on Dpre-tx **5 (~48 h after delivery of 1-124),** the subsequent PET/CT scans (e.g., at ~72, and ~120 h after delivery of 1-124) will not be performed.
- See **Table 10-1** for the baseline (pretreatment) 1-124 PET/CT schedule and requirements.

2) On-treatment procedures (D!I!.) (see Figure 3 below)

- The initiation of study drugs **(Dix 1)** will be scheduled to ensure an interval of at least approximately 4 weeks between the delivery of 1-124 tracer during the pretreatment 1-124 PET/CT and the on-treatment 1-124 PET/CT (to ensure sufficient elimination of the first 1-124 tracer during the pretreatment Thyrogen-stimulated 1-124 PET/CT lesional dosimetry process). If the first 1-124 PET/CT lesional dosimetry scan does not demonstrate any significant uptake, starting vemurafenib plus copanlisib earlier may be considered.
- On **Dtx 1,** patients will initiate vemurafenib at the dose determined by the dose escalation rules in **Section 9.2.** For ease of scheduling, if possible, **Dix1** should be scheduled for a fv1onday.
- On **Dtx8 (+/-1 day)** and **Day 15 (+/-1 day),** patients will receive the copanlisib infusions per the dose escalation rules in **Section 9.2.**
  - For guidance about meal times and glucose monitoring, please see the respective **Sections 9.3** and **9.4** and the table of events in **Section 10** (below). All patients must be fasting for a

minimum of 8 h before the first infusion of copanlisib. For patients with diabetes, consider holding insulin and sulfonylureas on the morning of the fast to avoid hypoglycemia. Fasting for 4 h or more before the second infusion of copanlisib should be considered.

- Pre-treatment glucose levels must be <160 mg/dl prior to infusions if fasting, or random glucose of <200 mg/dl if not fasting.
- Blood glucose will be measured approximately 1 hour after completion of infusion and subsequently if clinically indicated, at the discretion of the investigator.
- Low glycemic index meals should be eaten for approximately 48 hours after copanlisib infusion. For further guidance about mealtimes and glucose monitoring, please see **Sections 9.3** and **9.4** and the table of events in **Section 10** below.
- Please refer to **Table 11-13** and consider consultation with an endocrinologist for management of hyperglycemia.
- Blood pressure will be measured approximately every 5-10 minutes prior to each copanlisib dose until 2 consecutive results <150/90 mmHg are recorded. If blood pressure is 150/90 mmHg, the investigator can consider a medical intervention or can delay infusion of the study drug. The patient should rest before blood pressure is recorded.
- On infusion days, blood pressure will be measured at Oh (pre-dose), approximately 30 min (mid-infusion), approximately 60 min (end of infusion), and approximately 1 h after the end of infusion. **Note:** A window of ±15 min is allowed for all blood pressure measurements, except for the 0 h (pre-dose) measurement.
- No dose should be given if blood pressure is 150/90 mmHg. Antihypertensive medication may be given to control increased blood pressure. Dosing can proceed on the scheduled day if at least 2 consecutive measurements <150/90 mmHg are recorded. In the absence of these measurements, dosing must be delayed.

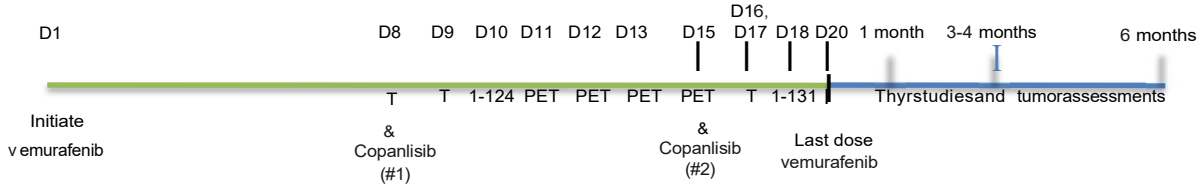
- Patients will initiate a low-iodine diet preferably 7 days before initiation of the lesional dosimetry process, but minimally 5 days before initiation of the lesional dosimetry process **(Appendix C)**.
- Patients will undergo a second biopsy while on therapy, unless the patient is exempt as defined in **Section 6.1.** When performing the second (on-treatment) biopsy, every attempt should be made to obtain tissue from the same tumor sampled at baseline (the pretreatment biopsy). Every effort will be made to perform the on-treatment biopsy on **Dtx15 or Dtx16** before the Thyrogen injection. However, the timing of the biopsy may be changed at the discretion of the Principle Investigator to account for patient preference and scheduling needs.
- For **DtxB** to **Dtx 15,** patients will complete a second (on-treatment) Thyrogen-stimulated 1-124 PET/CT lesional dosimetry while on therapy, as described above (see **Table 10-2** for the on-treatment Thyrogen-stimulated 1-124 PET/CT schedule and requirements). In addition to this, the second Thyrogen-stimulated 1-124 PET/CT process will incorporate routine analyses for determining the maximum tolerated activity (MTA), to guide subsequent 1-131 therapy. This analysis reproduces the standard-of-care MTA analysis used routinely with 1-131, and includes:
  - Routine blood samples will be collected (into green-top tubes) on days 1 (pre-Thyrogen), 3, 4, 5, 6, and 8 for radioiodine pharmacokinetics (enumeration of days here are relative to the day of the first Thyrogen injection [given on **DtxB]).** These blood collections are non-research and will be performed in the Nuclear fv1edicine clinic, therefore deviations from the specific timepoints or approach to collection will be allowed.
  - **Note:** Hour designations noted here are approximations of the intervals from the time that the 1-124 is orally administered, not specific hours at which the blood collections must be done.

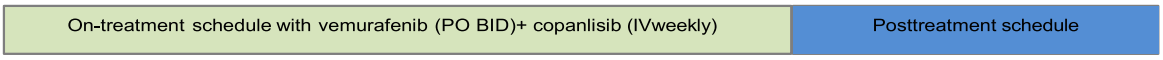
- Interpretation of the on-treatment 1-124 PET/CTscan(performed on **DtxBto Dtx15)**

- If lesional dosimetry with the second 1-124 PET/CT scan (at~ 2 days after delivery of 1-124 during the on-treatment Thyrogen-stimulated 1-124 PET/CT lesional dosimetry (Dtx **12** scan)) reveals that a dose of 2000 cGy can be delivered to at least 1 tumor with :::;300 mCi of I-131(the lesional dosimetry threshold), the Principal Investigator and treating physician(s)will decide whether 1-131 therapy should proceed. As an alternative to relying on the PET/CT performed just 2 days after 1-124, per the Principal Investigator's discretion, the decision to proceed with therapeutic 1-131 could also be determined after the biologic half-life has been calculated from the full complement of 1-124 PET/CT images collected (completed by Dtx **15** according to Table 10.2).
- If deemed appropriate, the patient will receive Thyrogen (0.9 mg) on Dtx **16** and Dtx **17** and then will be treated with 1-131 therapy on **Dtx 18.** (depending on scheduling issues, Thyrogen injection could also be given **Dtx 15** and **Dtx 16,** followed by 1-131 therapy on **Dtx 17.)**
- For patients who have sufficient uptake to warrant treatment with 1-131, the low-iodine diet must be continued for 2 days after administration of therapeutic 1-131 (1-131 activity administered for each patient will be guided by the calculated MTA). Vemurafenib will continue for 2 days after the administration of 1-131 therapy.
- For patients who did not meet the lesional dosimetry threshold required for treatment with 1-131, study drugs and low-iodine diet will be discontinued immediately, and a final tumor assessment will be performed. This includes not administering a second dose of copanlisib scheduled for **Day 15 (+/-1 day)** (these patients will have received only 1 dose of copanlisib).
- If there is evidence of disease progression before completing treatment with vemurafenib and copanlisib, study treatment with these drugs and 1-131 will be allowed to continue if the treating physician deems that such a decision is clinically justifiable.
- **Note:** *If no iodine uptake is detected* on the second 1-124 PET/CT scan done on **Dtx 12 (~2 days after 1-124),** the subsequent 1-124 PET/CT scans (e.g., at ~3 and ~5 days after 1-124) and the planned blood sample collections for MTA determination does not have to be completed. If the degree of iodine uptake measured on the **Dtx 12 (~2 days after 1-124)** 1-124 PET/CT scan is determined to be insufficient for 1-131 therapy, the planned blood sample collections for MTA determination may not be completed; however, the subsequent 1-124 PET/CT scans (e.g., at ~72 and ~120 h after 1-124) may still be performed to evaluate iodine retention.

- If a patient is unable to receive the on-treatment Thyrogen-stimulated 1-124 PET/CT lesional dosimetry process for unanticipated reasons (e.g., weather delays, holidays, travel issues, personal conflicts, availability of tracer), performance of the 1-124 PET/CT protocol will be rescheduled to the following week. To avoid unnecessary drug exposure, vemurafenib and copanlisib can be stopped and restarted 3 days before the rescheduled administration of 1-124 tracer.
- **Note:** If feasible, tumor measurements (per RECIST v1.1) will be performed with CT scans (without iodinated contrast) and/or MRI scans at separate times from the 1-124 PET/CT scans according to the schedule in **Section 10.0**.

Figure 3. On-treatment and posttreatment schedule of events for patients with sufficient uptake to warrant treatment with 1-131.





T = Thyrogen injection; PET= 1-124 PET/CT scans; 1-131 = radioiodine (RAI); Thyr studies= thyroglobulin, TSH, free T4, and thyroglobulin antibody.

9.2 Dose-escalation rules and definition of DLT

Dose escalation will proceed within each cohort according to a 3+3 design as outlined in the schema below.

Table 9-1: Dose levels (modified 3+3 design)

Dose Level	Vemurafenib Dose	Copanlisib Dose
2	960 mg PO bid	60 mg IV weekly
1 (start)	960 mg PO bid	45 mg IV weekly
-1	720 mg PO bid	45 mg IV weekly
-2	480 mg PO bid	45 mg IV weekly

Dose-escalation/de-escalation rules for the 3+3 design: Three patients viii be evaluated for the dose level being tested. If O of the initial 3 patients experience a DLT, the next higher dose level viii be tested. If 1 of the initial 3 patients at any dose level experiences a DLT, 3 additional patients w/1 be treated at the same dose level. Escalation to the next dose level viii only occur if no additional DLTs are observed. If 2 patients experience a DLT, the next lo'v\er dose level viii be tested. Please see below the specific plan for possible iterations that may be observed and how MTD viii be determined.

- If O of the initial 3 patients at dose level 1 experience a DLT, dose level 2 will be studied.
- If 1 of the initial 3 patients at dose level 1 experiences a DLT, 3 additional patients will be treated at the same dose level. Escalation to dose level 2 will proceed only if no additional DLTs have been observed.
- If 2 patients at dose level 1 experience a DLT, dose level -1 will be studied.
- If 2 patients at dose level -1 experience a DLT, dose level -2 will be studied.

MTD determinations:

- If only 3 patients have been treated at the dose under consideration as the MTD, an additional 3 patients will be treated at the same level. The dose will be declared the MTD if :::;;1 DLTwas observed among the 6 treated patients. If there is >1 DLT among the 6 treated patients, the next lower dose level will be considered the MTD.
- If 2 patients at dose level 2 experience a DLT, and :::;;1 out of 6 patients treated at dose level 1 experience a DLT, then dose level 1 will be declared the MTD.
- If 2 patients at dose level -2 experience a DLT, the combination will be determined to be unsafe, and the trial will end.

Once the MTD for vemurafenib plus copanlisib is established, up to an additional 4 patients will be enrolled in the cohort, bringing the total number of patients treated at the MTD to 10. As an added precaution for safety, if 2 of the additional 4 patients experience a DLT, further accrual will be halted.

