Participant Informed Consent for Clinical Research

Study title for participants: Vemurafenib plus Copanlisib in Radioiodine-Refractory (RAIR) Thyroid Cancers

Official study title for internet search on http://www.ClinicalTrials.gov: A Phase Ib Trial of Vemurafenib Plus Copanlisib to Enhance Radioiodine Avidity in Radioiodine-Refractory Thyroid Cancers

Lead Researcher: Alan Ho, MD, PhD (646-608-3774)

If you are the parent or legal guardian of the person who is being asked to participate in this research study, you may give consent on his or her behalf. The word "you" in this document refers to your child, if the participant is a minor, or to a person with a cognitive impairment for whom you are the Legally Authorized Representative (LAR).

Overview and Key Information

Why is this study being done?

We are asking you to take part in a clinical research study. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer.

You are being asked to take part in this study because you have thyroid cancer with a BRAF mutation, which makes your cancer unlikely to respond to radioiodine therapy (the cancer is considered radioiodine-refractory; RAIR). However, we have previously shown that in some patients inhibiting the BRAF mutation with a drug can reverse tumor resistance to radioiodine, making it an effective treatment for those patients. The purpose of this study is to develop a new drug treatment to reverse this resistance in BRAF mutant tumors so that radioiodine can be given to shrink tumors.

We are doing this study to find out (1) the highest doses of copanlisib and vemurafenib that, when given in combination, do not cause serious side effects, and (2) whether the study treatment will make radioiodine therapy work better in patients with BRAF-mutant thyroid cancers.

This use of copanlisib is considered investigational; it has not been approved by the US Food and Drug Administration (FDA) as a treatment for thyroid cancers, but researchers are allowed to test the drug in studies like this one. This study is the first time that copanlisib and vemurafenib will be given in combination with radioiodine therapy.

Taking part in this study is your choice.

You can choose to take part or not to take part in this study, and you can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document presents important information to help you make your choice. Please take time to read it carefully. Talk with your doctor, family, or friends about the risks and benefits of taking part in this study. It's important that you have as much information as you need, and that all your questions are answered.

What is the usual approach to radioiodine-refractory thyroid cancers?

People with radioiodine-refractory thyroid cancers who are not in a research study are usually treated with lenvatinib or sorafenib. The study doctor will discuss all the available treatment options with you.

What are my other choices if I decide not to take part in this study?

- You may choose to have the usual approach described above
- You may choose to take part in a different research study, if one is available
- You may choose not to be treated for cancer
- You may choose not to be treated for cancer, but to receive comfort care to help relieve your symptoms

What will happen if I decide to take part in this study?

If you decide to take part in this study, you will have a research biopsy procedure before you begin the study treatment. We will test your tumor biopsy samples during the study to find out whether your tumor is changing in response to the study treatment. We will also do a series of tumor imaging studies over the course of 5 days to see whether your cancer is likely to respond to radioiodine therapy.

After the imaging studies have been completed, you will receive treatment with a combination of vemurafenib and copanlisib for about 20 days. After you've received about 14 days of drug treatment, we will perform another research biopsy procedure. After you've received about 7 days of treatment, we will do a second series of tumor imaging studies to see whether the study treatment has increased the likelihood that radioiodine therapy could help shrink your thyroid tumor.

The results of the tumor imaging studies will determine whether you will continue the study treatment and receive radioiodine therapy. If your imaging studies show that you are unlikely to benefit from continuing the study treatment, you will stop receiving vemurafenib and copanlisib, and your study doctor will discuss your treatment options with you. If you continue to receive the study treatment, you will receive radioiodine (I-131) therapy on about Day 18 and continue vemurafenib until Day 20.

You will return to the clinic for follow-up visits 2 weeks, 1 month, 3-4 months, and 6 months after stopping the study treatment.

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important to think carefully about these as you make your decision.

Risks

We want to make sure that you know about a few key risks right now. We will also give you more information in the *What risks can I expect from taking part in this study?* section of this consent form.

If you choose to take part in this study, there is a risk that the study treatment may not be as good as the usual approach at shrinking or stabilizing your cancer.

There is also a risk that you could have side effects from the study treatment. These side effects may be worse, and they may be different than you would have with the usual approach for your cancer.

Some of the most common side effects that the study doctors know about are:

- Fatigue
- Skin rash
- High blood pressure
- Diarrhea
- Skin cancer

There may be some risks that the study doctors do not yet know about.

Benefits

Studies in animals and in living human cells have shown that the study treatment may increase the amount of radioiodine taken up (absorbed) by thyroid tumors with BRAF mutations, which helps the radioiodine treatment work better against the cancer. We do not know whether this will happen in everyone who has RAIR, BRAF-mutant thyroid cancers. What we learn from this study may help other people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop participating in the study at any time.

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

If you decide to stop, let the study doctor know as soon as possible. It's important that you stop safely. This may mean slowly stopping the study treatment to avoid a sudden unsafe change or risk to your health.

If you stop, you can decide whether to let the study doctor or a member of the study team continue to contact you to ask questions about your health. We will not be able to withdraw information about you that has been used or shared with others before you informed us of your decision to stop.

