ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE A051301

A RANDOMIZED DOUBLE-BLIND PHASE III STUDY OF IBRUTINIB DURING AND FOLLOWING AUTOLOGOUS STEM CELL TRANSPLANTATION VERSUS PLACEBO IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA OF THE ACTIVATED B-CELL SUBTYPE

NCI-supplied agent(s): Ibrutinib (NSC #748645, IND #117241); IND holder: NCI-CTEP
Commercial agent(s): BCNU (Carmustine) (NSC# 409962), Etoposide (NSC# 141540), Ara-C (Cytarabine) (NSC# 63878), Melphalan (NSC# 8806), Cyclophosphamide (NSC#26271)

[X]	**Update:**	[ ]	**Status Change:**
[ ]	Eligibility changes	[ ]	Activation
[X]	Therapy / Dose Modifications / Study Calendar changes	[ ]	Closure
[X]	Informed Consent changes	[ ]	Suspension / temporary closure
[X]	Scientific / Statistical Considerations changes	[ ]	Reactivation
[ ]	Data Submission / Forms changes		
[X]	Editorial / Administrative changes		
[ ]	Other:		

If your site utilizes the CIRB as your IRB of record for this study, no recommended level of IRB review is provided by the Alliance. This amendment must be implemented within 30 days after posting. Please refer to the CIRB amendment application and CIRB guidelines for further instructions.

If your site utilizes a local IRB as your IRB of record for this study, IRB approval (or disapproval) is required within 90 days. Expedited IRB Approval is allowed. Please follow your local IRB guidelines.

UPDATES TO THE PROTOCOL:

Cover Page

- Dr. Thomas Shea has been removed from the cover page.
- Dr. Miguel Perales has replaced Dr. Steven Devine as the Transplant Committee Chair.
- Dr. Kristy Richards has been removed from the cover page.
- Dr. Susan Geyer has replaced Dr. Amy Ruppert Stark as the Primary Statistician.

Study Resources
The contact information for the Alliance Biorepository at Washington University has been updated.

CTSU Contact Information
The table has been updated with the current CTSU template language.

Schema Page 3
- In the "Study Procedures" column, the continuation timing has been changed to "day +30 to +75."
- In footnote 3, the 21 day window has been changed to 45 days.

Section 3.3 (Eligibility Criteria [Step 1])
In Section 3.3.4 (Prior Treatment), the following has been added to the second criterion: "Prior CART therapy is allowed and counts as one line of therapy."

Section 4.2 (Cancer Trials Support Unit Registration Procedures)
This section has been updated with the current CTSU template language.

Section 4.5 (Patient registration/randomization procedures)
This section has been updated with the current CTSU template language.

Section 5.0 (Study Calendar)
- The two columns under "Cycles 2-13" have been combined.
- The requirement for the BM biopsy prior to registration has been removed.
- In footnote #, the ≤ 21 day window has been changed to ≤ 30 days.
- In footnote **, the first sentence has been revised to read: "Treatment assessment on Day 1 and Day 15 of Cycle 2 and Day 1 of Cycles 3 through 13 can be performed outside the study/transplant center, provided the results are made available to the treating study investigator."
- In footnote **, the +/- 4 day window has been changed to +/- 7 days.
- The former footnote *** has been removed.
- In footnote 2, the ≤ 21 day window has been changed to ≤ 45 days.
- Footnote 10 has been revised as follows: "Bone marrow biopsy and aspirate ~~per institutional standards within 84 days (12 weeks) prior to registration. Repeat~~ performed for response assessment at 3 months only if positive prior to registration or if there is a clinical concern."
- In the "Crossover Phase" study calendar, in footnote *, the +/- 4 day window has been changed to +/- 7 days.
- In the "Crossover Phase" study calendar, in footnote 2, the ≤ 21 day window has been changed to ≤ 28 days.

Section 6.1 (Data Collection and Submission)
This section has been updated with the current CTSU template language.

Section 7.0 (Treatment Plan/Intervention)
In the first sentence, the 21 day window has been changed to 45 days.

Section 7.3 (Continuation)
In the first sentence, "Day +60" has been changed to "Day +75."

Section 13.1 (Study Design)
This section has been updated to reflect the revised sample size with this amendment.

Section 13.2 (Sample Size, Accrual Time and Study Duration)
This section has been updated to describe the rationale for the sample size and statistical design changes being made with this amendment.