Definitions of DLTs:

Toxicities will be evaluated using CTCAE version 5.0 (CTCAE v5.0). Only toxicities that meet DLT definitions within the DLT assessment window (from the initiation of copanlisib study treatment to 7 days after completion of study drug administration) and are attributed to vemurafenib, copanlisib or copanlisib plus vemurafenib will be counted as DLTs. Toxicities unrelated to either drug will not be considered DLTs. If a patient withdraws from the study prior to the completion of the DLT assessment window for reasons other than a DLT, the patient may be replaced and no DLTwill be considered to have occurred, unless the Principal Investigator judges that the case should be considered a DLT. Dl Ts will otherwise be defined as:

1. Any grade 3 adverse event possibly, probably, or definitely related to vemurafenib, copanlisib or the combination of copanlisib and vemurafenib. Exceptions to this rule include nausea, vomiting, or diarrhea without maximal supportive therapy, grade 3 hypertension without optimal medical intervention or which is transient (improves without medical intervention), development of new nonmelanoma skin cancer, alopecia, asymptomatic lipase and/or amylase elevation, grade 3 fatigue lasting for -5.7 days, grade 3 decreased lymphocyte count, hyperglycemia, grade 3 rash or palmar-plantar erythrodysethesia that improves to grade 2 with supportive therapy within 7 days, grade 3 fever controlled with medication within 7 days and/or other grade 3 asymptomatic laboratory abnormalities that can be corrected within 7 days.
2. Any grade 5 adverse events, unless clearly not related to treatment.
3. Any adverse event that leads to a dose delay of 7 days.
4. Any adverse event that requires a permanent dose reduction.
5. Febrile neutropenia occurring from the time of initiating study drugs up to 4 weeks after therapeutic RAI (1-131) will be considered a DLT.

Patients who experience a DLT will be allowed to continue in the study at a lower dose, in accordance with the protocol-specified dose modification, following recovery of the toxicity to grade -5.1 or the baseline level of severity (see **Section 11**).

Patients who delay vemurafenib or copanlisib for 3 days as a result of unanticipated scheduling issues (e.g., weather, emergencies; not drug-related toxicity) will not be evaluable and be replaced for DLT evaluation but may continue on the protocol. All patients receiving at least one dose of copanlisib will be evaluable for DLT.

If a patient experiences intolerable or Grade 3 toxicities possibly, probably, or definitely related to vemurafenib before the first dose of copanlisib is administered, this will NOT be considered a DLT and the patient will be replaced. The patient can be taken off study OR continue on protocol with vemurafenib alone with dose reduction per Section 11.0.

9.3 Recommendations on meal timing with copanlisib

Because of its inhibitory effect on PI3Ka, which has been implicated in insulin metabolism, copanlisib infusions could be associated with a temporary increase in blood glucose. Consuming a meal in close proximity to copanlisib infusion may exacerbate glucose increase. It is recommended that the timing and content of caloric intake on infusion days are monitored by the investigators. Consultation with an endocrinologist may be necessary.

The investigator will review the glucose profile during and after copanlisib infusions. Timing and content of caloric intake on infusion days will be managed by the investigator.

To minimize glucose increases, the investigator may manage the timing of postinfusion meals on the basis of the glucose profile during prior infusion(s). This is in addition to glucose-lowering medication. For only the firstcopanlisib infusion, fasting is required (8-h minimum) before the first glucose measurement on the date of infusion. A low-glycemic-index meal may be taken 2 h after infusion. For all subsequent copanlisib infusions, the decision regarding meal timing can be made by the investigator on the basis of glucose-response patterns during prior treatment days. Generally, a low-glycemic-index meal may be taken within 4 h before the start of the study drug infusion.

A low-glycemic-index diet (see **Appendix D)** is recommended for the first 48 h after study drug infusion. However, caloric restriction is not intended for the population under study.

Note: Caloric intake and timing recommendations for patients with diabetes who require insulin treatment before the infusion at any time point should be managed by the investigator on the basis of consultation with the treating physician or diabetes/endocrinologist physician.

9.4 Recommendation on glucose monitoring with copanlisib

Glucose monitoring for the first copanlisib administration

- Blood glucose will be measured at Oh (predose) and ~1 h after completion of infusion and subsequently if clinically indicated, at the discretion of the investigator. Patients should be educated on the signs and symptoms of hyperglycemia, such as frequent urination, increased thirst, blurred vision, headaches, and difficulty concentrating, and must report these to the investigator or their physician immediately.

Glucose monitoring for the second copanlisib infusion

- If hyperglycemia is <250 mg/dl after the first copanlisib infusion, at the discretion of the investigator, post-infusion glucose monitoring may or may not be performed. Pre-infusion glucose testing before copanlisib is required to ensure fasting levels <160 mg/dl or random/nonfasting glucose levels <200 mg/dl.

Glucose monitoring at home

- For all patients who experience persistent glucose >250 mg/dl (13.9 mmol/L) or who receive antidiabetic treatment on the day of infusion, fasting glucose should be measured the next day. If the glucose reading is <100 mg/dl (5.5 mmol/L; nondiabetic) or <160 mg/dl (8.9 mmol/L; diabetic), record the reading and stop further glucose measurements until the next copanlisib infusion. If the glucose reading is >100 mg/dl (5.5 mmol/L; nondiabetic) or >160 mg/dl (8.9 mmol/L; diabetic), inform the study nurse or investigator. If the patient has known diabetes and already monitors his/her blood glucose as part of routine diabetes care, the routine measurements should not be replaced by the study-specific measurements. In this situation, patients should add the study-specific measurements to their routine.

- For patients without diabetes who experience persisting glucose >250 mg/dl (13.9 mmol/L) or who require treatment to maintain optimal glucose levels, consultation with an endocrinologist is encouraged. These patients without diabetes will be trained on how to measure their capillary blood glucose levels at home. If applicable, patients will be provided with a glucose meter and supplies (e.g., lancets, test strips, and diary) to register measured values and record oral glucose-lowering medication and/or insulin administration.

Please refer to **Table 11-13** and consider consultation with an endocrinologist for the management of hyperglycemia.

9.5 Concomitant medications and therapies

Permitted concomitant therapy:

- Standard therapies for concurrent medical conditions
- Treatment with nonconventional therapies (for example, herbs or acupuncture) and vitamin/mineral supplements is acceptable, provided they do not interfere with the study endpoints, in the opinion of the Investigator. St. John's wort is not permitted.
- Bisphosphonates or other bone-modifying agents (e.g., denosumab)
- Patients who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate, provided their medication dose and international normalized ratio/partial thromboplastin time is stable. Close monitoring is recommended, in accordance with the standard of care. If either of these values is above the therapeutic range, the doses should be modified and the assessments should be repeated weekly until the value(s) become(s) stable.
- Antiemetics: prophylactic anti-emetics may be administered in accordance with standard practice. The routine use of standard antiemetics, including 5-HT3 blockers, such as granisetron, ondansetron, or an equivalent agent, is allowed as needed.
- The use of corticosteroids as antiemetics before copanlisib administration will not be allowed (given the risk of worsened hyperglycemia).
- Palliative and supportive care for the other disease-related symptoms and for toxicities associated with treatment will be offered to all patients in this trial.
- Patients may receive palliative and supportive care for any underlying illness.
- Low-dose aspirin (maximum 100 mg/day) and low-dose heparin are permitted.
- Patients taking narrow-therapeutic-index medications should be monitored proactively if these medications cannot be avoided. These medications may include quinidine, cyclosporine, and digoxin.
- Therapeutic drugs known to be substrates of P-gp and/or BCRP with narrow therapeutic index should be used with caution, and patients should be monitored for any sign of toxicity. Furthermore, sensitive substrates of the renal drug transporter MATE2K (e.g., metformin) should be used with caution (see **Appendix E).** Metformin should be interrupted for 48 h after receipt of iodinated contrast media. Please see prescribing information for further information.
- Calcium channel blockers may be used to control preexisting hypertension. Nondihydropyridine calcium channel blockers (e.g., verapamil and diltiazem) should be avoided because of a potential interaction with CYP3A4.
- Short-term (up to 7 days) systemic corticosteroids >15 mg prednisone or equivalent will be allowed for the management of acute conditions (e.g., treatment of noninfectious pneumonitis [NIP]).

Prohibited concomitant therapy:

The following medications are prohibited during study treatment (see **Table 9-2** below).

This list is not comprehensive and is only meant to be used as a guide.

- Strong inhibitors or inducers of CYP3M/5
- Substrates of CYP3A4/5 with narrow therapeutic index
- Medications that carry a strong risk for QT prolongation
- Herbal medications/preparations (except for vitamins)
- Other investigational and antineoplastic therapies
- Anti-arrhythmic therapy other than beta blockers or digoxin
- Systemic corticosteroid therapy at a daily dose >15 mg prednisone or equivalent. Previous corticosteroid therapy must be stopped or reduced to the allowed dose at least 7 days before study registration. If a patient is on chronic corticosteroid therapy, corticosteroids should be de-escalated to the maximum allowed dose before the screening. Patients may be using topical or inhaled corticosteroids. Short-term (up to 7 days) systemic corticosteroids >15 mg prednisolone or equivalent will be allowed for the management of acute issues. The use of corticosteroids as antiemetics before copanlisib administration will not be allowed.
- Ongoing immunosuppressive therapy
- Concomitant radiotherapy
- Herbal medications, including but not limited to St. John's wort, Kava, ephedra (ma huang), ginkgo biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh, and ginseng. Patients should stop using all herbal medications at least 7 days before the first dose of study treatment.

Table 9-2: List of prohibited medications during the study

Category	Drug name
Strong CYP3A inhibitors	Voriconazole, boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, eltegravir/ritonavir, grapefruitjuice, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil,nefazodone, nelfinavir, posaconazole, ritonavir,saquinavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin
Moderate CYP3A inhibitors	Grapefruit, grapefruit hybrids,pum melos,star-fruit, Seville oranges (citrus paradisi fruitjuice)
Strong CYP3A inducers	Avasimibe, carbamazepine, mitotane, phenobarbi1al, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum)
CYP3A substrates with narrow therapeutic index (NTI)	Alfentanil, apixaban (doses >2.5 mg only), aprepitan astemizole, cisapride, cyclosporine, diergotamine, dihydroergotamine, ergotam ine, fentanyl, lovastatin, nicardipine, nisoldipine, pimozide, quinidine, rivaroxaban, simvastatin,sirolimus, tacrolimus, terfenadine, thioridazine

Other investigational and antineoplastic therapies	Other investigational therapies must not be used while the patient is on the study. Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study treatments must not be given to patients while the patient is on the study medication. If such agents are required for a patient, the patient mustdiscontinue the study.
Herbal preparations/medications	Herbal preparations/medications are prohibited throughout the study. These herbal medications include but are not limited to St. John's wort, Kava, ephedra (ma huang), ginkgo biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days before the first dose of study medication.

9.6 Correlative studies

Exploratory objective: To evaluate how vemurafenib and copanlisib affect MAPK/PI3K signaling and thyroid differentiation in tumors of patients with RAIR disease. Biopsies will be performed at baseline and on treatment with vemurafenib plus copanlisib (as in **Table 10-2),** unless the patient is exempt **(Section 6.1**). Biopsies of any tumor site is allowed, but metastatic tumors are preferred, and every attempt should be made when performing both biopsies to obtain tissue from the same tumor. The RNA and DNA assays suggested below may be substituted for other techniques or platforms, depending on availability.

Transcriptomic and protein-based analyses of serial biopsy specimens: As the amount of frozen tissue obtained from biopsies is limited, we will prioritize sensitive array-based technologies to quantify gene expression and to sequence cancer genes. We will isolate RNA from pre- and post-treatment biopsy specimens for interrogation. RNAseq will be performed to quantify transcripts regulated by MAPK (MAPK output},[22] the BRAF-RAS score (a 71-gene signature that distinguishes $BRAFv^{6}_{ooE}$ from *RAS* mutant tumors[5]), and the enhanced Thyroid Differentiation Score (which is a gene signature of thyroid-specific differentiation.[5] Each of these scores provides an average fold-change for all mRNAs in the respective gene sets, compared with the median of all samples. In addition, we will measure the effects of vemurafenib plus copanlisib on the transcription of iodine organification genes and PI3K transcriptional output. These transcriptomic readouts will then be analyzed in the context of change in lesional 1-124 concentration observed with 1-124 PET. The transcriptomic data will also be investigated for other exploratory pathways, signatures, and biologic parameters. Alternative platforms to RNAseq may also be used if appropriate and available. Other protein markers of interest, such as phospho-AKT, may be analyzed by the appropriate assay (e.g., immunohistochemistry, Western blot, mass spectrometry, reverse protein phase array).

