Alliance Central Protocol Operations Program Office
125 S. Wacker Dr., Suite 1600
Chicago, IL 60606
P: 773-702-9171
F: 312-345-0117

www.AllianceforClinicalTrialsinOncology.org

November 13, 2024

Dr. Nita L. Seibel, MD
Cancer Therapy Evaluation Program
9609 Medical Center Drive
NCI Shady Grove Room 5W426
Rockville, MD 20850

Re: Disapproval of Amendment #12 of Protocol #A091902: "A Multicenter Phase II Trial of Paclitaxel with and Without Nivolumab in Taxane Naïve, and Nivolumab and Cabozantinib in Taxane Pretreated Subjects with Angiosarcoma"

Dear Dr. Seibel,

We would like to thank the CTEP Reviewers for the November 07, 2024 review of the protocol and consent associated with the Alliance A091902 trial, "*A Multicenter Phase II Trial of Paclitaxel with and Without Nivolumab in Taxane Naïve, and Nivolumab and Cabozantinib in Taxane Pretreated Subjects with Angiosarcoma*." The Study Team's responses to each comment are included in bold text with references to each section of the protocol or consent that will contain the revision.

Please let us know what further information we may provide.

Sincerely,

Stephanie Berg, MD
Executive Officer
Alliance for Clinical Trials in Oncology

I. Comments Requiring a Response– Administrative & Editorial Issues:

#	Section	Comments
1.	10.2	Preparation, Storage and Stability – a possible formatting issue may have changed the degree symbol to the numeral zero (0). Please ensure the first two paragraphs read as noted below: Store intact bottles at controlled room temperature 20°C to 25°C (68°F to 77°F); temperature excursions are permitted between 15°C and 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. If a storage temperature excursion outside of 15°C and 30°C (59°F to 86°F) is identified, promptly return XL184 (Cabozantinib) to 20° to 25°C (68° to 77°F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability. **PI Response: In Section 10.2, "Preparation, Storage and Stability" have been updated to the appropriate text and formatting as noted above.**
2.	10.2	Based on new information, replace the last paragraph with the following: Refer to the drug label for expiration date. Cabozantinib must be dispensed in original bottles. **If dispensing the exact quantity of cabozantinib tablets is an institutional guideline:** • Removing the extra tablets from the original bottle is allowed, and it must be used within 30 days of the preparation date. Document the extra tablets as waste in Oral DARF. • Adding additional cabozantinib tablets into the original bottle in which the original bottle is exceeding its 30 Count bottle, is **Not Allowed**. Repackaging XL184 (Cabozantinib) for a short period of time is acceptable and limited to: • Up to 24 hours when dispensed in an open container such as a pill cup. • Up to 7 days when dispensed in a closed container (e.g., a pharmacy dispensing bottle). **PI Response: In Section 10.2 the last paragraph of "Preparation, Storage and Stability" has been replaced with the above requested text.**

Alliance Central Protocol Operations Program Office
125 S. Wacker Dr., Suite 1600
Chicago, IL 60606
P: 773-702-9171
F: 312-345-0117

www.AllianceforClinicalTrialsinOncology.org

November 07, 2024

Dr. Nita L. Seibel, MD
Cancer Therapy Evaluation Program
9609 Medical Center Drive
NCI Shady Grove Room 5W426
Rockville, MD 20850

Re: Review of Amendment #11 of Protocol #A091902: "A Multicenter Phase II Trial of Paclitaxel with and Without Nivolumab in Taxane Naïve, and Nivolumab and Cabozantinib in Taxane Pretreated Subjects with Angiosarcoma"

Dear Dr. Seibel,

We would like to thank the CTEP Reviewers for the October 16, 2023 review of the protocol and consent associated with the Alliance A091902 trial, "*A Multicenter Phase II Trial of Paclitaxel with and Without Nivolumab in Taxane Naïve, and Nivolumab and Cabozantinib in Taxane Pretreated Subjects with Angiosarcoma*." The Study Team's responses to each comment are included in bold text with references to each section of the protocol or consent that will contain the revision.

Please let us know what further information we may provide.

Sincerely,

Stephanie Berg, MD
Executive Officer
Alliance for Clinical Trials in Oncology

I. Recommendations:

<table>
<tr><th>#</th><th>Section</th><th>Comments</th></tr>
<tr><td>3.</td><td>4.1 CTEP Registration</td><td>
Please revise the following language:

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain ~~a~~ Cancer Therapy Evaluation Program (CTEP~~) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam~~ credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.
• Investigator (IVR)—MD, DO, or international equivalent;
• Non-Physician Investigator (NPIVR)—advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
• Associate Plus (AP)—clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave; acting as a primary site contact, or with consenting privileges
• Associate (A)—other clinical site staff involved in the conduct of NCI-sponsored trials; and
• Associate Basic (AB)—individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:
<table>
<tr><th>Documentation Required</th><th>IVR</th><th>NPIVR</th><th>AP</th><th>A</th><th>AB</th></tr>
<tr><td>FDA Form 1572</td><td>✓</td><td>✓</td><td></td><td></td><td></td></tr>
<tr><td>Financial Disclosure Form</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td></tr>
<tr><td>NCI Biosketch (education, training, employment, license, and certification)</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td></tr>
<tr><td>GCP training</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td></tr>
<tr><td>Agent Shipment Form (if applicable)</td><td>✓</td><td></td><td></td><td></td><td></td></tr>
<tr><td>CV (optional)</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td></tr>
</table>
In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