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

- Your health changes, and the study is no longer in your best interest
- New information becomes available, and the study is no longer in your best interest
- You do not follow the study rules
- For women who are able to have children: You become pregnant while you are in the study

- The study is stopped by the National Cancer Institute (NCI), Institutional Review Board (IRB), Food and Drug Administration (FDA), or the study sponsor, Memorial Sloan Kettering Cancer Center (MSK). The study sponsor is the organization that oversees the study.

It is important that you understand the information in this informed consent document before you make a decision about participating in this clinical trial. Please read, or have someone read to you, the rest of this document. If there is anything that you don't understand, ask the study doctor or nurse for more information.

What is the purpose of this study?

We are doing this study to find out (1) the highest doses of copanlisib and vemurafenib that, when given together, do not cause severe side effects, and (2) whether the study treatment will make radioiodine therapy work better in patients with BRAF-mutant thyroid cancers.

Many thyroid cancers absorb iodine so, as part of standard practice, we often use a form of iodine that emits a small amount of radiation – radioiodine – to both detect and treat thyroid cancers. In this study, we will use two different types of radioiodine:

- Iodine-124 (I-124), which is used only to detect thyroid cancers on imaging studies called PET/CT (positron emission tomography) scans. This use of iodine-124 is considered investigational; it has not been approved by the FDA.
- Iodine-131 (I-131), which is used to detect thyroid cancers on scans and to shrink thyroid tumors. Both these uses of I-131 have been approved by the FDA and are considered part of the standard practice for evaluating and treating thyroid cancers.

In this study, we will use I-124 with PET/CT scans to figure out how much radioiodine your tumors will absorb. Scanning with I-124 is called lesional dosimetry, and information from the scans that are done before and after you receive the study treatment will be used to figure out whether you should also receive therapy with I-131.

Treatment with I-131 can destroy thyroid tumors. But some tumors do not absorb enough I-131 to cause them to shrink. In some tumors, mutation of the BRAF gene is the primary reason I-131 cannot be absorbed and why it does not shrink those tumors. The drug vemurafenib inhibits BRAF, and in some patients this drug can increase the amount of radioiodine taken up by tumors with BRAF mutations. New research suggests that in addition to BRAF mutations, the PI3K protein also causes radioiodine resistance by forcing thyroid cancer cells to eliminate radioiodine before it can deliver radiation to kill the tumor. The idea behind this trial is that combining the BRAF inhibitor with a drug that blocks PI3K will help to make radioiodine therapy (I-131) more effective for more thyroid cancer patients whose tumors have the BRAF mutation.

Copanlisib blocks PI3K. Treating patients with BRAF mutant tumors with both vemurafenib and copanlisib could cause radioiodine to be better absorbed and held longer in thyroid cancer cells, making radioiodine treatment more effective. The purpose of this trial is to investigate how to safely combine these two drugs together and if this combination can enhance radioiodine absorption, retention, and effectiveness in patients.

Vemurafenib has been approved by the FDA to treat melanoma. The FDA has approved copanlisib as a treatment for follicular lymphoma, but not for use in any other cancers. The copanlisib used in this study will be provided by the Bayer Corporation. Vemurafenib and copanlisib has not previously been combined before.

About 32 people will take part in this study at Memorial Sloan Kettering Cancer Center (MSK).

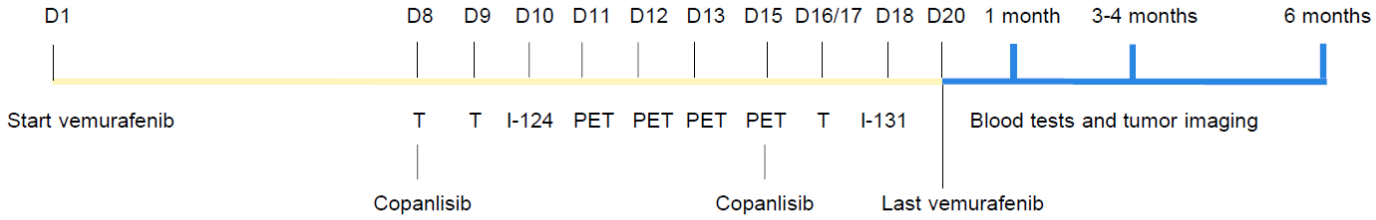
What are the study groups?

All study participants will get the same study intervention: first, vemurafenib taken by mouth, twice a day, every day throughout the study (Days 1-20) and the addition of an intravenous (IV) infusion of copanlisib into a vein in the arm, once a week (Days 8 and 15) for a maximum of 2 treatments. Study participants will also take an oral dose of I-124 before they start the study treatment and on treatment Day 10. If your doctor thinks that you are benefitting from the study treatment, you will also take an oral dose of I-131 on Day 18.

The first few study participants will take the standard dose of vemurafenib. Those participants will also receive the lowest dose of copanlisib. If the copanlisib infusion does not cause severe side effects, the next group of study participants will receive a higher dose of copanlisib with the same dose of vemurafenib. If any participants have significant side effects from the lowest dose of copanlisib, the dose of vemurafenib given with this dose of copanlisib will be lowered for the next groups of study participants.