Genomic Analysis: Baseline genomic analysis will be performed using MSK-IMPACT, a next-generation sequencing platform .[23] Alternative techniques may be considered or performed (e.g. Sequenom analysis, Sanger sequencing, whole-exome) at the time of analyses, if deemed appropriate.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Table 10-1: Screening and baseline (pretreatment) 1-124 PET/CT schedule

	Prestudy Screening Evaluations	Baseline 1-124 PET Protocol Dμ,..-tx·2	Baseline 1-124 PET Protocol Dp,e-tx 1	Baseline 1-124 PET Protocol Dp,e-tx 2	Baseline 1-124 PET Protocol Dp,e-tx 3	Baseline 1-124 PET Protocol Dp,e-tx 4, O.,,e-tx 5, Di,,e-tx 6, O.,,e-tx 8
Serum beta-HCG						
Confirmation of *BRAF* mutation in tumor						
Informed consent	X					
Iv'edical history	X					
Concurrent meds	X					
Rlysical exam	X					
Vital signs	X					
Weight	X					
CBC w/diff, platelets	X					
Comprehensive panel	X					
Lipase	X					
Hgb A1c	X					
ClV1V PCR	X					
HIV serologies	X					
HBV serologies	X"					
HCV serologies	X'					
EKG (or ECG)	X					
Echocardiogram	X					
Dermatologic exam	X					
Archival tissue						
Research blood sample						
Research biopsy		X•				
Adherence to low -iodine diet[1]		X----------				
Thyrogen[9]			X	X		
1-124 adninistrationh					X	
1-124 PET/CT'"						X
TSH, free T4, thyroglobulin, thyroglobulin antibody			xn		X	X'
Radiologic evaluation (CT[s] and/or MRI[s]) for tumor measurements	)(I					

•serum pregnancy test (for women of child-bearing potential). The prestudy test must be done within 7 days of starting the study.
bTumor genotyping can be conducted on the primary tumor, recurrent tumor, or a metastasis. Results can be obtained anytime before the patient is registered to the study.
cAvailability of archival tumor tissue needs to be confirmed before study enrollment (if tissue is not already available at MSK, physical receipt of tissue is not required for study enrollment or initiation).
dThe research blood sample can be obtained anytime before the start of the study.
[0]Research biopsy can be performed anytime before starting vemurafenib and copanlisib **(Section 6.1**).
[1]Patients should adhere to a low -iodine diet for preferably 7 days before the initiation of the lesional dosimetry, but minimally 5 days, before the initiation of the lesional dosimetry until its completion. Rease see **Appendix C** for details of the low -iodine diet.
[9]Thyrogen (0.9 mg) will be administered intramuscularly on the 2 consecutive days beforeadninistration of 1-124 6 mCi (4-7 mCi) orally for both baseline and on-treatment Thyrogen-stimulated 1-124 PET/CT scans.
hl-124 6 mCi (4-7 mCi) will be adninistered orally before the pretreatment and on-treatment Thyrogen-stimulated 1-124 PET/CT scans.
; TSH, thyroglobulin, and thyroglobulin antibody will be drawn on Dp,e-tx **5.**
iNo iodinated IV contrast is pernitted with CT scans. MRI contrast is pernitted.
kHBV serologies include HBV surface antigen, surface antibody, and core antibody. If patients are positive for the surface antigen

or core antibody, they will require further testing with HBV DNA PCR.
'HCV antibody is required. If positive, HCV RNA PCR will be required.
mIf no iodine uptake is detected on the PET/CT scans done on **Dp„.-1x 5 (-48 h after 1-124 administration),** the subsequent PET/CT scans (e.g., at -72 and -120 hours) will not be performed.
nBlood draw (s) for TSH, free T4, thyroglobulin, and thyroglobulin antibody (thyroid studies) will be collected before Thyrogen injection on **Di„e-tx 1**.

Table 10-2: On-treatment schedule

	Dix 1	Dix 5	Dix 6	Dix 8	Dix 9	Dix 10	Dix 11	Dix 12	Dix 13	Dix 15	Dix 16	Dix 17	Dix 18
Vemurafenib	xa									xo			xo
Copanlisibc				X						X			
Fasting and adherence to low-glycerric diet													
Glucose monitoring				X'						X'			
Adherenceto low-iodine diet	xg												
Thyrogenn				X	X						X	X	
1-124 adrrinistration'						X							
I-124PET/C							X	X	X	X			
Green-top tube blooc collectionp.q				X		X	X	X	X	X			
Radioiodine treatment (1-131)													xn
Serum beta-HCG				xo							xo		
A1ysical exam'				X				X		X			
Vital signs (see blocxJ pressure monitoring parametersm)				xm				xm		X			
Weight				X				X		X			
Performance status				X				X		X			
CBC w /diff, platelels	X			X						X			
Comprehensive panel	X			X						X			
Lipase	X			X						X			
Concurrent meds				X						X			
Adverse event and DLT monitoring	xi												--·><
TSH, free T4, thyroglobulin, thyroglobulin antibody						X					X		
Radiobgic evaluation (CT(s] and/or MRI[s]) for tumor measurements'								X'					
Research biopsy			XK										

avernurafenib will be initiated on day 1 at the dose prev eiously being studied.
bFor patients for w homthe second 1-124 scan does not establish criteria for adrrinistration of 1-131 treatment, vemurafenib will be discontinued (last dose on day 12-15). For patients who have lesional dosimetry on the second 1-124 scan tow arrant treatment with 1-131, vernurafenib will continue until about 2 days after adrrinistration of 1-131 (last dose, day 20).
°Copanlisib can be given on the indicated day within aw indow of ±1 day. Only patients who will receive 1-131 will be given the second copanlisib dose.
dFasting is required for at least 8 h before the first infusion of copanlisib. A low-glycemic meal can be consumed 2 h after the first infusim of copanlisib. A low-glycemic diet is recommended for 48 h after the copanlisib infusion.
"Fasting for 4 h or more before the second and third infusions of copanlisib should be considered. The decision regarding meal timing after infusion can be made by the investigator on the basis of glucose response patterns during prior treatment days. A low-glycemic diet is recommended for 48 h after the infusion of copanlisib (see Sections 9.3 and 9.4).
'See Sections 9.3 and 9.4.
9Patients should adhere to a low-iodine diet for preferably 7 days prior to the initiation of lesional dosimetry, but minimally 5 days before the initiation of the lesional dosimetry (see Section 9.1). Rease see **Appendix C** for details of the low-iodine diet.
hThyrogen (0.9 mg) will be administered intramuscularly on the 2 consecutive days beforeadrrinistration of 1-124 (5-7 mCi). For patients

with lesional dosimetry on the second 1-124 scan tow arrant treatment with 1-131, Thyrogen will be given on the 2 consecutive calendar days and 1-131 treatment will be given on the day after the second Thyrogen injection. (Depending on scheduling concerns, Thyrogen coL.tl also be given Days 15 and 16, with 1-131 admnistration on Day 17).

;1-124 6 rrCi (4-7 rrCi) will be administered orally before on-treatment 1-124 PET/CT scans.

iTSH, thyroglobulin, and thyroglobulin antibody will be evaluated on Dix12.

n-treatment biopsy to be performed while on study treatment, unless exempt according to **Section 6.1.** Every effort will be made to do the biopsy on **Dix 15 or 16** prior to Thyrogen injection. How ever, the timng of the biopsy may be changed at the discretion of the A-inciple Investigator to account for patient preference and scheduling needs.

[1]The screening period for DLTs will be from the initiation of study treatment to 7 days after completion of study drug admnistration. The continuous nature of this monitoring does not imply the need for daily communication with the patient; the reporting of adverse events or DLTs that are brought to the attention of the study team will be captured.

mBlood pressure will be measured approximately every 5-10 mn before each copanlisib dose, until 2 consecutive results <150/90 mmHg are recorded (no more than 4 measurements). If blood pressure is 150/90 mmHg, the investigator can consider medical intervention or delay the infusion of the study drug. The patient should rest before blood pressure is recorded. On infusion days, blood pressure will be measured at O h, 30 mn (midinfusion), 60 mn (end of infusion), and 1 h (all approximate time points) after the end of the infusion. Of note, aw indo,v of ±15 mn is allowed for all blood pressure measurements, except for the 0-h (pre-dose)measurement.

[0]If patients meet the lesional dosimetry requirements tow arrant treatment with radioiodine (I-131), they will receive this treatment on **Dix 18,** with a total activity guided by the MTA determination performed. (depending on scheduling concerns, Thyrogen and 1-131 admnistration could also be performed a day earlier (I-131 admnistered on D17).

°For women of child-bearing potential, a serum beta-HCG test must be performed up to 2 days before the administration of 1-124 or 1-131.

Pfor RAI MTA determnation performed with the second 1-124 PET dosimetry process:

- Routine blood draws into green-top tubes on days 1 (pre-Thyrogen), 3, 4, 5, 6, and 8 for radioiodine pharmacokinetics will be collected (enumeration of days here are relative to the day of the first Thyrogen injection).
- **Note**:Hour designations above are only approximations of the intervals for assay collection and are not specific hours for which these tasks must be done.

q If no iodine uptake is detected on the PET/CT scans done on **Dix 12 (~48 h after 1-124 administration),** the subsequent PET/CT scans (e.g. at -72 and -120 h after 1-124) and the blood sample collections for MTA determination will not be completed. If the degree of iodine uptake is determned to be insufficient for 1-131 therapy, as measured on the **Dix 12 (-48 h after 1-124 administration)** 1-124 PET/CT scan, the blood sample collections for MTA determnation will not be completed; how ever, the subsequent 1-124 PET/CT scans may still be performed to evaluate iodine retention.

'If feasible (not mandatory), tumor measurements (per RECIST v1.1) will be performed with CT scans (without iodinated contrast) and/or MRI scans wnle on study therapy and prior to 1-131 admnistration.

[5]This draw is to be done prior to Thyrogen administration.

TPhysical exam can be done up to 3 days before each copanlisib dose. The last physical exam can be performed any day during the designated week (week of **Day 15).**

Table 10-3: Post-treatment follow-up schedule

	Poststudy (No RAI) **Day 15 (+1 week)**[3]	**Poststudy** (Yes RAI) 7 **days (±2 days) s/p RAI**	**Poststudy** (Yes RAI) **14 days(± 2 days) s/p RAI**	**Poststudy** (Yes RAI) **1 month{± 1 week) s/p RAI**	**Poststudy** (Yes RAI) **3-4 months s/p RAI**	**Poststudy** (Yes RAI) **6 months {± 2 weeks) s/p RAI**	**Observation Phasec (all patients) Up to 1 year after study drug discontinuation**
Thyroglobulin, TSH, free T4, thyroglobulin antibody				X	X	X	
CBC w /diff, platelets	X	X	X	X	X	X	
Comprehensive panel	X	X	X	X	X	X	
Lipase	X	X	X	X			
Radiologic evaluation (CT[s] and/or MRI[sI) for tumor measurements[b]	X				X	X	
Collect data on tumor changes in radiologic scans, serum thyroglobulin/TSH, initiation of new thyroid cancertreatments and survival							X

•Relative to the on-treatment calendar; for patients in w homthe second 1-124 scan does not meet the criteria for admnistration of 1-131 treatment, a post-therapy scan can be obtained up to -1 week after discontinuation of vemurafenib and copanlisib.

bl\Jo iodinated IV contrast is permtted with CT scans. MRI contrast is permtted.

cThe observation period encompasses up to 1 year after study drug is discontinued for all patients. Data regarding radiographic disease progression, thyroglobulin/TSHserum values, survival and initiation of new treatments will be collected. Evaluating radiographic disease progression will be performed on both protocol-mandated scans and scans performed as per standard of care after protocol-mandated scans have been completed. If progression of disease and initiation of drug therapy, or death, occurs then the observation phase may be discontinued.

11.0 TOXICITIES/SIDE EFFECTS

11.1 Clinical Toxicity Data forVemurafenib

Vemurafenib is FDA approved for the treatment of unresectable or metastatic melanoma with BRAF V600E mutation and for Erdheim-Chester disease with BRAF V600 mutation. Vemurafenib is also NCCN compendium-approved for BRAF-positive OTC. Because clinical studies are conducted under widely varying conditions, adverse-reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not predict the rates observed in a broader patient population in clinical practice. This section describes adverse drug reactions identified from analyses of 2 trials: trial 1[18] and trial 2.[19] Trial 1 randomized (1:1) 675 treatment-naive patients with unresectable or metastatic melanoma to receive either vemurafenib (960 mg PO BID) or dacarbazine (1000 mg/m^2 IV every 3 weeks). In trial 2, 132 patients with metastatic melanoma and failure of at least 1 prior systemic therapy received treatment with vemurafenib (960 mg PO BID).

