NCI Community Oncology Research Program – Kansas City
(NCORP-KC)

S1320, "A Randomized Phase II Trial of Intermittent Versus Continuous Dosing of Dabrafenib (NSC-763760) and Trametinib (NSC-763093) in BRAFV600E/K Mutant Melanoma."

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

What is the usual approach to my advanced melanoma?

You are being asked to take part in this study because you have melanoma, a type of skin cancer, which has a BRAF mutation. BRAF is a human gene that makes a protein called B-raf. This protein signals cells to grow. There are several types of treatments that are used to treat this type of cancer such as immunotherapy or antibody treatments. One of the usual treatments is the combination of dabrafenib and trametinib which prevent the B-raf protein from sending a signal for cells to grow.

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

Your other choices may include:

- **you may choose to have the usual approach described above**
- **you may choose to take part in a different study, if one is available**
- **or you could decide not to be treated for cancer but you may want to receive comfort care to relieve symptoms.**

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

Why is this study being done?

The purpose of this study is to compare any good and bad effects of receiving the drugs dabrafenib and trametinib continuously to receiving dabrafenib and trametinib with a break in treatment. Dabrafenib and trametinib are similar to vemurafenib and have been tested together and found to be safe and effective for patients with advanced melanoma. The combination has

been approved by the FDA for the treatment of advanced melanoma. This study is testing whether receiving dabrafenib and trametinib with a break in treatment could extend the time before your cancer gets worse. It could also cause side effects. This study will allow the researchers to know whether a break in treatment is better, the same, or worse than continuous treatment of dabrafenib and trametinib. To be better, the break in treatment approach should extend the time before cancer gets worse by about 4 to 6 months compared to the continuous treatment approach. There will be about 280 people taking part in this study

If your BRAF mutation was determined by a test that is not FDA approved, there may be a higher probability that the test was false positive, which could result in risk with no potential for benefit from dabrafenib.

What are the study groups?

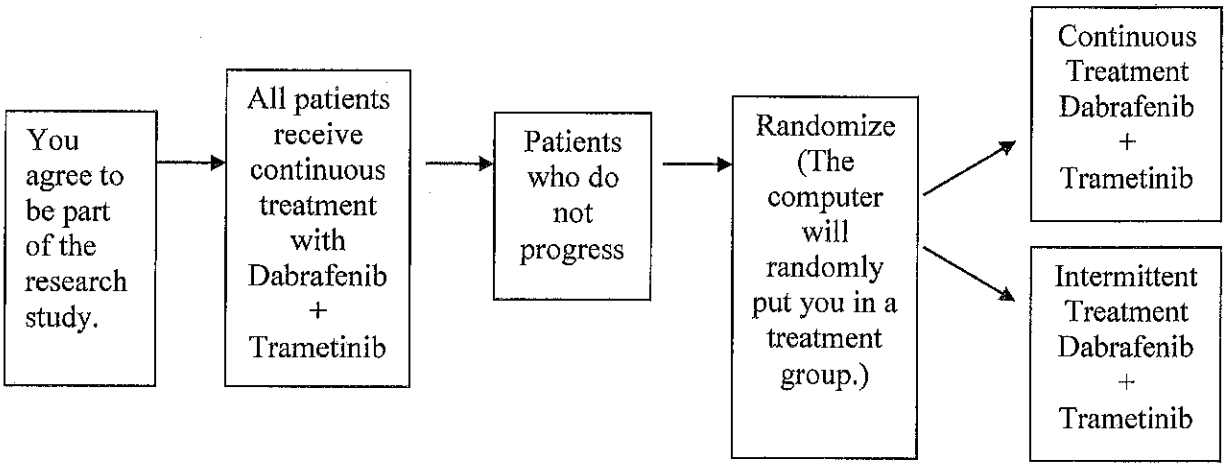
All patients on this study will receive a lead-in of continuous treatment for 56 days of dabrafenib (twice daily) and trametinib (once daily). If after receiving this continuous lead-in period of dabrafenib and trametinib your disease has not gotten worse you will be put into one of two treatment groups described below.

A computer will by chance assign you to one of two treatment groups in the study. This is called randomization. This is done by chance because no one knows if one study group is better or worse than the other.

Group 1 will receive dabrafenib (twice daily) and trametinib (once daily) for a 56 day cycle. This repeats until your disease gets worse or you come off study for some other reason.