The study will be stopped when the highest, safest doses of vemurafenib and copanlisib, given together, are identified.

The diagram below shows a simplified timeline of study treatments and assessments (not depicted is the schedule for the first I-124 PET/CT scan that occurs prior to starting the study drugs). Please note that only those participants who are benefitting from the study treatment after the Day 10 PET scan will continue to receive this treatment.



T = Thyrogen injection; PET= I-124 PET/CT scans; I-131 = radioiodine (RAI)

What extra tests and procedures will I have if I take part in this study?

Before you begin the main part of the study:

The study doctor will review your medical records and the results of your exams, tests, and procedures to see if it is safe for you to take part in the study. This first part of the study is called screening. Most of the screening exams, tests, and procedures are part of the usual care that you would have if you were not in a study.

Before you start the study treatment, we will do four I-124 PET/CT scans over the course of 5 days to find out how much iodine your tumors absorb and hold onto (retain).

Pre-treatment preparation and scheduling for I-124 PET/CT scans:

- We will ask you to follow a diet that is low in iodine, starting 5-7 days before the pre-treatment scans begin and continuing until you have had the last on-treatment scan. A low-iodine diet can help the I-124 PET/CT scans work as well as possible. Your study doctor will talk with you about foods that are low in iodine.
- You will receive injections of the drug Thyrogen into a large muscle, 2 days in a row before your imaging scans. Thyrogen is the drug form of a human hormone that increases the amount of iodine absorbed by thyroid cells.
- The day after your second Thyrogen injection, you will receive an oral dose of I-124.
- We will do PET/CT scans 1, 2, 3, and 5 days after you receive the oral dose of I-124 to find out how well your tumors take up, hold, and eliminate iodine.
- After the fourth PET/CT scan is done, you will not receive any study treatment or have any imaging scans done for about 3 weeks to make sure that all the I-124 is out of your body before you begin treatment with the study drugs. If your tumors do not show significant I-124 uptake on that initial PET/CT scan, it is possible that treatment may start sooner.

The tests and procedures that will be done only for research purposes, or that may be done more often because you are participating in this study, are listed below.

- We will collect a blood sample (about 2 teaspoons) for a genetic test called genomic sequencing; this test looks at the order (sequence) of your genes and proteins to find out whether you have any genetic mutations (changes) that could increase your risk of disease, or show whether you might respond to a particular type of treatment
- If you have stored (archival) tumor tissue available from a previous biopsy or surgical procedure, we will obtain a portion of that sample for research testing to track any changes that may happen in your tumor while you are receiving the study treatment
- If no archival tissue is available, you will have a tumor biopsy procedure so that we can track the tumor's response to treatment. Your study doctor will tell you if you will need to have this procedure.

During the study:

Initial study treatment:
Approximately 3 weeks after the I-124 PET/CT scans are completed (or sooner if the first I-124 PET/CT scan did not show much iodine uptake), you will begin the study treatment with vemurafenib alone for about 1 week, followed by the addition of copanlisib to vemurafenib.

You will receive IV infusions of copanlisib once a week, and take vemurafenib by mouth, twice a day.

Since copanlisib can affect blood sugar levels, you will not be able to eat or drink anything for at least 8 hours before and 2 hours after your first infusion of copanlisib. For your second infusion, your physician will decide if fasting before the infusion is necessary or if eating a low sugar meal within 4 hours of treatment is allowed.

The study doctor will monitor your blood glucose (sugar) levels during the study since copanlisib can cause elevations. Your doctor will tell you which foods to eat for 48 hours after copanlisib to keep your glucose levels low. Examples of low glucose foods include milk, apples, chickpeas, corn and meat. Specifics about the low glucose diet to follow will be reviewed with you by your physician and his/her team.

Study participants who have high glucose levels or diabetes while receiving the study treatment will be monitored more frequently and asked to check their glucose levels at home. Your study doctor will discuss any additional monitoring activities with you.

A member of the study team will give you a pill diary, so that you can write down, every day, when you take vemurafanib. Instructions about how to take vemurafenib are included in the pill diary. Bring your completed diary to all your study appointments, and bring your medication bottle(s), even if the bottle is empty.

- About 7 days after you start the study drugs, you will receive Thyrogen injections, as described above, to prepare for a second series of I-124 PET/CT scans
- You will receive another oral dose of I-124 on Day 10, and we will do a second series of PET/CT scans on Days 11, 12, 13, and 15. These scans will show whether the study treatment has changed the way your tumor absorbs and retains iodine.
- We will take measurements with a whole-body radiation scan on Days 10, 11, 12, 13, and 15 to calculate how your body gets rid of the iodine
- We will also do a second research biopsy procedure possibly before or during the I-124 PET/CTs, if your doctor decides that it is safe for you to have this procedure.
- Fasting/low sugar diet

Continuing study treatment:
If your second set of I-124 PET/CT scans shows that the study treatment has improved your tumor's ability to absorb iodine, you will continue the study treatment and receive radioiodine (I-131) therapy.