Table 11-1 presents the adverse reactions reported in at least 10% of patients treated with vemurafenib. The most common adverse reactions of any grade (30% in either study) in vemurafenib-treated patients were arthralgia, rash, alopecia, fatigue, photosensitivity reaction, nausea, pruritus, and skin papilloma. The most common (5%) grade 3 adverse reactions were cutaneous squamous cell carcinoma (SCC) and rash. The incidence of grade 4 adverse reactions was :54% in both studies. In trial 1, the incidence of adverse events resulting in permanent discontinuation of study medication was 7% for the vemurafenib arm and 4% for the dacarbazine arm. In trial 2, the incidence of adverse events resulting in permanent discontinuation of study medication was 3%. In trial 1, the median duration of study treatment was 4.2 months for vemurafenib and 0.8 months for dacarbazine; in trial 2, the median duration of study treatment was 5.7 months.

Table 11-1: Adverse reactions reported in 10% of patient treated with vemurafenib

Adverse Drug Reactions (Reported using MedDRAand graded by CTCAE v.5.0)	**Trial 1: Treatment-Naive Patients**				**Trial 2: Patients with Failure of At Least One Prior Systemic Therapy**	
	Vemurafenib (n=336)		Dacarbazine (n=287)		Vemurafenib (n=132)	
	All Grades (%)	Grade 3a (%)	All Grades (%)	Grade 3 (%)	All Grades (%)	Grade 3a (%)
Skin and subcutaneous tissue disorders						
Rash	37	8	2	0	52	7
Photosensitivity reaction	33	3	4	0	49	3
Alopecia	45	<1	2	0	36	0
Pruritus	23	1	1	0	30	2
Hyperkeratosis	24	1	<1	0	28	0
Rash maculo-papular	9	2	<1	0	21	6
Actinic keratosis	8	0	3	0	17	0
Dry skin	19	0	1	0	16	0
Rash papular	5	<1	0	0	13	0
Erythema	14	0	2	0	8	0
Musculoskeletal and connective tissue disorders						
Mhralgia	53	4	3	<1	67	8
Myalgia	13	<1	1	0	24	<1
Pain in extremity	18	<1	6	2	9	0
Musculoskeletal pain	8	0	4	<1	11	0
Back pain	8	<1	5	<1	11	<1

General disorders and administration site conditions						
Fatigue	38	2	33	2	54	4
Edema (peripheral)	17	<1	5	0	23	0
Pyrexia	19	<1	9	<1	17	2
Asthenia	11	<1	9	<1	2	0
Gastrointestinal disorders						
Nausea	35	2	43	2	37	2
Diarrhea	28	<1	13	<1	29	<1
Vomiting	18	1	26	1	26	2
Constipation	12	<1	24	0	16	0
Nervous system disorders						
Headache	23	<1	10	0	27	0
Dysgeusia	14	0	3	0	11	0
Neoplasms benign, malignant, and unspecified (includes cysts and polyps)						
Skin papilloma	21	<1	0	0	30	0
Cutaneous SCCb	24	22	<1	<1	24	24
Seborrheic keratos is	10	<1	1	0	14	0
Investigations						
GGT increased	5	<1		0	15	6
Metabolism and nutrition disorders						
Decreased appetite	18	0	8	<1	21	0
Respiratory, thoracic, and mediastinal disorders						
Cough	8	0	7	0	12	0
Injury, poising, and procedural complications						
Sunburn	10	0	0	0	14	0

• Grade 4 adverse reactions lirrited to ganma-glutamyl transferase increases (<1% in trial 1 and 4% in trial 2).
blncludes both sec of the skin and keratoacanthorra;cases of cutaneous sec were required to be reported as grade 3, per the protocol.

Clinically relevant adverse reactions reported in <10% of patients treated with vemurafenib in the phase II and phase III studies include:

- *Skin and subcutaneous tissue disorders:* Palmar-plantar erythrodysesthesia syndrome, keratosis pilaris, panniculitis, erythema nodosum, Stevens-Johnson syndrome, toxic epidermal necrolysis
- *Musculoskeletal and connective tissue disorders:* Arthritis
- *Nervous system disorders:* Neuropathy peripheral, VIIth nerve paralysis
- *Neoplasms benign, malignant, and unspecified (includes cysts and polyps):* Basal cell carcinoma, oropharyngeal squamous cell carcinoma
- *Infections and infestations:* Folliculitis
- *Eye disorders:* Retinal vein occlusion
- *Vascular disorders:* Vasculitis
- *Cardiac disorders:* Atrial fibrillation

Postmarketing experience: The following adverse reactions have been identified during postapproval use of vemurafenib (Zelboraf). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Neoplasms benign, malignant, and unspecified (including cysts and polyps):* Progression of preexisting chronic myelomonocytic leukemia with NRAS mutation
- *Skin and subcutaneous tissue disorders:* Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)
- *Blood and lymphatic systems disorder:* Neutropenia
- *Injury, poisoning, and procedural complications:* Radiation sensitization and recall

- *Gastrointestinal disorders:* Pancreatitis
- *Renal and urinary disorders:* Acute interstitial nephritis, acute tubular necrosis
- *Musculoskeletal and connective tissue disorders:* Dupuytren's contracture and plantar fascial fibromatosis

Table 11-2: Change in baseline to grade 3 or 4 liver abnormalities

Parameter	Change from Baseline to Grade 3 or 4 Liver Abnormalities	
	Vemurafenib (%)	Dacarbazine (%)
GGT	11.5	8.6
AST	0.9	0.4
ALP	2.8	1.9
Alkaline phosphate[8]	2.9	0.4
Bilirubin[8]	1.9	0

•For ALT, alkaline phosphatase, and bilirubin, there were no patients with a change to grade 4 in either treatment arm.

11.2 Clinical toxicity data for copanlisib

Copanlisib is FDA approved for the treatment of patients with relapsed follicular lymphoma who have had at least 2 prior systemic therapies. This approval was based on a large phase II study of copanlisib in 142 patients with relapsed/refractory indolent lymphoma who had received 2 or more prior therapies. The objective response rate was 59% (84/142 patients), with a median duration of response of 22.6 months.[20] The overall safety profile of copanlisib is based on data from 317 subjects treated in clinical studies. In clinical studies, the most commonly reported suspected adverse reactions in patients with non-Hodgkin's lymphoma (indolent and aggressive) and solid tumors treated with copanlisib monotherapy included pneumonitis, lower respiratory tract infections (including pneumonia), and febrile neutropenia; the most common adverse reactions (20%) were hyperglycemia, decreased general strength and energy (including fatigue and asthenia), hypertension, diarrhea, nausea, leukopenia, and neutropenia.

Table 11-3: Adverse drug reactions in patients treated with copanlisib monotherapy reported in multiple clinical trials

System Organ Class	Very Common (1/10)	Common (1/100to <1/10)	Uncommon (1/1000 to <1/100)
Blood and lymphatic system disorders	Leukopenia, neutropenia,[8] thrombocytopenia	Lymphopenia, febrile neutropenia,[8] eosinophilia	
Gastrointestinal disorders	Diarrhea, nausea, stomatitis (including oropharyngeal erosion and ulcer and oral pain)	Dysgeusia, dry mouth, dysphagia	Pancreatitis
General disorders and administration site conditions	Decreased general strength and energy (including fatigue and asthenia)	Mucosal inflammation, injection site reactions	
Immune system disorders		Hypersensitivityreactions (including allergic edema and angioedema, vasodilatation and flushing, and infusion-related reaction)	
Infections and infestations	Lower respiratorytract infectionb (including terms pneumonia,b pneumonia bacterial, pneumonia pneumococcal, pneumonia fungal, pneumonia viral,		

	Pneumocystisjirovecii pneumonia, bronchopulmonary aspergillosis, and lung infectionb)		
Investigations		Increase in lipase, increase in amylase	
Metabolism and nutrition disorders	Hyperglycemiaa	Hyperlipidem ia, hyperinsulinemia, polydipsia	
Nervous system disorders		Paresthesia and dysesthesia	
Respiratory, thoracic, and mediastinal Disorders		Pneumonitis (including interstitial lung disease and noninfectious pneumonitis)	
Skin and subcutaneous tissue disorders	Rash (including exfoliati-..e skin reactions)	Alopecia	
Vascular disorders	Hypertension (including secondary hypertension)		

[8]life-threateningcases have been reported.
bFatal cases have been reported.

Table 11-4: Treatment-emergent laboratory test abnormalities (10%) in patients with non-Hodgkin's lymphoma and solid tumors from open-label phase I and phase II monotherapy studies

Laboratory Parameter (Copanlisib Monotherapy n=317)	**All Grades**[3] (%)	**Grade 3a** (%)	**Grade 4a** (%)
Blood and lymphatic system			
Hgb decreased	84	8	0
Lymphocyte countdecreased	75	28	5
Platelet count decreased	56	6	3
Neutrophil count decreased	53	11	13
Metabolism and nutrition			
Elevated blood glucose	96	38	3
Hypophosphatemia	40	13	0
Investigations			
Serum amylase increased	21	2	
Serum lipase increased	18	5	

[8]CTCAE v 5.03.

Special warnings with copanlisib monotherapy:

- Infections: Serious infections (including fatal infections) occurred in 19% of 317 subjects treated with copanlisib monotherapy. The most common infections were pneumonia, lung infection, and lower respiratory tract infection. *Pneumocystis jirovecii* pneumonia occurred in 0.6% of 317 subjects treated with copanlisib monotherapy. Before initiating treatment with copanlisib, consider *Pneumocystisjiroveciipneumonia* prophylaxis for populations at risk.

- Noninfectious pneumonitis (NIP): NIP (all events grade S3) occurred in 5.0% of 317 subjects treated with copanlisib monotherapy.

- Neutropenia/febrile neutropenia: Grade 4 neutropenia (febrile and nonfebrile) occurred in 9.1% of 317 subjects treated with copanlisib monotherapy. Serious febrile neutropenia occurred in 1.9%.

- Transient hypertension: Serious hypertension (all events grade 3) occurred in 0.9% of 317 subjects treated with copanlisib monotherapy. Treatment with copanlisib may result in transient hypertension. The mean systolic blood pressure and diastolic blood pressure increased after dosing on cycle 1, day 1 and started to decrease approximately 2 h postinfusion.

- Transient hyperglycemia: Serious grade 4 hyperglycemia (>500 mg/dl) occurred in 0.9% of 317 subjects treated with copanlisib monotherapy. Treatment with copanlisib may result in transient hyperglycemia. Blood glucose levels typically peaked 5 to 8 h postinfusion and subsequently declined to baseline levels. Optimal blood glucose control should be achieved before starting each copanlisib infusion. Of the 20 subjects with diabetes mellitus treated in CHRONOS-1, 7 developed grade 4 hyperglycemia and 2 discontinued treatment.

- Embryofetal toxicity: On the basis of its mechanism of action and findings in a rat embryofetal development study, copanlisib may cause embryofetal harm.

General guidelines for dose modification and toxicity management

The recommendations for the management of adverse events in this section are to serve as general guidelines; dose reductions or delays for any event of any CTCAE grade may always be considered for safety reasons, at the discretion of the treating investigator.

Patients who require discontinuation of either drug may continue to receive the remaining drug (vemurafenib or copanlisib).

Table 11-5: Dose levels for dose modification of vemurafenib-related adverse events

Dose Level	Vemurafenib Dose/Schedule
0	960 mg PO BID
-1	720 mg PO BID
-2	480 mg PO BID

Table 11-6: General criteria for dose modification for vemurafenib-related adverse events

Related Adverse Events	Intervention
Grade 1	Continue at the same dose level
Grade 2	Continue at the same dose level
Grade 3 nonhematologictreatment-related toxicity"	Interrupt dosing until resolution to grade 1 and then restart at 1 dose level lower
Grade 4 nonhematologic treatment-related toxicity or grade 4 hematologic toxicity'	On the basis of investigator judgment, discontinue study treatment or interrupttreatment until resolution to grade 1 and then restart at dose level-2 (480 mg PO BID)

[3]For manageable grade 3 nonhematologic toxicities (e.g., cutaneous SCC) or those that can be controlled with medications, treatment may continue at the same dose level without interruption, at the discretion of the investigator.

bPatients who develop grade :::;4 lymphopenia or grade :::;4 asymptomatic biochemical laboratory abnormality may continue study treatment at the same dose level without interruption, on the basis of the investigator's judgment.