Section 13.5 (Interim Analysis Design for Primary Endpoint)
This section has been completely revised to reflect the updated statistical design with this amendment.

Section 13.6 (Analysis Plan for Secondary Endpoints)
This section has been completely revised to reflect the updated statistical design with this amendment.

Section 13.9 (Inclusion of Women and Minorities)

- The enrollment table has been updated to reflect the revised sample size.
- The ethnic and racial categories have been removed from under the enrollment table to align with the current Alliance model protocol template.

Section 14.1 (Imaging Correlative Science)
Section 14.1.4 (Statistical Design) has been revised to reflect the updated statistical design and sample size for the main study.

Section 14.2 (Pharmacogenetics [Alliance A051301-PP1])
In Section 14.2.4 (Statistical Design), the second paragraph has been revised to reflect the updated sample size of the main study.

Section 14.3 (Biomarkers studies in Alliance A051301 [Alliance A051301-ST1])

- In Section 14.3.1 (BCR Mutational Analysis), the "Statistical Design" section has been revised to reflect the updated statistical design and sample size for the main study.
- In Section 14.3.2 (BCL2 and MYC assessment prognostic markers), the "Statistical Design" section has been revised to reflect the updated statistical design and sample size for the main study.

UPDATES TO THE EARLY SAFETY MODEL CONSENT:

No changes have been made to the Early Safety model consent.

UPDATES TO THE RANDOMIZED STUDY MODEL CONSENT:

Why is this study being done?
The last sentence has been revised to read: "There will be about 160 people with "ABC" subtype DLBCL taking part in this study."

Replacement protocol and model consent documents have been issued.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

NOTES FOR LOCAL INVESTIGATORS*:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices about participating in research. The consent form provides a summary of the study, of the individual's rights as a study participant, and documents their willingness to participate. The consent form is, however, only one piece of an ongoing exchange of information between the investigator and study participant. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/

- A blank line, "_____", indicates that the local investigator should provide the appropriate information before submitting to the IRB.

*These notes for investigators are instructional and should not be included in the consent form sent to IRBs.

Early Safety Monitoring consent for A051301

Study Title for Study Participants: Testing the addition of the oral medication ibrutinib to autologous stem cell transplantation for patients with relapsed diffuse large B-Cell lymphoma

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: A randomized double-blind phase III study of ibrutinib during and following autologous stem cell transplantation versus placebo in patients with relapsed or refractory diffuse large B-Cell lymphoma of the activated B-Cell subtype

What is the usual approach to my relapsed diffuse large B-Cell lymphoma?

You are being asked to take part in this study because you have a certain type of diffuse large B-Cell lymphoma (DLBCL), called "Activated B-Cell" (or "ABC") subtype, that did not get better with treatment or has returned after previous treatment. You have subsequently received or are currently receiving second line therapy, and you are being considered for an autologous hematopoietic stem cell transplantation (AutoHCT). AutoHCT is the usual treatment for your lymphoma and is a way to deliver higher doses of chemotherapy to patients like you in an attempt to eliminate any surviving lymphoma cells from your body. It requires an infusion of some of your own blood cells, called stem cells, in order to rebuild your bone marrow after this chemotherapy and allow you to make normal blood cells. In DLBCL, AutoHCT is a well-established approach that can lead to about 40 out of 100 patients like you being free of DLBCL 5 years after the AutoHCT.

One of two forms of chemotherapy, known as BEAM (BCNU, etoposide, Ara-C, melphalan) or CBV (BCNU, etoposide, cyclophosphamide), is the usual chemotherapy given with AutoHCT for patients with your lymphoma.

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

If you decide not to take part in this study, you have other choices. For example:

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

Why is this early safety study being done?

The purpose of this early safety study is to test whether an oral medication, ibrutinib, can be safely combined with the chemotherapy medications given during an autologous stem cell transplant. Ibrutinib is a cancer-fighting drug that may be effective against a certain type of DLBCL called "Activated B-Cell Subtype" (or "ABC"). Ibrutinib may also be effective for patients who relapse after AutoHCT. Ibrutinib is already FDA-approved for use in patients with other types of cancers, such as chronic lymphocytic leukemia, mantle cell lymphoma, and Waldenstrom's Macroglobulinemia. Though ibrutinib is FDA approved for use in patients with other types of cancer, it is investigational for this study. The researchers want to know if adding ibrutinib to the usual chemotherapy given with AutoHCT could prevent your lymphoma from returning in the future. However, addition of this medication could also cause side effects that we do not yet know about. There will be 6 patients enrolled to this early safety part of the study before opening enrollment to about 296 people with "ABC" subtype DLBCL.