- You will receive Thyrogen injections on Days 16 and 17
- On Day 18, you will receive an oral dose of I-131 (This dose will be determined by the blood tests and whole-body radiation measurements done with the second set of PET/CT scans.)
- You will receive a final infusion of copanlisib on Day 15

- You will continue to take vemurafenib for 2 more days (Days 15 and 16) after you receive the oral dose of I-131, and then you will stop the study treatment.

You will have received treatment with the study drugs for about 20 days, if there are no changes in your treatment schedule.

If the study doctors find that the second set of I-124 PET/CT scans do not show that the study treatment has improved your tumor's ability to absorb radioiodine, you will stop all study treatment. No additional Thyrogen, vemurafenib, or copanlisib will be given, and you will not receive radioiodine therapy. We may do additional imaging scans to see whether the vemurafenib and copanlisib caused any shrinkage of your tumor.

End-of-Treatment and follow-up visits:

When you finish the study treatment, you will come back to the clinic about 7 days, 14 days, 1 month, 3-4 months, and 6 months after you received your last dose of the study drugs for routine blood tests and tumor imaging studies.

A Study Calendar that shows how often you will have these exams, tests, and procedures is provided at the end of this consent form. The calendar also includes exams, tests, and procedures that are part of your usual care.

It is possible, though not likely, that before you complete treatment with vemurafenib, copanlisib, and radioiodine that your tumors may grow, and your physician may decide that completing the treatment may still be of benefit and recommend that you continue on the trial.

While you are being monitored with blood tests and tumor imaging studies after treatment, if there is evidence that your tumor is worsening, then your physician may recommend that you be removed from the study to pursue other treatments. Alternatively, your physician may suggest that you continue to be monitored on the trial because sometimes radioiodine takes time to work, and tumors may still shrink even after an earlier scan shows some initial growth.

Will I receive the results of my research tests?

You will receive the results of the following tests done for research purposes:

- The I-124 PET/CT scan results to determine if the drug therapies have changed radioiodine uptake and retention in your tumors.

What risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that:

- You may lose time at work, school, or at home, and you may spend more time than usual in the hospital or doctor's office
- You may be asked sensitive or private questions that you do not usually discuss
- There may be a risk in finding out new genetic information about yourself. New health information about inherited traits that might affect you or your family (blood relatives) could be found during a research study

The drugs used in this study may affect how different parts of your body work, such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood throughout the study, and he or she will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Important information about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, and some may never go away.
- Some side effects may make it difficult for you to have children.
- Some side effects may be mild. Others may be very serious and may even result in death.

Important information about how you and the study doctor can make side effects less of a problem for you:

- If you notice or feel anything different, tell the study doctor. He or she can check to see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce your side effects.

The tables below show the most common and the most serious side effects that researchers know about. There may be other side effects that the doctors do not yet know about. If important new side effects are found during this study, the study doctor will discuss them with you.

Possible side effects of vemurafenib:

Common, some may be serious In 100 people receiving vemurafenib, more than 20 and as many as 100 may have:
• Skin rash • Fatigue (tiredness) • Hair loss • Sunburn or sensitivity of the skin to light. Avoid sun exposure, wear protective clothing and use broad-spectrum UVA/UVB sunscreen and lip balm (SPF ≥ 30) when you are outdoors. • Muscle or joint pain • Warts • Squamous cell skin cancer (a frequently occurring type of skin cancer) • Itchiness (pruritus)

Occasional, some may be serious In 100 people receiving vemurafenib, between 4 and 20 may have:
• Elevation of liver enzymes • Elevation of bilirubin (a color tint in blood cells that causes jaundice) • Decreased neutrophils (cells that help fight infection) • Fever • Nausea or vomiting • Diarrhea

Occasional, some may be serious In 100 people receiving vemurafenib, between 4 and 20 may have:
• Loss of appetite • Weight loss • Tingling or burning feelings in the hands or feet • Headache • Change in sense of taste • Abnormal heart rhythm (changes in a measurement called QTc in your ECG) • Dupuytren's contracture: A deformity of the hand in which one or more fingers is pulled into a bent position • Plantar fascial fibromatosis: a noncancerous growth in the arch of the foot

Rare, and serious In 100 people receiving vemurafenib, 3 or fewer may have:
• Basal cell carcinoma (cancer of the skin) • Inflammation or infection in the pancreas • Inflammation of the lining that surrounds the heart (pericarditis) • Kidney dysfunction (renal failure) • Difficulty swallowing • Joint inflammation • Vision changes, including inflammation of the middle layer of the eye (uveitis), causing blurry vision, and sensitivity of the eyes to light, causing discomfort or pain • Allergic reactions, causing rash, facial swelling, and difficulty breathing • Severe skin and digestive tract reaction (Stevens-Johnson syndrome), which may cause a rash and sloughing or breakdown of tissue. This condition may cause blisters, hives, and damage to other parts of the body, including the face, palms of the hands, and soles of the feet. This condition is serious and may be life-threatening. • New malignancies caused by activation of proteins called RAS, which control cell growth

Possible side effects of copanlisib:

Common, some may be serious In 100 people receiving copanlisib, more than 10 and as many as 100 may have:
• Decreased number of red blood cells (anemia), which causes tiredness, pale skin and shortness of breath • Too much sugar in the blood (hyperglycemia), which can cause frequent urination, increased thirst, blurred vision, headaches, and difficulty concentrating. If you have any of these symptoms, tell the study doctor immediately; this condition may be severe and life-threatening. Severe hyperglycemia may require hospitalization and urgent treatment with glucose-lowering medications (insulin and/or an oral medication).