Table 11-7: Dose levels for necessarydose modification of copanlisib-related adverse events

Dose Level	Copanlisib Dose/Schedule
0	60 mg IV weekly
-1	45 mg IV weekly

Table 11-8: Dose modification for copanlisib-related nonhematological toxicity (except

glucose increases, dermatologic toxicity, noninfectious pneumonitis, and blood pressure increases)

Toxicitya	Occurrence	!For current course of therapy	For next course of therapy
Grade 1-2	Any appearance	No change	No change
Grade Jb	1st appearance	Delay until grade :::;2	No change
	2nd appearance	Delay until grade :s:;2	Decrease by **1** dose levelc
	3rd appearance	Permanently discontinue	
Grade 4	Any appearance	Permanently discontinue	
!Toxicity requiring delay for >21 days		Permanently discontinue	

•Toxicities according to CTCAE version 5.0.
bDespite rnaxirrum supportive therapy.
[0]Not applicable for 45-mg dose level.

Table 11-9: Dose modification for copanlisib-related hematologic toxicity

Hematological toxicity (any of the following)	Study treatment action (for any toxicity)
• CTCAE grade 3 thrombocytopenia (platelet<50,000/mm^3) • Febrile neutropenia • CTCAE grade 3 neutropenia (ANC <1000/mm^3) • INR or PTT CTCAE grade 3 with bleeding[a] • CTCAE grade 3 anemia (Hb <8 g/dl)	Delay infusion until Hgb 8, platelets 75, and ANC 1500/m m^{3}withoutfever.[0] Patient can be treated at 1 dose level lower, at the investigator's discretion.[b]If more dose reductions are required than are allowed per the protocol, discontinue copanlisib permanently.

ANC = absolute neutrophil count;Hb = hemoglobin;INR = international normalized ratio; PTT= partial thromboplastin time.
[8]INR and PTT should have returned to s;1.5 and s;1.5 x ULN, respectively, with no signs of bleeding.
bMer full recovery from toxicity and in the absence of any criteria for further dose reduction or study drug discontinuation, re-escalation to dose level -1 or 1 is allowed, at the investigator's discretion.
[0]Treatmentwith transfusion or growth factors is allowed, atthe investigator's discretion.

Table 11-10: Dose modification for copanlisib-related dermatologic toxicity

Toxicity"	Occurrence	For current course of therapy	For next course of therapy
Grade 1	Any appearance	No change	No change
Grade 2[b]	1st appearance	Interruption until grade s;1	No change
	2nd appearance	Interruption until grade s;1	Decrease by one dose level[0]
	3rd appearance	Permanent discontinuation	
Grade 3b	1st appearance	Interruption until grade s;1	Decrease by one dose level[0]
	2nd appearance	Permanentdiscontinuation	
Grade 4	pt appearance	Permanent discontinuation	

aToxicities according to CTCAE version 5.0.
bDespite maximum supportive therapy.
[0]Not applicable for 45-mg dose level.
The lowest dose level is 45 mg; if a patient is already at the 45-mg dose level and meets criteria for a further decrease of dose, the study drug will be discontinued permanently.

Recommendations for Non-infectious Pneurnonitis (NIP)

In the event of suspected NIP of any grade, copanlisib must be interrupted and diagnostic examination of the patient experiencing pulmonary symptoms conducted. If NIP is the final diagnosis, copanlisib must be permanently discontinued if CTC grade 3. For CTC grade 2, the patient should be treated until resolution or improvement to CTC grade 1; the next lower dose level of copanlisib should then be given. Pneumonitis is to be reported as such only in the event of NIP. If NIP related to copanlisib is confirmed, the treating investigator should administer systemic steroids.

The investigator is requested to differentiate between NIP and infectious pneumonitis (viral, bacterial, fungal), aspiration pneumonitis, or other pneumonitis clearly not due to a potential hypersensitivity reaction to the copanlisib infusion; the investigator must provide the basis for their assessment of infectious or other diagnosis, as appropriate. The investigator is requested to use the most-specific clinical terms to describe the condition in their report, not simply "pneumonitis."

Table 11-11: Dose adjustment in cases of NIP

Suspected or confirmed NIP per CTCAE	Action Taken	Retreatment dose after recovery
Grade 1	No change	NA
Grade 2	Dose interruption until recovery to grade :::;1	Decrease dose to the next lowest dose levela
Grade 2 second re-occurrence	Permanent discontinuation	NA
Grade 3	Permanent discontinuation	NA
Grade 4	Permanent discontinuation	NA

NA= Not applicable.

aNot applicable for45-mg dose level. No re-escalation is allowed after the dose reduction.

The lowest dose level is 45 mg; if the patient is already at the 45-mg dose level and cannottolerate treatment, the study treatmentwill be discontinued permanently.

Recommendations for arterial hypertension

Blood pressure will be measured every 5-10 min before each copanlisib dose (no more than 4 measurements) until 2 consecutive results <150/90 mmHg are recorded. If blood pressure is 150/90 mmHg, the investigator can consider a medical intervention or delay infusion of the study drug. The patient should rest for 5-10 min before blood pressure is recorded.

On infusion days, blood pressure will be measured at Oh (predose), 30 min (midinfusion), 60 min (end of infusion), and 1 h after the end of infusion

Note: A window of ±10 min is allowed for all blood pressure measurements, except for the 0-h (predose) measurement.

No dose should be given if blood pressure is 150/90 mmHg. Antihypertensive medication may be given to control increased blood pressure. Dosing can proceed on the scheduled day if at least 2 consecutive measurements <150/90 mmHg are recorded. Otherwise, dosing must be delayed.

If drug-related arterial hypertension (postdose blood pressure of CTCAE grade 3 or 160/100 mmHg) is not manageable with optimal antihypertensive treatment, the dose for the subsequent copanlisib administrations should be at the next lowest dose level. Patients with a postdose blood pressure that may have life-threatening consequences (e.g., malignant arterial hypertension, transient or permanent neurologic deficit, hypertensive crisis) must permanently discontinue the study drug.

It is important that patients with preexisting arterial hypertension adhere to their regular medication schedule and take their usual doses on the days of study drug infusion.

The management of acute blood pressure increases following copanlisib will be individualized for each patient, but the experience in phase I study has suggested a benefit of dihydropyridine calcium channel blockers (i.e., amlodipine, felodipine). Nitrates should also be considered. Verapamil and diltiazem (non-dihydropyridine calcium channel blockers and moderate inhibitors of CYP3M) should be used with caution, owing to a potential interaction with CYP3M. In general, it is advisable for sites to be prepared so that antihypertensive medication is readily available if needed.

In the event of arterial hypertension 150/90 mmHg during infusion of copanlisib during any cycle, antihypertensive treatment is suggested, as indicated in Table 8. In the event of CTCAE grade 3 arterial hypertension (160/100 mmHg) during infusion of copanlisib, the infusion should be interrupted and antihypertensive treatment administered, as suggested above. Infusion can be resumed when blood pressure has returned to <150/90 mmHg.

Table 11-12: Dose modification for copanlisib-related arterial hypertension

Toxicity (CTCAE)	Study drug action	Recommendation
Predose measurements **Blood pressure 150/90 mmHg**	No dose should be given until recovery to <150/90mmHg.	Blood pressure-lowering medication should be considered.Dosing can proceed on the scheduled day if 2 consecutive measurements <150/90 mmHg are recorded.If blood pressure doesn't return to <150/90 mmHg, delaydosing until the next visit.
During infusion: CTCAE hypertension of grade 3 or 160/100 mmHg	Infusion can be interrupted or slowed down, and administration of blood pressure--lowering therapy should be initiated.	Infusion maybe resumed when blood pressure has returned to <150/90 mmHg, at the investigator's discretion, or it can be skipped. Subsequentstudydrug administrations maybe reduced by 1 dose level, at the investigator's discretion.b
Postdose: **Drug-related CTCAE hypertension of grade 3 or 160/100 mmHg•**		Administration of blood pressure-lowering therapy should be initiated, in accordance with the local standard of care. Additional measurements to be performed as clinically indicated until recovery to <150/90mmHg. Subsequentstudydrug administrations maybe reduced by 1 dose level, at the investigator's discretion.b
CTCAE hypertension of grade 4	Permanently discontinue study drug.	

[3]Not manageable despite optimal antihypertensive treatment.
bThe lowest dose level is 30 mg.

Table 11-13 Management of copanlisib-related infusion-related hyperglycemia

Criteria	Recommendation	Suggested Treatment
A5ymptomaticglucose increase :5250 mg/dl (13.9 mmol/L)	Does notgenerallyrequire treatment with glucose-lowering medication	Oral hydration
A5ymptomaticglucose increase >250 mg/dl (13.9 mmol/L)	• Repeatglucose testing • If glucose value is decreasing, glucose levels may be followed withoutglucose-lowering medication treatment if hydration status is normal, as clinicallyassessed	Oral and/or IV hydration as appropriate

	• Consultation with endocrinologist can be considered	
Symptomatic or persisting glucose increase >250 mg/dl (13.9 mmol/L)	• Hydration status should be clinically assessed • If clinical assessment is consistent with dehydration,fluids should be given as clinicallyappropriate (orallyor IV) • Laboratorytestconfirming increase should be repeated.If the repeated glucose value is persistent and/or the patient is symptom atic and/or the hydration status indicates the need for hydration, glucose-lowering medication should be administered • Promptinputfrom an endocrinologist should be obtained	• Keep well-hydrated.Rapid/short-acting insulin maybe given if glucose persisting at>250 mg/dl (13.9 mmol/L) and the patient is symptomatic Rapid/short-acting insulin, according to the institution's sliding scale coverage of glucose persisting at >250 mg/dl (13.9 mmol/L},is recommended, with oral or IV hydration, as clinically appropriate
Asymptomatic glucose increase >500 mg/dl	• Will require dose reduction for subsequent treatment infusion • Repeat glucose testing • If glucose value is decreasing, glucose levels may be followed withoutglucose-lowering medication treatment, if hydration status is normal, as clinicallyassessed • Consultation with endocrinologist is recommended	• Keep well-hydrated.Rapid/short-acting insulin maybe given if glucose persisting at>250 mg/dl (13.9 mmol/L) and the patient is symptomatic • For insulin-naive patients, monitor for signs of hypoglycemia 3 h after insulin administration due to risk for hypoglycemic events
Persistent glucose >200 mg/dl(11.1 mmol/L} nonfasting or>160 mg/dl (8.9 mmol/L)fasting postinfusion	• Oral glucose-lowering medications and consultation with endocrinologist can be considered	• The use of sulphonylurea/metaglnides,insulin secretagogues medications to manage increased glucose levels following drug infusions is not recommended • Treatmentwith glucose-lowering medication is suggested,in accordance with the local standards of practice

Treatment of copanlisib-related vomiting and diarrhea

The hydration status of the patient should be clinically assessed and fluid replacement (oral or IV) given as appropriate. Adequate hydration through appropriate fluid maintenance is essential for the treatment of diarrhea or vomiting. Antidiarrhea medications may be introduced if symptoms occur.

The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 h until diarrhea-free for 12 h; a maximum daily dose of 16 mg is not to be exceeded. If clinically indicated, diphenoxylate hydrochloride with or without atropine sulfate can be used. The routine use of standard antiemetics, including 5-HT3 blockers, is allowed (see permitted concomitant therapy

section below). In the event of CTCAE grade 3 diarrhea with maximal pharmacological support, administration of the study drug should be delayed.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

For the purposes of this study, patients should be re-evaluated for response as per the study calendars in Section 10.0. Confirmatory scans for assessment of partial and complete responses should also be obtained no less than 4 weeks after initial documentation of objective response.

Response and progression will be evaluated using the new international criteria proposed by the revised RECIST guidelines (version 1.1)24, with some amendments, as indicated below for this protocol. Changes in the largest diameter (unidimensional measurement) of the tumor lesion and the shortest diameter, in the case of malignant lymph nodes, are included in RECIST 1.1.