What are the study groups?

This early safety study has one treatment group. You will get the usual chemotherapy (BEAM or CBV) given for AutoHCT at your institution plus the study drug, ibrutinib, during and for 12 months following AutoHCT.

Ibrutinib is provided in capsule form and will be taken by mouth once daily for 6 days during cycle 1 and once daily continuously during cycles 2 to 13. Ibrutinib should be swallowed whole with water. You should avoid grapefruit, Seville oranges, and their juices while taking ibrutinib. You will be asked to complete a daily drug diary to track doses taken or missed.

How long will I be in this study?

You will receive chemotherapy with ibrutinib and AutoHCT followed by one year of ibrutinib. After you finish treatment, your doctor will continue to watch you for side effects and follow your condition for up to 5 years since you started the study. If you do not complete a year of treatment, your doctor will still watch you for side effects and follow your condition for up to 5 years since you started the study.

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

Most of the exams, tests, and procedures you will have are part of the usual approach for your lymphoma. However, there are some extra tests and procedures that you will need to have if you take part in this study. These tests and procedures may not all be part of the usual care of your lymphoma:

- Blood tests (about 1-2 tablespoons will be drawn) and clinic visits every month for the first 3 months, then every 3 months for the first 2 years.
- CT scans of the chest, abdomen and pelvis at 6, 12, 18 and 24 months.
- PET scan at 3 months.

The study researchers also would like to learn more about fatigue and quality of life. All study participants will be asked to complete a questionnaire with 2 questions. If you choose to answer these questions, it will take less than one minute to complete.

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.
- You may be asked sensitive or private questions which you normally do not discuss.

The oral medication ibrutinib that is 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.

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 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.

Possible Side Effects of Ibrutinib

COMMON, SOME MAY BE SERIOUS In 100 people receiving ibrutinib, more than 20 and up to 100 may have:
• Diarrhea

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving ibrutinib, from 4 to 20 may have:
• Anemia which may require blood transfusion • Infection, especially when white blood cell count is low • Abnormal heartbeat which may cause fainting • Blurred vision • Pain • Constipation, nausea, vomiting • Sores in the mouth which may cause difficulty swallowing • Swelling of arms, legs • Tiredness, fever

- Bruising, bleeding
- Loss of appetite, dehydration
- A new skin growth that is not cancerous
- Dizziness, headache
- Cough, shortness of breath
- Rash
- High blood pressure

RARE, AND SERIOUS
In 100 people receiving ibrutinib, 3 or fewer may have:

- Blood clot
- Heart failure which may cause shortness of breath, swelling of ankles, and tiredness
- Death
- Liver damage which may cause yellowing of eyes and skin, swelling
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Fungal infection of the lungs or central nervous system which may cause cough, shortness of breath, fever, confusion, headache, or stiff neck
- Kidney damage which may require dialysis
- A new cancer resulting from treatment of earlier cancer
- Numbness, tingling or pain of the arms and legs
- Damage to lungs which may cause shortness of breath
- Severe skin rash with blisters and peeling which can involve mouth and other parts of the body
- Low blood pressure

The *CT and PET scans* that you will receive in this study will expose you to low amounts of radiation. Every day, people are naturally exposed to low levels of radiation that come from the sun and the environment. This type of radiation is called "background radiation". No one knows for sure whether exposure to low amounts of radiation is harmful for your body. However, scientists believe that being exposed to too much radiation can cause harmful side effects, including causing a new cancer.

The *CT and PET scans* that you will receive in this study will expose you to extra radiation that is equal to about 3 and a half years' worth of background radiation. Most of the time, this low amount of extra radiation is not harmful to you and these follow up scans would be considered standard procedures following an autologous stem cell transplant for DLBCL. However, scientists believe that if you get extra radiation that is more than about 30 years' worth of background radiation, there is a chance of having a harmful side effect, including causing a new cancer. It is estimated that this could occur in about 1 out of every 1000 people who get a very large amount of extra radiation.