Common, some may be serious

In 100 people receiving copanlisib, more than 10 and as many as 100 may have:

- You may experience mild to moderate increases in blood glucose after the infusion of copanlisib, with larger increases possibly occurring after eating a meal.
- High blood pressure (hypertension)
- Fatigue
- Inflammation of the mucous lining in the body, including the mouth, causing a sore or ulcerated mouth (mucosal inflammation including stomatitis and mouth ulceration)
- Diarrhea
- Nausea
- Vomiting
- Decreased number of white bloods cells called neutrophils (neutropenia), which increases the risk of infection
- Decreased number of blood cells called platelets (thrombocytopenia), which may cause bleeding and bruising
- Infections (including respiratory infections such as pneumonia) that can cause fever, sneezing, coughing, diarrhea, and fatigue; some infections may be severe and life-threatening. If you experience any of these symptoms, contact your doctor.
- Localized or generalized skin rash, which can be itchy, acne-like, cause skin peeling and blistering, or create bumps that contain fluid or pus.

Occasional, some may be serious

In 100 people receiving copanlisib, between 4 and 20 may have:

- Taste changes that may make some foods taste different
- Sores in the mouth and esophagus, which may be painful and cause difficulty swallowing
- Dry mouth
- Chills
- Decreased number of two types of white blood cells called leukocytes and lymphocytes (leukopenia and lymphopenia), which increases the risk of infection
- Increase in white blood cells called eosinophils (eosinophilia), which can be a sign of inflammation
- Hair loss (alopecia)
- Muscle spasms
- Increase in blood levels of the enzymes amylase and lipase, which could suggest damage to your pancreas and may be a sign of pancreatitis
- Low levels of magnesium in the blood (hypomagnesemia), which could cause weakness and muscle cramping
- Increase in blood levels of insulin (hyperinsulinemia), which can affect your blood sugar levels
- Tingling, tickling, pricking, or burning sensation in skin or mouth (paraesthesia, oral paraesthesia)

Occasional, some may be serious In 100 people receiving copanlisib, between 4 and 20 may have:
• Inflammation of the lungs (pneumonitis), which can cause shortness of breath and difficulty breathing; severe instances of lung inflammation can be life-threatening or fatal. Tell your doctor if you experience any of these symptoms. • Inflammation of the bowels/gut (colitis), may cause pain in your belly and loose or watery stools • Allergic reaction/hypersensitivity: Allergic reactions may be mild (such as skin rash or hives) to severe (such as breathing difficulties or shock)

Rare, and serious In 100 people receiving copanlisib, 3 or fewer may have:
• Inflammation of the pancreas, causing pain in the upper abdomen (pancreatitis) • Severe skin and digestive tract reaction (Stevens-Johnson syndrome), which may cause a rash and sloughing or breakdown of tissue. This condition may cause blisters, hives, and damage to other parts of the body, including the face, palms of the hands, and soles of the feet. This condition is serious and may be life-threatening. • During treatment with copanlisib, you may develop a bacterial or viral infection (including cytomegalovirus [CMV] infection) that can become serious and may lead to death. Your doctor may give you medication(s) to treat the infection while you are receiving copanlisib. • Infusion-related reaction, similar to an allergic reaction, that occurs while the study drug is being given into your vein or shortly after it is given. These reactions could cause fever and chills, skin rash, swelling, nausea, vomiting, headache, cold-like symptoms, difficulty breathing, or low blood pressure.

Possible side effects of Thyrogen:

Common, some may be serious In 100 people receiving Thyrogen, more than 20 and up to 100 may have:
• Nausea • Change in taste for 3-4 weeks • Salivary gland swelling or tenderness • Temporary dry mouth

Occasional, some may be serious In 100 people receiving Thyrogen, from 4 to 20 may have:
• Vomiting

Rare, and serious In 100 people receiving Thyrogen, 3 or fewer may have:
• Allergic rash

• Serious, life-threatening allergic reaction that could cause difficulty breathing, difficulty swallowing, abnormal heartbeat, chest pain, and abnormal blood pressure changes

Possible side effects of iodine-131:

Common, some may be serious In 100 people receiving iodine-131, more than 20 and up to 100 may have:
• Nausea • Change in taste for 3-4 weeks • Salivary gland swelling or tenderness • Temporary dry mouth • Vomiting

Occasional, some may be serious In 100 people receiving iodine-131, from 4 to 20 may have:
• Permanent dry mouth • Decreased white cell counts which can increase the risk of infection • Decreased platelets that can increase the risk of bleeding and/or bruising • Decreased fertility (menopause in women, low testosterone/sperm counts in men)

Rare, and serious In 100 people receiving iodine-131, 3 or fewer may have:
• Leukemia • Salivary gland cancers • GI (gastrointestinal) cancers

When vemurafenib and copanlisib are given in combination with I-131, the side effects or the severity of some of the side effects associated with either treatment may be increased. The study researchers do not know whether increased risks will occur, or what they may be.