Definitions

Evaluable for DLT: All patients will be evaluable for DLT from the time of their first treatment with vemurafenib and copanlisib.

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

Evaluable for objective response: Please see Section 14 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.

Disease Parameters

rvleasurable disease: rvleasurable 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 Vlthich 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 2::10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardia! 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.

rv1ethods for Evaluation of rv1easurable 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 study.

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, 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.

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.

FOG-PET: While FOG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FOG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FOG-PET imaging can be identified according to the following algorithm:

a. Negative FOG-PET at baseline, with a positive FOG-PET at follow-up is a sign of PD based on a new lesion.
b. No FOG-PET at baseline and a positive FOG-PET at follow-up: If the positive FOG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FOG-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 FOG-PET scan). If the positive FOG-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. FOG-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 FOG-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 FOG-PET and biopsy resolution/sensitivity.

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

Response Criteria

Evaluation of Target Lesions:

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

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

Progressive Disease (PD): At least a 20% increase in the sum of 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.

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).

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 atleast 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 manuscriptforfurther details on what is evidence of a new lesion.
inly for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-targetlesions maybe accepted as disease progression.

::>atients with a global deterioration of health status requiring discontinuation oftreatmentwithoutobjective evidence of disease progression atthat time should be reported as" *symptomatic deterioration."* Every effort should be made to documentthe 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 categorywhen no lesions can be measured is not advised

NOTE: Patients with clinical and/or radiographic evidence of disease progression (as described above) on assessments performed before the 6-month evaluation post-vemurafenib and copanlisib plus 1-131 evaluation (i.e. on scans and/or evaluations performed prior to the evaluation scheduled for 6 months after therapeutic 1-131is co-administered with vemurafenib/copanlisib) will be allowed to continue on study treatment and will be assessed as mandated by the protocol, if deemed clinically reasonable by the treating physician. For these patients, the final objective response assessment will be based on a comparison between the 6-month post-vemurafenib plus ^{131}I radiologic scan(s)/evaluations and the baseline, pretreatment radiologic scans.

PFS

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

13.0 CRITERIAFOR REMOVAL FROM STUDY

- Disease progression. *Hovi.ever,* patients with evidence of clinical disease progression or radiographic progression (such as on the 1-124 PET/CTs or other scans) before the 6-month evaluation following vemurafenib, copanlisib, and 1-131 may continue on the protocol to complete all mandated assessments if the treating physician deems it clinically reasonable. If there is evidence of disease progression before completing treatment with vemurafenib and copanlisib, study treatment with these drugs and 1-131 will be allowed to continue if the treating physician deems that such a decision is clinically justifiable.

- Initiation of new drug treatment for thyroid cancer.

- Death

- Decision of patient to withdraw from the study.

- Completion of all planned study therapies and assessments.

14.0 BIOSTATISTICS

The primary objective of this study is to determine the MTD of vemurafenib plus copanlisib in patients with advanced BRAF mutant RAIR thyroid cancer. The MTD is defined as the highest dose at which no more than 1 of 6 patients treated at that dose experience a DLT. The dose levels of vemurafenib plus copanlisib will be tested in a standard 3+3 dose-escalation design, as outlined in **Section 9.2**.

If a patient withdraws from the study prior to the completion of DLT assessment window (from the initiation of copanlisib study treatment to 7 days after completion of study drug administration) for reasons other than a DLT, the patient may be replaced and no DLTwill be considered to have occurred, unless the Principal Investigator judges that the case should be considered a DLT.

Patients who experience a DLT will be allowed to continue in the study at a lower dose, according to

the protocol-specified dose modification, following recovery of the toxicity to grade =:;;1 or the baseline level of severity. If a patient experiences intolerable or.:::, Grade 3 toxicities related to vemurafenib before the first dose of copanlisib is administered, this will NOT be considered a DLT and the patient will be replaced. The patient can be taken off study OR continue on protocol with vemurafenib alone with dose reduction per Section 11.0.

In addition to the formal DLT evaluation, longer term laboratory monitoring will be conducted up to 6 months following 1-131 to provide greater insight into the overall safety of the study regimen.

October 2021 amendment: In a prior version of the protocol, only patients who received 2 doses of copanlisib or experienced a DLT with just 1 dose of copanlisib would have been considered evaluable for DLT. After four patients completed Dose Level 1, we observed two patients receive $^{131}1$ with 2 doses of copanlisib and two receive only 1 dose of copanlisib without the $^{131}1$.No DLTs were observed and no clear differences in toxicity were noted between 1 vs. 2 doses of copanlisib in combination with vemurafenib. All Grade 3 and higher adverse events definitely, probably and possibly related to vemurafenib, copanlisib or both for each patient are noted below.

Patient #1 (2 doses of copanlisib)
Grade 3 maculopapular rash, possibly related to copanlisib and vemurafenib, not a DLT given improvement to grade 2 within 7 days.

Patient #2 (1 dose of copanlisib)
- Grade 3 hypertension, possibly related to copanlisib infusion, occurred same day as copanlisib infusion and improved to grade 2 the same day without intervention and did not recur.
- Grade 3 decreased lymphocyte count, possibly related to vemurafenib (not DLT).

Patient #3 (1 dose of copanlisib):
Grade 3 maculopapular rash, probably related to copanlisib and possibly related to vemurafenib, not a DLT given improvement to grade 2 within 7 days.

Patient #4 (2 doses of copanlisib):
No Grade 3 or higher adverse events were observed.

Given the safety observed thus far, the protocol will include all patients who have received at least 1 dose of copanlisib in the DLT evaluation, regardless of whether 1-131 is given. With this rule, the first four patients treated at Dose Level 1 will count towards DLT assessment. Since those 4 patients did not experience a DLT, the protocol will proceed to evaluating Dose Level 2 according to the rules outlined in **Section 9.2.** With historical redifferentiation rates, we would then anticipate that 6 of the 10 patients treated at the MTD with the planned expansion will have been treated with 2 doses of copanlisib and evaluated for safety.

Secondary objectives:

- To determine the proportion of patients with BRAFmutant RAIR thyroid cancer treated with vemurafenib and copanlisib at the MTD who meet the criteria for 1-131 treatment as determined by 1-124 PET/CT lesional dosimetry.

- To determine the proportion of patients with BRAFmutant RAIR thyroid cancer treated with vemurafenib and copanlisib (all dose levels) who meet the criteria for 1-131 treatment as determined by 1-124 PET/CT lesional dosimetry.

- To quantify the effect of vemurafenib and copanlisib on RAI uptake and retention using serial 1-124 PET/CT scans.

- To evaluate whether the combination of vemurafenib and copanlisib enhances 1-131 activity, by determining the ORR (per RECIST v1.1) at 6 months after treatment with vemurafenib plus copanlis ib and 1-131.

- To evaluate whether the combination of vemurafenib and copanlisib enhances 1-131 activity, by determining progression-free survival (PFS) at 6 months (per RECIST v1.1) after treatment with vemurafenib plus copanlisib and 1-131.

We will determine the proportion of patients with *BRAF* mutant RAIR thyroid cancer in which the combination of vemurafenib and copanlisib administered at the MTD increases iodine incorporation in thyroid cancer metastases such that a dose of 2000 cGy can be delivered to at least 1 tumor with :5300 mCi of 1-131. Once the MTD is identified, up to an additional 4 patients will be enrolled in the cohort, to bring the total number of patients treated at the MTD to 10. As an added precaution for safety, if 2 of the additional 4 patients experience a DLT, further accrual will be halted; the next dose 1 level below will be evaluated for DLTin a minimum of 6 patients, and expanded to include 10 total if 1 experience DLT. The proportion of patients treated at all vemurafenib and copanlisib dose levels who experienced increased iodine incorporation sufficient to warrant 1-131 treatment will also be calculated. The number of patients with sufficiently increased RAI uptake to warrant treatment with 1-131 will be analyzed using proportions and corresponding confidence intervals.

We will also determine the ORR (per RECIST v1.1) and the proportion of patients who are alive without disease progression (per RECIST v1.1) at the 6-month time point (this refers to the assessments designated to occur ~6 months after 1-131 therapy) for patients who receive 1-131 therapy. Patients who have completed the second 1-124 PET/CT and received 1-131 therapy, but did not complete the 6-month evaluation, will be considered to have had a progression/death event for the PFS analysis and will be categorized as nonresponders for the ORR analysis. The ORR will be analyzed using proportions and corresponding confidence intervals.

It is possible that patients will have clinical or RECIST v1.1 radiologic evidence of disease progression before the 6-month evaluation for several reasons: (1) vemurafenib and copanlisib, without the addition of 1-131, 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 1-131 can be delayed; and (4) evidence of progression may be present before administration of 1-131. Hence, patients with evidence of disease progress ion after 1-131, but prior to the 6-month evaluation, may remain on the study to complete the 6-month assessments if the treating physician deems that such a decision is clinically justifiable. If there is evidence of disease progression before completing treatment with vemurafenib and copanlisib, study treatment with these drugs and 1-131 will be allowed to continue if the treating physician deems that such a decision is clinically justifiable. The final objective response and disease progression assessments at 6 months for these patients will be based on a comparison between the 6-month radiologic scan(s) and the baseline, prestudy radiologic scans. However, if in the opinion of the treating physician, patients with evidence of progression before the 6-month assessment are unlikely to experience benefit by the 6-month time point, the patients will be considered to have had a

progression/death event for the PFS analysis, categorized as nonresponders for the ORR analysis, and removed from the study.

Patients who receive additional treatment for thyroid cancer outside of this protocol before the 6-month time point (except for TSH suppression, palliative radiation to a nontarget 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 for the PFS analysis and will be categorized as nonresponders for the ORR analysis.

To characterize how the combination of vemurafenib plus copanlisib affects RAI uptake and retention within select index lesions, we propose to analyze the 4 PET/CT scans obtained in each the pretreatment and on-treatment periods. This analysis will directly test our hypothesis that the combination of vemurafenib plus copanlisib affects not only RAI uptake but also retention within thyroid tumors. These data will be analyzed using descriptive statistics.

Exploratory Objectives:

We will perform correlative studies on serial research biopsy specimens and archival tumor tissue in order to evaluate the effect of vemurafenib on (1) expression and phosphorylation of 1\/IAPK signaling pathway proteins; (2) expression and phosphorylation of negative feedback loops connected to the 1\/IAPK pathway (such as HER3); (3) quantitative levels of mRNA transcripts for 1\/IAPK, PI3K, and SI\tIAD signaling pathways, as well as thyroid-specific gene products; and (4) the presence of other genetic alterations (through the use of MSK-IMPACT, supplemented, if needed, by the RNA Targeted Archer Solid Tumorfusion panel). These analyses will be descriptive and exploratory, given the limited number of samples examined. Changes in these molecular profiles will be correlated directly with the changes in RAI uptake and retention measured on the 1-124 PET/CT scans. These data will be analyzed using descriptive statistics.

Another exploratory objective will be to evaluate time to next thyroid cancer treatment, tumor size changes after study therapy, serum thyroglobulin changes and survival. This data will be important for gaining more insight into the degree of tumor control that may be achieved with vemurafenib plus copanlisib +/- 1-131. To collect this data beyond the protocol-mandated scans and tests, an observation period to collect data for up to 1 year after study drug discontinuation will be completed for all patients. Data that to be collected will include RECIST measurements of both protocol-mandated scans and scans conducted as part of standard of care. Thyroglobulin/TSH serum values draw on protocol and as part of standard of care will also be collected. Other data to be collected are survival status and initiation of new treatments (radiation, surgery and drug therapy). If RECST disease progression and initiation of drug therapy, or death, is observed, the observation phase may be discontinued. Data encompassing this observation phase may also be collected/analyzed retrospectively. This exploratory analysis will be conducted using descriptive statistics.

Sample size: 6-32 patients. We plan to accrue about 1-2 patient(s) per month for a total accrual time of 1-2 years.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. 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 whether or not 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).

15.2 Randomization

Not applicable.

16.0 DATA MANAGEMENT ISSUES

A Clinical Research Coordinator (CRC) will be assigned to the study. The responsibilities of the CRC include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinating the activities of the protocol study team.

The data collected for this study will be entered into a secure database, Medidata Rave. Source documentation will be available to support the computerized patient record.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. 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.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring Plan utilized for this study must align with the MSK DSM Plan, where applicable.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials."