Group 2 will receive dabrafenib (twice daily) and trametinib (once daily)with a break in treatment during the 56 day cycle. You will take the drugs for days 1-7, skip days 8-28, and then take the drugs again days 29-56. This 56 day cycle repeats until your disease gets worse or you come off study for some other reason.

Both dabrafenib and trametinib are taken by mouth on an empty stomach (either one hour before you eat or two hours after you eat). If you miss a dose of dabrafenib, you can make it up as long as your next dose is at least 6 hours later. If you miss a dose of trametinib, you can make it up as long as your next dose is at least 12 hours later. If your next scheduled dose is sooner than that, skip the missed dose. The once daily dose of trametinib may be taken at the same time as one of the doses of dabrafenib.



How long will I be in this study?

You will receive the drugs until your disease gets worse or you come off study for some other reason. After you finish study treatment, your doctor will continue to watch you for side effects and follow your condition for up to five years from when you began study treatment. Your doctor will ask you to come in at least once every six months for the first three years, then once a year through Year 5. The doctor may ask you to come in more often if they think they need to see you. These visits are standard of care.

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

Before you begin the study:

You will need to have the following extra tests to find out if you can be in the study. Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Blood tests to evaluate your blood counts, kidney, liver and pancreatic function, blood clotting time, cholesterol levels and blood sugar level control
- FDA-approved BRAF mutation detection assay
- ECHO/MUGA scan and ECG to check adequate cardiac function
- Either a whole body PET/CT scan or CT scan of the neck, chest, abdomen and pelvis
- Eye exam
- Dermatology exam

If your cancer can be removed by biopsy without image guidance, small pieces of cancer tissue will be taken for the study before you begin study treatment and again after 2 weeks on study treatment. This sample is required in order for you to take part in this study because the research on the sample is an important part of the study. This tissue will be used to look at biologic markers to see if they are able to better predict which treatment may work better. Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, pain at the biopsy site, which can be treated with regular pain medications, and bruising. Rarely, an infection can occur. You will sign a separate consent form before the biopsy is taken. This will be a standard surgical consent form from the institution where the biopsy procedure takes place.

If you have the biopsies described above performed, you will also have blood taken as follows:
• before you begin the study: about 2 Tablespoons
• Day 15 of Cycle 3: about 4 teaspoons

This sample is required in order for you to participate because the research on the sample is an important part of the study. This blood sample will be used to look at changes to your tumor DNA during your study treatment.

Your privacy is very important and the researchers will make every effort to protect it. Your test results will be identified by a unique code and the list that links the code to your name will be kept separate from your sample and health information. The results will not be available to you or your study doctor.

Neither you nor your health care plan/insurance carrier will be billed for the collection of the blood and tissue that will be used for this study.

During the study:

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures during follow-up as outlined below. They are part of regular cancer care.

- Blood tests to evaluate your blood counts, kidney, liver and pancreatic function
- ECHO/MUGA scan and ECG to check adequate cardiac function
- Either a whole body PET/CT scan or CT scan of the neck, chest, abdomen and pelvis
- Eye exam
- Dermatology exam

What possible 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 or home and spend more time in the hospital or doctor's office than usual**

- **The study approach may not be better, and could possibly be worse, than the usual approach for your cancer.**

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 and 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.

Here are important points 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, or some may never go away.**
- **Some side effects may interfere with your ability to have children.**
- **Some side effects may be serious and may even result in death.**

Here are important points about how you and the study doctor can make side effects less of a problem:

- **Tell the study doctor if you notice or feel anything different so they can 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 side effects.**

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

Risk Profile for Dabrafenib mesylate

*Please note that the text in italics applies to combination studies of dabrafenib mesylate and trametinib dimethyl sulfoxide.