Possible risks of iodine-124: You will receive two additional diagnostic (low-dose) administrations of iodine-124 for research purposes. Iodine-124 can be associated with the same side effects listed above for iodine-131. However, the study researchers think that those side effects are unlikely to occur with the low doses of iodine-124 that will be given in this study.

Possible risks of radiation-based diagnostic imaging: You will be exposed to low amounts of radiation from the scan(s) performed during this research study. The PET/CT scans provide detailed pictures of the inside of the body using radiation, like an x-ray. Every day, people are exposed to low levels of radiation that comes from the sun and the environment. Scientists think that exposure to too much radiation can be harmful.

The amounts of radiation associated with the scan(s) included in this study are similar to those from standard-of-care imaging procedures. Each year, many thousands of patients routinely undergo similar scans and receive similar doses of radiation with no short- or long-term adverse effects.

Possible risks associated with research biopsy procedures: Risks associated with biopsies include pain, redness, swelling, bleeding, bruising, infection and, rarely, death. The doctor performing the biopsy will explain the details and risks of the procedure, which may vary, depending on how the biopsy sample will be obtained. You will sign a separate consent document before you undergo this procedure.

Reproductive risks: You should not get pregnant, breastfeed, father a baby, or donate sperm while you are in this study. The drugs used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control or pregnancy prevention to use while you are in this study. You must continue to use these methods for at least 6 months after completing the study treatments.

Let the study doctor know about any questions you may have about possible side effects. You can ask the study doctor questions about side effects at any time.

What are my responsibilities in this study?

If you choose to take part in this study, you will need to:

- Keep your study appointments
- Tell the study doctor about:
  - All medications and any supplements you are taking
  - Any side effects from these medications or supplements
  - Any doctor visits or hospital stays outside of this study
  - Whether you have been or are currently in another research study
- Remember to bring your completed pill diary to all your clinic appointments, along with your medication bottle(s), even if the bottle is empty.
- Follow a low-iodine diet
- Follow your doctor's recommendations about foods that do not increase your glucose (sugar) levels

Is there a conflict of interest for this study?

This study is sponsored by Memorial Sloan Kettering Cancer Center and funded by Bayer Corporation. One of the investigators involved in this study receives extra money from Bayer Corporation for work that is not part of the study. These activities may include consulting, serving on advisory boards, giving speeches, or writing reports.

If you would like to know more about the steps MSK has taken to protect your best interests while you are in this study, please contact the MSK Patient Representative Department at 212-639-7202.

What are the costs of taking part in this study?

You will not have to pay for the copanlisib or for tests and procedures don only for research purposes, including:

- Biopsy procedures being done for research purposes before beginning the study treatment and during treatment

- I-124 administration before beginning the study treatment and on Day 7
- PET/CT scans listed in the *During the Study* section of this consent form
- Collection and testing of blood samples for research purposes

It is possible that copanlisib may not continue to be supplied while you are in the study. This possibility is unlikely, but if it occurs, your study doctor will talk with you about your options.

You and/or your health plan/insurance company will have to pay for all the other costs of treating your cancer while you are in this study. These charges include the costs of insurance co-pays and deductibles, as well as vemurafenib, tests, procedures, or drugs that you get during the study to monitor your safety, and to prevent or manage any side effects.

Although you do not have to pay for the study drug, the cost of getting the copanlisib ready and giving it to you is not paid by the study sponsor, so you or your insurance company may have to pay for this.

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it does not pay for if you take part in this clinical trial. Also find out if you need approval from your health plan before you can take part in this study.

The study doctor or nurse can help you find the right person to talk to if you are not sure which costs will be billed to you or your insurance provider.

Will I receive payment for taking part in this study?

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

Your biospecimens (blood and tissue) may be used in the development of new tests, drugs, or other products for sale. If they are, you will not receive any payment from the sale of these products.

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

You will get medical treatment if you are injured as a result of taking part in this study.

If you think that you have been injured as a result of taking part in this research study, tell the study doctor or the person in charge of the study as soon as possible. The name and telephone number of the person in charge of this research are listed on the first page of this consent form.

We will offer you treatment for research injuries that happen as a result of your taking part in this study. You and/or your health plan will be charged for this treatment. Medical services will be offered at the usual charge. You will be responsible for any costs not covered by your health plan/insurance company.

If you think that your injury was a result of medical error, you keep all your legal rights to receive payment for treating the injury, even though you are in a study.

Who will see my medical information?

Your privacy is very important to us, and the researchers will make every effort to protect it. Trained staff at Memorial Hospital may review your records, if necessary.

Access to your protected health information will be limited to those listed in the Research Authorization form, which is a part of the informed consent process.

Your information may be given out, if required by law. For example, some states require doctors to make a report to the state health board if they find that a participant in a research study has a contagious disease like tuberculosis. However, the researchers will do their best to make sure that any information about you that may be released will not identify you.

In the future, your information (data) and biospecimens may be de-identified, which means that your data and/or biospecimens will be assigned a unique code, and the list that links the code to your name will be stored separately from your biospecimens and data. Your de-identified information and biospecimens may be used for research that has not been described in this consent form, and they may be shared with another investigator for future research. You will not be asked if you agree to take part in future research studies.