There are several different mechanisms by which clinical studies are monitored for data, safety and quality. At a departmental/PI level there exists procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Deputy Physician-in-Chief, Clinical Research.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

- MSK Investigator Initiated Trials (IITs; MSK as sponsor)
- External studies where MSK is the data coordinating center
- Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participanUor by the end of the year one if no accruals and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.

17.0 PROTECTION OF HUMAN SUBJECTS

Inclusion of Children in Research

This protocol/project does not include children, because the number of children with this disease is limited and because the majority of affected children are already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

Risks, Benefits, Toxicities/Side Effects

Potential risks to human subjects include drug-related toxicities, placement of IV catheters, phlebotomy, and possible psychological discomfort from the stresses associated with obtaining imaging studies (e.g., CT scan, PET scan). All efforts will be made to avoid any complication by completely reviewing patients' symptoms, providing appropriate management, and monitoring blood tests.

If an adverse medical event occurs, the patient will first contact the primary oncologist or the Principal Investigator. At nights and on weekends, there is an oncology physician on call at all times. Patients may either call or come directly to the urgent care center at Memorial Hospital (or to their local emergency room) to be seen. Patients suffering serious adverse reactions must be carefully followed and all follow-up information also recorded.

Alternatives/0ptions

Participation in this trial is voluntary. Depending on the specific details of the situation, patient options without being in a study might include:

• Other palliative chemotherapy off-study.

• Participation in a different clinical trial.

• Best supportive care.

Financial Costs/Burdens

The patient will be responsible for all costs related to treatment and complications of treatment. Costs to the patient (third-party insurer) will include hospitalizations, routine blood tests and diagnostic studies, office visits, baseline EKG, and doctor fees. Patients will not be charged the cost of analysis for the research correlates. Bayer will financially support the study, and Copanlisib will be supplied by Bayer. The patient will not be charged for the subsequent research analysis of these specimens. Vemurafenib is an NCCN compendium-approved medication. Serial 1-124 lesion dosimetry scans will be supported through R01 CA201250-03.

17.1 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).

17.2 Serious Adverse Event (SAE) Reporting

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

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- 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

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- 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
- The grade of the 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
    - A 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
- If the SAE is an Unanticipated Problem

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

For IND/IDE protocols:
The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office

17.2.1 Other Adverse Events Reporting

Adverse events of special safety interest
On the basis of data from clinical studies of copanlisib in patients with lymphoma, as soon as there is reasonable suspicion of the following adverse event, the investigator should immediately notify Bayer (within 24 h), regardless of whether the event is assessed as causally related/not related to the study drug or as serious/nonserious. The adverse event of special interest should be entered on an SAE form; if the event is assessed as nonserious, the nonserious assessment should be noted in the form.

- Noninfectious pneumonitis (NIP)

Pregnancies

The investigator must report all pregnancies occurring in female study patients during their participation in this study. The outcome of the pregnancy should be followed up carefully, and any outcome of the mother and the child at delivery should be reported.

For a pregnancy in the partner of a male study patient, all efforts will be made to obtain similar information on course and outcome if the partner or the male participant chooses to disclose that information.

The investigator should submit such events within the same timelines as for an SAE.

SAE Reporting Requirements:

The SPONSOR is responsible for all of the pharmacovigilance obligations and safety reporting pursuant to the applicable laws and regulations in the country/countries where the STUDY is performed.

Additionally, the SPONSOR shall immediately, within 24 hours at the latest, report to BAYER by fax and/or e-mail: (973) 709-2185 DrugSafety.GPV.US@bayer.com

- All Serious Adverse Events occurring after start of administration of BAYER product, independent of their causal relationship to the STUDY DRUG
- Any other relevant safety information including but not limited to:
    - Reports of drug exposure via mother/ father with and without adverse events (exposure during conception, pregnancy, childbirth and breastfeeding) including their outcome;
    - If linked to a serious adverse event, reports of misuse, abuse, overdose, medication error and other uses outside what is foreseen in the protocol, drug dependency, occupational exposure suspected transmission of an infectious agent, withdrawal syndrome, drug interactions with respect to the STUDY DRUG;

  and
- Any communication concerning safety related information to regulatory authorities or ethics committees including but not limited to:
- Development Safety Update Reports / relevant parts of IND reports for the STUDY;
- Any other safety related reports, issues and queries that are either raised by or communicated to regulatory authorities or ethics committees (e.g., reportable non-serious cases).

18.0 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 IRS/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.

19.0 REFERENCES

1. Durante C, Haddy N, Baudin E, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: Benefits and limits of radioiodine therapy. *J Clin Endocrinol Metab.* 2006;91(8):2892-2899. doi:10.1210/jc.2005-2838

2. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus Placebo in Radioiodine-Refractory Thyroid Cancer. *N Engl J Med.* 2015;372(7):621-630. doi:10.1056/NEJMoa1406470

3. Brose MS, Nutting CM, Jarzab B, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet (London, England).* 2014;384(9940):319-328. doi:10.1016/S0140-6736(14)60421-9

4. Kimura ET, Nikiforova MN, Zhu Z, Knauf JA, Nikiforov YE, Fagin JA. Advances in Brief High Prevalence of BRAF Mutations in Thyroid Cancer: Genetic Evidence for Constitutive Activation of the RET / PTC-RAS-BRAF Signaling Pathway in Papillary Thyroid Carcinoma 1. *CANCER Res.* 2003;63(7):1454-1457.

5. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. *Cell.* 2014;159(3):676-690. doi:10.1016/j.cell.2014.09.050

6. Chakravarty D, Santos E, Ryder M, et al. Small-molecule rv1APK inhibitors restore radioiodine incorporation in mouse thyroid cancers with conditional BRAF activation. *J Clin Invest.* 2011;121(12):4700-4711. doi:10.1172/JCI46382

7. Nagarajah J, Le M, Knauf JA, et al. Sustained ERK inhibition maximizes responses of BraN600E thyroid cancers to radioiodine. *J Clin Invest.* 2016;126(11):4119-4124. doi:10.1172/JCI89067

8. Ho AL, Grewal RK, Leboeuf R, et al. Selumetinib-Enhanced Radioiodine Uptake in Advanced Thyroid Cancer. *N Engl J Med.* 2013;368(7):623-632. doi:10.1056/NEJMoa1209288

9. Dunn L, Sherman EJ, Baxi SS, et al. Enhancing radioiodine (RAI) incorporation into BRAFV600E-mutant, RAI-refractory thyroid cancers with the BRAF inhibitor vemurafenib: A pilot study. *J Clin Oneal.* 2016;34(15_suppl):6099. doi:10.1200/JCO.2016.34.15_suppl.6099

10. Dunn LA, Sherman, E.J., Baxi, S.S., Tchekmedyian, V., Grewal, R., Larson, S.M., Pentlow,

K.S., Haque, S., Tuttle, R.M., Sabra, M.M., Fish, F., Boucai, L., Walters, J., Ghossein, R.A., Seshan, V.E., Ni, A., Knauf, J.A., Pfister, D.G., Fagin, J.A., Ho AL. Vemurafenib Redifferentiation of BRAF-mutant, RAI-Refractory Thyroid Cancers. *J Clin Endocrinol Metab.* 2018;In press.

11. Xing M, Alzahrani AS, Carson KA, et al. Association Between BRAF V600E Mutation and Mortality in Patients With Papillary Thyroid Cancer. *JAMA.* 2013. doi:10.1001/jama.2013.3190

12. Xing M, Westra WH, Tufano RP, et al. BRAF mutation predicts a poorer clinical prognosis for papillary thyroid cancer. *J Clin Endocrinol Metab.* 2005. doi:10.1210/jc.2005-0987

13. Brose MS, Cabanillas ME, Cohen EEW, et al. Vemurafenib in patients with BRAFV600E-positive metastatic or unresectable papillary thyroid cancer refractory to radioactive iodine: a non-randomised, multicentre, open-label, phase 2 trial. *Lancet Oneal.* 2016. doi:10.1016/S1470-2045(16)30166-8

14. Robert C, Karaszewska B, Schachter J, et al. Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib. *N Engl J Med.* 2015. doi:10.1056/NEJMoa1412690

15. Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med.* 2014. doi:10.1056/NEJMoa1408868

16. Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAFV600-Mutant Anaplastic Thyroid Cancer. *J Clin Oneal.* 2017. doi:10.1200/JCO.2017.73.6785

17. Shah MH, Wei L, Wirth LJ, et al. Results of randomized phase II trial of dabrafenib versus dabrafenib plus trametinib in BRAF-mutated papillary thyroid carcinoma.JC/in *Oneal.* 2017. doi:10.1200/JCO.2017.35.15_suppl.6022

18. Chapman PB, Hauschild A, Robert C, et al. Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation. *N Engl J Med.* 2011;364(26):2507-2516. doi:10.1056/NEJMoa1103782

19. Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-Mutant Advanced Melanoma Treated with Vemurafenib. *N Engl J Med.* 2012. doi:10.1056/NEJMoa1112302

20. Dreyling M, Santoro A, Mollica L, et al. Phosphatidylinositol 3-kinase inhibition by Copanlisib in relapsed or refractory indolent lymphoma. *J Clin Oneal.* 2017. doi:10.1200/JCO.2017.75.4648

21. Fruman DA, Rommel C. PI3K and cancer: Lessons, challenges and opportunities. *Nat Rev Drug Discov.* 2014. doi:10.1038/nrd4204

22. Pratilas CA, Taylor BS, Ye Q, et al. V600EBRAF is associated with disabled feedback inhibition of RAF-MEK signaling and elevated transcriptional output of the pathway. *Proc Natl Acad Sci.* 2009;106(11):4519-4524. doi:10.1073/pnas.0900780106

23. Cheng OT, Mitchell TN, Zehir A, et al. Memorial sloan kettering-integrated mutation profiling of actionable cancer targets (MSK-IMPACT): A hybridization capture-based next-generation sequencing clinical assay for solid tumor molecular oncology. *J Mo/ Diagnostics.* 2015;17(3):251-264. doi:10.1016/j.jmoldx.2014.12.006

24. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247. doi:10.1016/j.ejca.2008.10.026

20.0 APPENDICES

Appendix *A:*. 1-124 Normal Organ Radiation Dosimetry

Appendix B: 1-124 PET/CT-based Lesional Dosimetry Image Acquisition, Analysis, and Interpretation

Appendix C: The Low-Iodine Diet

Appendix D: Glycemic Index Foods

Appendix E: Permeability Glycoprotein (Pg-p) Substrates, Breast Cancer Resistance Protein (BCRP) Substrates, and Multidrug and Toxin Extrusion Protein 2 (MATE2K) Substrates

Appendix A: 1-124 Normal Organ Radiation Dosimetry

124Uodide Normal Organ Radiation Dosimetry

	Absorbed Doses			
			1 'r:'J:Jogide PEJ-CT 1c10	2 ?1:fodidePET.CT scans
			0,9 rad1.	2 0,9 rad 1.
	1t&t,.fOC1ide 1		6 mCi 1tAt.IO<lide	6 mCi 1tAt.IO<lide
Target Organ	rad/mCi	raiWmCl	rad	rad
Adrenals	0.21	1.3	2.2	4 . 3
Brain	0.57	3.4	4.3	8..6
Bone Surfaces	0 .42	25	3.4	6.8
Breasts-	0 .23	u	2.3	4 ; 6
Gal Bladder Wal	0.26	116	2.5	4 . 9
HeaJtWa l	0 .37	2.2	3.1	6.2
Kidn	0.20	1.2	2.1	4.2
Large Intestme - lower Wal	O .:J.7	2.2	3.1	6.2
Large Intes&le - Upper Wal	0.29	1.7	2,6	5.3
Lens oif Eye,	0 .41	2.5	3.4	8.7
Uver	0 .36	2'.2	3;1	6.1
Lungs	0 .38	2.2	3.1	6.1
uselei	0All	2'.5	3.4	8.7
Panc,e,n	0 .32	1.9	2.8	5,6
Red Jarrow	0 .42	2;5	3.4	6.8
Smatlestine	1.0	1.0	1.9	I. 8
Sl:oma Wal	1.7	1.7	2,6	5.2
Testes,	0.24	1.4	2.3	.7
Thyroid &	MIA	H/A	H/A	NIA
Total Body 1,	0.41	2.5	3.4	8.7
Umary Bladder Wal				
2-ttr VOiOigg Mlet"lal	0 .37	2.2	3.1	6.2

1 Hays r 1etal. tJIRD Dose est.mate:Report No 5. J NuClea16 857-660, 1975. As.91.unes 25% 2'4..n Illyrod uplake.

2 Wu et al Eur.JNua ed t ol maging 31:38-43, 2004.

3 Lens.cf-Eye allSo dose equaled wll'l lhe lll!Sde absorbed dpse

4 Ill post-Hlyroidectcmyand post-all&atieln thyroid cancer p atients lhere is. NO functional lhyol'd lo **n-adiate.** For Ule --0% 'thyroid uplake tor sudl palienls, lhe normal-organ doses. are 11.ety LOMR man mose presented.