COMMON, SOME MAY BE SERIOUS In 100 people receiving dabrafenib mesylate, more than 20 and up to 100 may have:
• **Nausea** • **Tiredness** • **Fever** ***(Fever and complications of fever are more frequent and severe when dabrafenib mesylate is used together with trametinib dimethyl sulfoxide.)*** • **Pain** • **Headache** • **Hair loss** • **Skin changes including rash, wart, thickening**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving dabrafenib mesylate, from 4 to 20 may have:
• **Anemia which may require blood transfusion** • **Constipation, diarrhea, vomiting** • **Chills** • **Swelling of arms, legs** • **Flu-like symptoms including body aches** • **Bleeding** ***(The risk of bleeding is increased when dabrafenib mesylate is used together with trametinib dimethyl sulfoxide.)*** • **Infection, especially when white blood cell count is low** • **Loss of appetite** • **A new skin cancer resulting from treatment of earlier cancer** • **Dizziness** • **Cough** • **Dry skin** • **Increased sweating** • **Redness, pain or peeling of palms and soles** • **Itching** • **Change in hair** • **Blood clot which may cause swelling, pain, shortness of breath** ***(The risk is increased when dabrafenib mesylate is used together with trametinib dimethyl sulfoxide.)***

RARE, AND SERIOUS In 100 people receiving dabrafenib mesylate, 3 or fewer may have:
• **Swelling and redness of the eye** • **Changes in the eyes that may cause blurred vision or blindness** • **Pain in belly (pancreas) that may require hospitalization** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Fainting** • **Kidney damage which may cause swelling, may require dialysis** ***(The risk is increased when dabrafenib mesylate is used together with trametinib dimethyl sulfoxide.)*** • **Swelling and redness of the skin**

Possible Side Effects of Trametinib

COMMON, SOME MAY BE SERIOUS In 100 people receiving Trametinib dimethyl sulfoxide, more than 20 and up to 100 may have:
• **Diarrhea, nausea** • **Tiredness** • **Skin changes including rash, acne** • **Swelling of the body**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Trametinib dimethyl sulfoxide, from 4 to 20 may have:
• **Anemia which may require blood transfusion** • **Abnormal heartbeat** • **Blurred vision or other visual disturbances** • **Dry eye, mouth, skin** • **Pain** • **Constipation, heartburn, vomiting** • **Sores in the mouth which may cause difficulty swallowing** • **Chills, fever** • **Infection** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Infection** • **Change in heart function** • **Loss of appetite, dehydration** • **Dizziness, headache** • **Cough, shortness of breath** • **Hair loss, itching** • **Swelling of the eye** • **High blood pressure** • **Bleeding**

RARE, AND SERIOUS In 100 people receiving Trametinib dimethyl sulfoxide, 3 or fewer may have:
• **Heart failure which may cause shortness of breath, swelling of ankles, and tiredness** • **Changes in the eyes (blood clot or retinal detachment) which may cause blindness** • **Damage to the muscles** • **Redness, pain or peeling of palms and soles** • **Damage of the lungs which may cause shortness of breath**

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

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while 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 in this study. With regard to dabrafenib, women of child bearing potential and men must agree to use adequate contraception (barrier method of birth control or abstinence) prior

to study entry and for the duration of study participation. Hormonal contraception is not allowed while you are on the study and or at least 2 weeks after treatment with dabrafenib due to drug-drug interactions.

For MALE patients: Based on studies in animals, dabrafenib may cause damage to the tissue that makes sperm. This may cause sperm to be abnormal in shape and size and could lead to infertility, which may be irreversible.

Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation and 2 weeks after completion of dabrafenib and trametinib administration.

Will I benefit from this study?

This study may or may not help you because it is not possible to know at this time if a break in treatment is better than continuous treatment with dabrafenib and trametenib. This study may help researchers learn things that may help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

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.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, Institutional Review Board or Food and Drug Administration.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call NCI Community Oncology Research Program – Kansas City Institutional Review Board at 913-948-5588.

What are the costs of taking part in this study?

The dabrafenib and trametinib will be supplied at no charge while you take part in this study. It is possible that the drugs may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

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

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

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this 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. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The study sponsor, SWOG, and any drug company supporting the study.
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.
- Qualified representative(s) of the Pharmaceutical Collaborator(s)

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or 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.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

This section is about optional studies you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records, nor will you or your study doctor know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say 'no' to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

1. Future Contact

I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.

Yes No

Optional Research Studies that Involve Specimens

Please note: This section of the Informed Consent Form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be part of the main study even if you say "no" to taking part in the additional studies.

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

If you choose to take part, samples of your tissue and blood will be used. The researchers ask your permission to store and use your samples and health information for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called "biobanking". The Biobank is being run by SWOG and supported by the National Cancer Institute.

What is involved?