If your information from this study is used in any reports or publications, your name and anything else that could identify you will not be used. It is possible that your de-identified information from this study will be shared with other researchers outside of MSK. All requests for data sharing will be reviewed by MSK, and if individual results are included in the data, they will not contain any identifiable information about you, such as your name, address, telephone number, or Social Security number. Your privacy is very important to us and we use many safety procedures to protect your privacy. However, we cannot guarantee that no one will ever be able to use your information to identify you.

The study doctors have a Certificate of Confidentiality from the National Institutes of Health for this study. This gives MSK an additional way to protect sensitive information that identifies you in your records if it is requested as part of a legal proceeding. However, MSK may still be required to share some of your medical information if required by law.

A Federal law, the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you, or when setting the terms of your employment.

Be aware that this Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, long-term care insurance, or if you are a member of the military.

Where can I get more information?

You may visit the NCI web site at http://cancer.gov/ for more information about research studies, or for general information about cancer. You may also call the NCI Cancer Information Service to get the same information at 1-800-4-CANCER (1-800-422-6237).

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

You can talk to the study doctor about any questions or concerns that you may have about this study, or to report side effects or injuries. You may also contact the lead researcher listed on the first page of this consent.

For questions about your rights while you are participating in this study, call the MSK Institutional Review Board (IRB) at 212-639-7592. If you have concerns, complaints, or input on research, or if you would like more information about the informed consent process, please contact the MSK Patient Representative Department at 212-639-7202.

Research Authorization for the Use and Disclosure of Protected Health Information (PHI)

Vemurafenib plus Copanlisib in Radioiodine-Refractive (RAIR) Thyroid Cancers

Federal law requires Memorial Sloan Kettering Cancer Center (MSK) to protect the privacy of information that identifies you and relates to your past, present, and future medical conditions (protected health information; PHI). We are committed to protecting the privacy of your information.

If you enroll in this research study, your protected health information will be used and shared with others, as explained below. MSK must obtain your permission before using or sharing your protected health information for research purposes. This form helps to make sure that you are informed of the ways in which your information will be used or shared in the future.

Carefully read the information below before you sign this form. By signing this form, you agree to the use and disclosure of your information for this research study.

1. What protected health information about me will be used or shared with others during this research?

- Your medical records
- Your research records, including new health information created from study-related tests, procedures, visits, and/or questionnaires
- Any health information or clinical data associated with your biospecimens, if the information or data could be reasonably used to identify you. This information or data will be shared only if you have agreed to it by signing this informed consent document.
- HIV-related information, including any information indicating that you have had an HIV-related test; or that you have HIV infection, HIV-related illness, or AIDS; or any information that could indicate that you may have been exposed to HIV. (New York State requires us to obtain your consent to use or share this information.)

2. Who will use or share my protected health information?

MSK will use and share your protected health information. People and offices that deal with research oversight, quality assurance, and/or billing will be able to use and share your protected health information, including:

- The study's Principal Investigator and Co-Principal Investigators: Alan Ho, MD, PhD; James A. Fagin, MD; David G. Pfister, MD; and Ravinder K. Grewal, MD
- Your research team at MSK, including the participating investigators, research staff, research nurses, fellows/residents, and clerical support staff
- Any healthcare personnel who provide services to you in connection with this study
- Members and staff of MSK's Institutional Review Board (IRB) and Privacy Board (PB)
- Staff of MSK's Clinical Research Administration, which oversees clinical studies, and Clinical Research Information Technology Group, which manages research databases
- Members of MSK's Data Safety Monitoring Board/Committee and the Quality Assurance Committee

3. With whom outside of MSK may my protected health information be shared?

Although all reasonable efforts will be made to maintain the confidentiality of your protected health information, it may be shared with and used by the following:

- The company or organization that provides the funding for the study, Bayer.
- MSK's research collaborators, business partners, subcontractors and agent(s), in the United States or in other countries, working to conduct the study, to monitor the study, or to analyze the study information for this study or for other research about the study intervention.
- Other research doctors and medical centers participating in this research.
- Federal and state agencies, and other domestic or foreign government bodies, if required by law and/or necessary for oversight purposes, including:
    - Office for Human Research Protections (OHRP) of the US Department of Health and Human Services (HHS)
    - US Food and Drug Administration (FDA) and other regulatory agencies responsible for oversight of research
    - National Cancer Institute (NCI)/National Institutes of Health (NIH)
- Other qualified researchers, approved by Memorial Sloan Kettering Cancer Center, who may receive individual research results that do not identify you.

Some of the organizations that may receive your protected health information may not have to satisfy the privacy rules and requirements; they may share your information with others without your permission.

4. Why will my protected health information be used by or shared by MSK or others?

The main reasons for the use or sharing of your information include the following:

- To conduct the study, to monitor your health status, to measure the effects of the drug(s)/device(s)/procedure(s) being studied, and to determine the research results
- To ensure that the research meets legal and institutional requirements
- To develop new tests, procedures, and commercial products
- To enhance research databases, so that scientists can design better research studies to develop new therapies for patients and to gain a better understanding of disease
- To assist with MSK medical treatment, billing, or healthcare operations. For example, medical information produced by this research study will become part of your hospital medical record.