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. Discussion about the side effects of the usual chemotherapy given with AutoHCT (BEAM or CBV) should occur during discussions with your doctor about the details of the transplant.

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. You should continue to use birth control for at least one month from the last dose of ibrutinib.

What possible benefits can I expect from taking part in this study?

This study has only a small chance of helping you because we do not know if the study drug/study approach is effective. 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 that changes the management of patients with your lymphoma.
- If you do not follow the study rules.
- If the study is stopped by the sponsor, IRB or the FDA.

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 the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

The medication ibrutinib will be supplied at no charge while you take part in this study. It is possible that the ibrutinib may not continue to be supplied in the future 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 lymphoma 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. This includes paying for the extra tests and procedures listed on page 2 that may not be a part of the usual care for your lymphoma. 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 Alliance, the study sponsor (NCI), 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.

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).*

ADDITIONAL STUDIES SECTION: 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 these optional studies hope the results will help other people with lymphoma in the future.

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.

Optional Sample Collections for Laboratory Studies and/or Biobanking for Possible Future Studies

Researchers are trying to learn more about cancer and other health problems. Much of this research is done using samples from your tissue or blood. 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.

The researchers ask your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for future 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 the Alliance and is supported by the National Cancer Institute.

There are two optional laboratory studies that you can choose to take part in. You have the option to participate in either or both of these studies:

1. **Optional Blood Study**

   If you choose to take part in this study, researchers would like to use a small sample of your blood (~2 teaspoons) to look for variations in your DNA that may affect how you individually respond to treatment or experience side effects from treatment. DNA is the genetic code that we are born with that determines how our bodies work. It codes for molecules in the body that for example, determine how we metabolize chemotherapy, experience side effects or respond to medications. We each carry individual genetic variations from the general population that may affect our ability to metabolize the chemotherapy drugs given in this study and experience toxicities from these drugs.

2. **Optional Tissue Study**

   If you choose to take part in this study, the researchers would like to use leftover samples of your diagnostic lymphoma biopsy and any future lymphoma biopsy to determine whether certain molecules present on lymphoma cells might predict which patients may respond better to treatment. These are tissue blocks that have already been obtained or may be obtained if your lymphoma should return at any time.

WHAT IS INVOLVED?

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

1) If you choose to take part in the optional blood study, about 10 milliliters (or about 2 teaspoons) of blood will be collected from a vein in your arm before you begin study treatment.
2) If you choose to take part in the optional tissue study, a sample of tissue will be collected from the original tissue biopsy submitted during your pre-registration to the main study. An additional sample of tissue may be collected in the future from a biopsy performed should your lymphoma return. This

biopsy might not be performed if you were not on this study. You may decline to have this biopsy performed.

3) Your sample and some related health information will be sent to a researcher for use in the study described above. Remaining samples may be stored in the Biobank, along with samples from other people who take part. The samples will be kept until they are used up.
4) Qualified researchers can submit a request to use the materials stored in the Biobank. A science committee at the clinical trials organization (Alliance), 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.
5) 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.
6) 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) The most common risks related to drawing blood from your arm are brief pain and possibly a bruise.
2) If you choose to take part in the optional tissue study, and you choose to have a biopsy in this study when your lymphoma returns, the risks of collecting a biopsy are potential discomfort or bleeding at the biopsy site.
3) 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.
4) 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.
5) 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 Alliance central pathology office staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom Alliance 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 in these studies. However, 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 and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

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:

SAMPLES FOR THE LABORATORY STUDIES:

1. I agree to have my **blood** specimen collected, and I agree that my specimen sample(s) and related information may be used for the **blood study** described above.

   YES NO

2. I agree to have my **tissue** specimen collected from the biopsies noted in the Optional Tissue Study section above, and I agree that my specimen sample(s) and related information may be used for the **tissue study** described above.

   YES NO

3. I agree that my study doctor, or their representative, may contact me or my physician to see if I wish to learn about results from these studies.

   YES NO

SAMPLES FOR FUTURE RESEARCH STUDIES:

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

   YES NO

5. I agree that my study doctor, or their representative, may contact me or my physician to see if I wish to participate in other research in the future.

   YES NO

This is the end of the section about optional studies.

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's signature_____

Date of signature_____

(The following signature and date lines for the person(s) conducting the discussion may be included at the discretion of the study sponsor.)

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____