6 Total-Bady *allSo* dose equaled wll'l lhe ' uscie absorbed dose

Appendix B: 1-124 PET/CT-based Lesional Dosimetry Image Acquisition, Analysis, and Interpretation

The 1-124 PET/CT scan will be performed on a PET/CT scanner 2 days after administration of 5-7 mCi of 1-124, 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 coinvestigators. The index lesion volume (in milliliters), V1esion, will be estimated by the CT study performed for attenuation correction and anatomic registration as part of the 1-124 PET/CT scan on the PET/CT scanner. This "low-dose" attenuation-correction CT scan will be performed without contrast or (respiratory) gating and with acquisition and processing parameters routinely used for such scans at the participating sites. 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 V1esion. **Only lesions on the first 1-124 PET/CT scan that are ::_5 mm in length in the maximal diameter will be used as an index lesion for this analysis.**

Using the PET acquisition and processing parameters routinely used for PET/CT scans, 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, SUV lesion; alternatively, the lesion ROIs drawn on the CT scan (see above) may be superimposed on the registered PET images to yield SUV1esion. From the definition of the SUV (above), the mean PET-derived 1-124 concentration (in µCi/ml) in the index lesion not corrected for partial-volume-averaging, $(\overline{[^{124}1A]}\ \text{lesion})\text{RC-uncorrected}$, will be calculated from SUV lesion:

$$(\overline{[^{124}1A]}\ \text{lesion})\text{RC-uncorrected} = \text{SUV1esion}\ \frac{AA}{Mm} \quad (1)$$

where AA is the 1-124 administered activity (in µCi) and Mrs 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, V1esion, and the volume (V)--dependent recovery coefficient (i.e., 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 1-124 concentration (in µCi/ml) in the index lesion *not* corrected for partial-volume averaging, ($[^{124}1A]$ 1esion)Rc-uncorrected, will be corrected to yield the actual mean 1-124 concentration in the index lesion,

$(\overline{[^{124}1A]}\text{lesion})\text{RC-corrected}$:

$$([\overline{^{124}1\ A]}\text{lesion})\text{RC-corrected} = \frac{([\overline{^{124}1\ A]}\text{lesion})\text{RC-uncorrected}}{\text{RC(V1esion)}} \quad (2)$$

The mean 1-124 activity concentration in the index lesion per 1-124 administered activity (in µCi/ml/mCi), ($[\overline{^{124}1\ A\_ier\ mci]}$ lesion)Rc-corrected, will then be calculated:

$$(\overline{[^{124}I\ A\_ier\ mCi]}\ \text{lesion})\text{RC-corrected} = \frac{([\overline{^{124}1\ A]}\text{lesion})\text{RC-corrected}}{AA/1000} \quad (3)$$

($\overline{[^{124}1\ A\_ier\ mCi]}$ lesion)RC-corrected can be converted to the mean 1-131 activity concentration in the index lesion per 1-131 administered activity (in µCi/mUmCi), ($[^{131}I\ \overline{A\_iermCi]}$ lesion)RC-corrected, 1-131 (and not **1-**124) being used for therapy:

$$(\overline{[^{131}I\ A\_ier\ mCi]}\ \text{lesion})\text{RC-corrected} = (\overline{[^{124}I\ A\_ier\ mCi]}\ \text{lesion})\text{RC-corrected}\ \mathbf{eP.}^{-J124\cdot} \text{"-}^{131})\text{timaging} \quad \mathbf{(4)}$$

where 11,1124 and 11,1131 are the physical decay constants of 1-124 (0.00693/h) and 1-131 (0.00359/h), respectively, and !imaging is the time after administration of PET/CT imaging (in hours).

On the basis of prior clinical experience, the biological half-life, Tb, of iodine in metastatic thyroid cancer lesions is typically 2 d (48 h) to 4 d (96 h), which will be the assumed range of biologic half-life used in these calculations. For 1-131, with a physical half-life TP of 8.04 d = 193 h, the effective half-life, Te, of 1-131 in the index lesion is therefore (if assuming 48 h biologic half-life):

$$Te = \frac{Tb\ Tp}{Tb + Tp} \quad (5a)$$

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

$$= 38.4\ h \quad (5c)$$

Assuming, as usual, that the uptake of radioiodine in the index lesion (i.e., the 24- to 48-h uptake value) will be instantaneous and that 1-131 lesion irradiation will be due exclusively to complete local absorption of 1-131 beta rays, the mean lesion absorbed dose (in rad/mCi 1-131), $[\overline{^{131}1\text{Opermci}]}$ lesion, will be:

$$\overline{[^{131}I\ \text{Oper mCi}]}\ \text{lesion} = 1.44\ Te\ (\overline{[^{131}I\ A\_ier\ mCi]}\ \text{lesion})\text{RC-corrected}\ np \quad (6a)$$

$$= 1.44 \cdot \mathbf{38.4\ h}\ (\overline{[^{131}\mathbf{1}A\_ier\ mCi]}\ \text{lesion}\}\text{RC-corrected}$$

$$0.405\ \text{g-rad/µCi-h} \quad (6b)$$

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

where L'.1np = 0.405 g-rad/μCi-h is the equilibrium dose constant for nonpenetrating radiations (i.e., beta rays) for 1-131.

Finally, the 1-131 administered activity (in mCi) required to deliver the stipulated mean absorbed dose of 2,000 rad to the index lesion, ^{131}1Mooo rad lesion, will be:

$$^{131}\text{I}_{\text{AA2000}}\ \text{rad lesion} = \textbf{2,000 rad/[}^{131}\text{I Oper mci]lesion} \quad (7)$$

If the projected ^{131}1Mooo rad lesion is reasonable (300 mCi) (assuming a 48h to 96 h iodine biologic half-life), the Principal Investigator and the Co-Investigator(s) will decide whether 1-131 therapy should proceed.

While the foregoing analysis will be performed on data from the second 1-124 PET/CT scan performed at ~48 hours after 1-124 with the noted assumptions about the biologic half-life of iodine, per the Principal Investigator's discretion, the decision to proceed with therapeutic 1-131 could also be determined after the biologic half-life has been calculated from the full complement of 1-124 PET/CT images collected (completed by **D_{1x}15** according to Table 10.2).

Appendix C: The Low-Iodine Diet

What is iodine?
Iodine is a mineral. It plays an important role in several processes thattake 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 1 or 2 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, and soy burgers (e.g., Boca)
- All canned foods, because the lining of the can contains iodine

Do not stop taking any of your medicines unless your doctor tells you to. 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: 2-3
(1 serving equals 3 ounces of meat, fish, poultry, or 2 tablespoons of unsalted peanut or almond butter)

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

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: 0

Include
None allowed.

Exception: Only 1 ounce of milk a day in your coffee or tea.

Avoid

All milk (except for 1 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, and macaroni and cheese.

Fruits

Total number of servings per day: 5
(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: 4
(1 serving equals 1/2 cup of cooked or 1 cup of raw vegetables)

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: 4-6
(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
(1 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: 2
(See below for serving equivalents)

Include
Each of the following equals 1 serving:
- 1 cup Knox clear gelatin
- 2 tablespoons sugar
- 2 tablespoons honey
- 2 tablespoons 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-0, 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 noniodized 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 112 cup orange juice
3 breads 112 cup oatmeal (no milk)
1 plain unsalted matzah
1 meat 1 egg white omelet
Misc. 2 teaspoons sugar
1 beverage 1 cup brewed coffee

MIDMORNING SNACK
1 fruit 2 rice cakes
1 teaspoon unsalted butter
1 cup water

LUNCH
1 meat 3-oz fresh turkey breast
2 fats 2 teaspoons oil

2 breads 2 slices homemade white bread
1 vegetable 1 cup romaine lettuce
1 beverage 1 cup fresh lemonade

MIDAFTERNOON 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 teaspoons 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 D: Glycemic Index Foods

Foods are categorized as having a low glycemic index if the glucose reference index is 55. High-glycemic-index foods have a glucose reference index >55. The summary table below contains glucose references for common foods.

High-carbohydrate foods		Breakfast cereals		Fruit and fruit products		Vegetables	
White wheat bread*	75 ± 2	Cornflakes	81 ± 6	Apple, raw†	36 ± 2	Potato, boiled	78 ± 4
Whole wheat/whole meal bread	74 ± 2	Wheat flake biscuits	69 ± 2	Orange, raw†	43 ± 3	Potato, instant mash	87 ± 3
Specialty grain bread	53 ± 2	Porridge, rolled oats	55 ± 2	Banana, raw†	51 ± 3	Potato, french fries	63 ± 5
Unleavened wheat bread	70 ± 5	Instant oat porridge	79 ± 3	Pineapple, raw	59 ± 8	Carrots, boiled	39 ± 4
Wheat roti	62 ± 3	Rice porridge/congee	78 ± 9	Mango, raw†	51 ± 5	Sweet potato, boiled	63 ± 6
Chapatti	52 ± 4	Millet porridge	67 ± 5	Watermelon, raw	76 ± 4	Pumpkin, boiled	64 ± 7
Corn tortilla	46 ± 4	Muesli	57 ± 2	Dates, raw	42 ± 4	Plantain/green banana	55 ± 6
White rice, boiled*	73 ± 4			Peaches, canned†	43 ± 5	Taro, boiled	53 ± 2
Brown rice, boiled	68 ± 4			Strawberry jam/jelly	49 ± 3	Vegetable soup	48 ± 5
Barley	28 ± 2			Apple juice	41 ± 2		
Sweet corn	52 ± 5			Orange juice	50 ± 2		
Spaghetti, white	49 ± 2						
Spaghetti, whole meal	48 ± 5						
Rice noodles†	53 ± 7						
Udon noodles	55 ± 7						
Couscous†	65 ± 4						

Dairy products and alternatives		Legumes		Snack products		Sugars	
Milk, full fat	39 ± 3	Chickpeas	28 ± 9	Chocolate	40 ± 3	Fructose	15 ± 4
Milk, skim	37 ± 4	Kidney beans	24 ± 4	Popcorn	65 ± 5	Sucrose	65 ± 4
Ice cream	51 ± 3	Lentils	32 ± 5	Potato crisps	56 ± 3	Glucose	103 ± 3
Yogurt, fruit	41 ± 2	Soya beans	16 ± 1	Soft drink/soda	59 ± 3	Honey	61 ± 3
Soy milk	34 ± 4			Rice crackers/crisps	87 ± 2		
Rice milk	86 ± 7						

Data are means ± SEM. *Low-GI varieties were also identified. †Average of all available data.

GI = glycemic index.

Appendix E: Permeability Glycoprotein (Pg-p) Substrates, Breast Cancer Resistance Protein (BCRP) Substrates, and Multidrug and Toxin Extrusion Protein 2 (MATE2K) Substrates

A list of drugs to be used with caution.

Copanlisib is an inhibitor of BCRP, P-gp and MATE2K *in vitro*. Therefore substrates, especially those with a narrow therapeutic range, should be used with **caution.Pgp-Substrates**	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxina", everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan
BCRP substrates	Zidovudine, pantoprazole, cirnetidine, sulfasalazine, nitrofurantoin, ands everal s tatins (lovas tatin, s irnvas tatin, cerivastatin, pitavastatin), mitoxantrone, methotrexate, topotecan, irnatinib, and irinotecan
MATE2K substrates	Metforrnin, cimetidine, procainamide and N methylnicotinamide

BCRP = Breast cancer resistance protein; MATE2K = Multidrug and toxin extrusion protein 2, P-gp = Perrneability glycoprotein
a:Narrow therapeutic window