5. For how long will my protected health information be used or shared with others?

There is no set date at which your protected health information that is being used or shared for this research study will be destroyed or no longer used. The information used and created during the study may be analyzed for many years, and it is not possible to know when this analysis will be completed.

6. Statement of privacy rights:

- It is your right to refuse to sign this authorization form. If you do not sign this form, you will not be able to participate in this research study. However, if you do not sign, it will not affect your ongoing medical treatment or healthcare coverage.

- You have the right to withdraw your permission for MSK to use or share your protected health information. Please note that we will not be able to withdraw all the information about you that already has been used or shared with others to carry out research-related activities such as oversight, or information that is needed to ensure the quality of the study. To withdraw your permission, write to the study doctor listed on the first page of this consent form at: Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065. If you withdraw permission for us to use or share your protected health information, you will not be able to continue to participate in this research study.

- You have the right to request access to your protected health information that is being used or shared during this research and that is related to the research or to payment for the research. However, you may access this information only after the study is completed. You may have access to your medical record at any time. To request this information, please contact the study doctor whose name and telephone number are listed on the first page of this consent form. You may also ask the study doctor to correct any study-related information about you that is wrong.

Notice concerning HIV-related information

Individuals/organizations are prohibited from sharing any HIV-related information about you without your approval, unless they are permitted to do so under federal or state law. You have a right to request the list of people who may receive or use your HIV-related information without your authorization.

If you experience discrimination because of the release or disclosure of your HIV-related information, you may contact the New York State Division of Human Rights at 888-392-3644 or the New York City Commission on Human Rights at 212-306-7500. These agencies are responsible for protecting your rights.

Memorial Sloan Kettering Cancer Center
IRB Number: 20-053 A(4)
Approval date: 09-Nov-2021

Participant Informed Consent/Research Authorization for Clinical Research

Statement of professional obtaining consent
I have fully explained this clinical research study to the participant or to his/her Legally Authorized Representative (LAR). In my judgment, and in that of the participant or his/her LAR, sufficient information, including risks and benefits, was provided for the participant or his/her LAR to make an informed decision. The consent discussion will be documented in the participant's EMR.

Consenting professional must personally sign and date		
Consenting professional's signature		**Date:**
Consenting professional's name (Print)		

Participant's (or Legally Authorized Representative's [LAR's)]) statement
I have read this form that describes the clinical research study. I have also talked it over to my satisfaction with the consenting professional. By signing below, I agree to the following: (1) to voluntarily participate in this clinical research study; (2) to authorize the use and disclosure of my/the participant's protected health information (data about myself/the participant); and (3) to state that I have received a signed and dated copy of this consent form.

Participant/LAR must personally sign and date		
Participant/LAR signature		**Date:**
Participant/LAR name (Print)		
LAR relationship to participant		

Witness signature (if required)

- ❑ Witness for non-English speaking participant: I declare that I am fluent in both English and in the participant's (or LAR's) language, and I confirm that the consent discussion was appropriately interpreted for the participant (or LAR).
- ❑ Other: I confirm that the consent discussion occurred, and that the participant agreed to participate in this study by signing this form, making his/her mark, or verbally agreeing.

Name of witness: _____

Signature of witness: _____ **Date:** _____
(The name of the witness must be documented in the EMR.)

Interpreter (if required)
Name of interpreter (if present): _____
ID number (if phone interpreter): _____
(The interpreter's name or ID number must be documented in the EMR.)

The participant/Legally Authorized Representative must be provided with a **signed copy** of this form.

Study Calendar:

This calendar shows the exams, tests, and procedures that will be done as part of this research study, as well as the tests and procedures that are part of your usual care.

	Screening	Pre-treatment	D 1	D 3	D 5	D 6	D 7	D 8	D 9	D 10	D 11	D 12	D 13	D 15	D 16 - 20	Follow-up (7 days, 14 days, 1 month, 3-4 months, and 6 months)	Observation Phase (Up to 1 year post treatment)
The tests, exams and procedures listed below are standard and part of the usual care for your cancer																	
Pregnancy test	X							X							X		
MD clinic visit	X		X					X						X			
Routine blood tests	X		Days 1, 8, 10, 11, 12, 13											X		X	
Electrocardiogram (ECG)	X																
Echocardiogram (ECHO)	X																
Dermatology exam	X																
Tumor imaging (CT/MRI scans)	X				If possible/needed, before administration of I-131											At 3-4 months and 6-month visits	
Thyrogen injections		X						X	X						X		
Radioiodine treatment (I-131)															X		
The tests, exams and procedures listed below are being done for research purposes because you are taking part in this study																	
Collection of archival tissue or research biopsy	X																
Collection of blood for research tests	X																
Research biopsy	X												X				
I-124 administration		X								X							
Research PET/CT scans		4 scans over 5 days									X	X	X	X			
Vemurafenib administration			Twice a day														
Copanlisib infusion								X						X			
Fasting/Low sugar diet								X						X			
Low-iodine diet		X															
Follow up data collection																	X