If you agree to take part, here is what will happen next:

1) A sample from the tissue and blood that was collected at the time of your surgery or biopsy will be sent to the Biobank before you begin the study. Two more blood samples will be collected, one during Week 1 and one during Week 4 of your second cycle of treatment. One more blood sample will be taken if your disease comes back or gets worse.

2) Your samples will be stored in the Biobank, along with samples and information from other people who take part. The samples will be kept until they are used up.
3) Qualified researchers can submit a request to use the materials stored in the Biobanks. A science committee at the clinical trials organization, and/or the National Cancer Institute, will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
4) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
5) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

What are the possible risks?

1) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
2) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
3) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

How will Information about me be kept private?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your sample(s) is sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.

2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and SWOG staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom SWOG sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.

5) If research results are published, your name and other personal information will not be used.

What are the possible benefits?

You will not benefit from taking part. Your samples may be helpful to research whether you do or do not have cancer.) The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are there any costs or payments?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

What if I change my mind?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used. Samples or related information that have already been given to or used by researchers will not be returned.

If you decide to withdraw your specimens from a SWOG Specimen Repository in the future, a written withdrawal of consent should be submitted through your study doctor to the SWOG Operations Office. Please designate in the written withdrawal whether you would prefer to have the specimens destroyed or returned to the study doctor.

What if I have more questions?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial).*

Please circle your answer to show whether or not you would like to take part in each option *(include only applicable questions)*:

SAMPLES FOR FUTURE RESEARCH STUDIES:

2. My samples and related information may be kept in a Biobank for use in future health research.

Yes No

Release

By signing this form you authorize NCORP-KC to access and obtain information that is required for the study. This may include your medical records, labs, radiologic films and reports and pathology specimens. This authorization to disclose your medical records shall not expire, even upon death, unless specifically revoked in writing by you.

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

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

Participant _____

Participant's signature _____

Date of signature_____

Person obtaining consent _____

Person obtaining consent signature_____

Date of Signature _____

Specimen Consent Supplemental Sheets

How are Specimens Used for Research?

Where do specimens come from?

A specimen may be from a blood sample or from tissue, bone marrow, skin, toenails or other body materials. People who are trained to handle specimens and protect donors' rights make sure that the highest standards of quality control are followed by SWOG. Your doctor does not work for SWOG, but has agreed to help collect specimens from many patients. Many doctors across the country are helping in the same way.

Why do people do research with specimens?

Research with specimens can help to find out more about what causes cancer, how to prevent it, how to treat it, and how to cure it. Research using specimens can also answer other health questions. Some of these include finding the causes of diabetes and heart disease, or finding genetic links to Alzheimer's.

What type of research will be done with my specimen?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. Some research looks at diseases that are passed on in families (called genetic research). Research done with your specimen may look for genetic causes and signs of disease.

How do researchers get the specimen?

Researchers from universities, hospitals, and other health organizations conduct research using specimens. They contact SWOG and request samples for their studies. SWOG reviews the way that these studies will be done, and decides if any of the samples can be used. SWOG gets the specimen and information about you from your hospital, and sends the specimen samples and some information about you to the researcher. SWOG will not send your name, address, phone number, social security number or any other identifying information to the researcher.

Will I find out the results of the research using my specimen?

You will not receive the results of research done with your specimen. This is because research can take a long time and must use specimen samples from many people before results are known. Results from research using your specimen may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

Why do you need information from my health records?

In order to do research with your specimen, researchers may need to know some things about you. (For example: Are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher may include your age, sex, race, diagnosis, treatments and family history. This information is collected by your hospital from your health record and sent to SWOG. If more information is needed, SWOG will send it to the researcher.

Will my name be attached to the records that are given to the researcher?

No. Your name, address, phone number and anything else that could identify you will be removed before they go to the researcher. The researcher will not know who you are.

How could the records be used in ways that might be harmful to me?

Sometimes, health records have been used against patients and their families. For example, insurance companies may deny a patient insurance or employers may not hire someone with a certain illness (such as AIDS or cancer). The results of genetic research may not apply only to you, but to your family members too. For disease caused by gene changes, the information in one person's health record could be used against family members.

How am I protected?

SWOG is in charge of making sure that information about you is kept private. SWOG will take careful steps to prevent misuse of records. Your name, address, phone number and any other identifying information will be taken off anything associated with your specimen before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person which will help to protect your privacy.

What if I have more questions?

If you have any questions, please talk to your doctor or nurse, or call our research review board at 913-948-5588.