<u>PI Response:</u> Section 4.1 has been updated to reflect the current CTSU boilerplate language (Version 01/25/2024).
</td></tr>
<tr><td>4.</td><td>10.1.1</td><td>Agent Ordering – replace the third paragraph with:</td></tr>
</table>

#	Section	Comments
		Submit agent requests through the PMB AURORA application. Access to AURORA requires the establishment of credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems, maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time or use the dialog function in AURORA to communicate with PMB staff. Refer to the PMB's website for specific policies and guidelines related to agent management. **PI Response: In Section 10.1.1, Agent Ordering, the third paragraph has been updated according to the above requested changes.**
5.	10.1.2	Agent Inventory Records – replace the section with: The investigator, or a responsible party designated by the investigator, must maintain a complete accountability of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol. Product Quality Complaint (PQC): A product quality complaint is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a study subject. Lot or batch numbers are of high significance and need to be provided where and when possible. PQC must be reported to the PMB as soon as the PQC is identified. Report PQC to PMB at PMBAfterHours@mail.nih.gov or by using the dialog function in AURORA to communicate with PMB staff. **PI Response: In Section 10.1.2, Agent Inventory Records has been updated according to the above requested changes.**
6.	10.1.3	Investigator Brochure Availability – replace section with: The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB AURORA application. Access to AURORA requires the establishment of credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems, maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email. **PI Response: In Section 10.1.3, Investigator Brochure Availability has been updated according to the above requested changes.**
7.	10.1	Insert a new subsection: Agent Shortages Specific guidance on how to address agent shortages for patients already enrolled on a clinical study as well as how to manage potential enrollment of new patients is provided at https://ctep.cancer.gov/branches/pmb/drug_shortages.htm.

#	Section	Comments
		Treatment plan modifications being made to avoid immediate hazard to patients is permissible under the Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b)(4)(iii). In accordance with HHS regulations, local investigators must promptly inform the IRB of record of this unanticipated problem and the management plan for the trial. **PI Response: In Section 10.1.1, Agent Shortages, has been added as a new subsection according to the above requested changes.**
8.	10.1	Insert a new subsection: Material Safety Data Sheets The current versions of the material safety data sheets (MSDS or SDS) for PMB-distributed agents will be accessible to site investigators and research staff through the PMB AURORA application. Questions about MSDS access may be directed to the PMB at PMBAfterHours@mail.nih.gov or by using the dialog function in AURORA to communicate with PMB staff. **PI Response: In Section 10.1.1, Material Safety Data Sheets, has been added as a new subsection according to the above requested changes.**
9.	10.2	Replace storage with: **Storage:** Store intact bottles at controlled room temperature 20^0 C to 25^0C (68^0 F to 77^0 F); temperature excursions are permitted between 15^0 C and 30^0 C (59^0 F to 86^0 F) [see USP Controlled Room Temperature]. If a storage temperature excursion outside of 15^0 C and 30^0 C (59^0 F to 86^0 F) is identified, promptly return XL184 (Cabozantinib) to 20^0 to 25^0C (68^0 to 77^0 F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability. **PI Response: In Section 10.2, "Preparation, Storage and Stability," the first two paragraphs have been updated according to the above requested changes.**

Update #08

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE A091902

A MULTICENTER PHASE II TRIAL OF PACLITAXEL WITH AND WITHOUT NIVOLUMAB IN TAXANE NAÏVE, AND NIVOLUMAB AND CABOZANTINIB IN TAXANE PRETREATED SUBJECTS WITH ANGIOSARCOMA

[X]	**Update:**	[ ]	**Status Change:**
[X]	Editorial/Administrative changes	[ ]	Activation
[ ]	Eligibility changes	[ ]	Closure
[ ]	Therapy/Dose Modifications/Study Calendar changes	[ ]	Suspension
[ ]	Scientific/Statistical Considerations changes	[ ]	Reactivation
[ ]	Correlative Science/BioMS changes		
[X]	Informed Consent changes		
[X]	Other: Updated CAEPR for cabozantinib, updated expedited AE reporting table, and updated CTSU boilerplate language		

The changes included in this update to A091902 have been made in response to an RRA from Dr. Rabih Said (rabih.said@nih.gov). This Action Letter is posted on the A091902 study page on the CTSU website. A revised CAEPR for cabozantinib with new risks has been added to the protocol. Therefore, the model consent form has been revised to incorporate these new risks, consistent with the NCI Model Consent Template instructions. Additionally, a revised table for expedited AE reporting requirements has been added to the protocol.

No recommended IRB level of review is provided by the Alliance since the CIRB is the IRB of record for this trial. The site has 30 days after the posting of this amendment to implement it at their site.

Reconsent is required for all patients currently on active protocol treatment with cabozantinib. Please refer to the amendment application and CIRB guidelines for further instructions.

UPDATES TO THE PROTOCOL:

Title Page
Leah Norton has replaced Jordan Nemerov as the Data Manager. All contact information has been updated accordingly.

Section 4.1 (Investigator and Research Associate ~~r~~Registration with CTEP)
The section has been completely replaced with the most current CTSU boilerplate language.

Section 9.3.1 (Late Phase 2 and Phase 3 Studies)
- The title has been updated to, "Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE~~≤~~ Within 30 Days of the Last Administration of the Investigational Agent/Intervention"
- The Expedited Adverse Event Reporting Table has been updated to the most current CTEP version dated August 30, 2024.

Section 9.3.2 (Expedited AE reporting timelines defined)
- This sub-section has been completely removed as the information no longer pertains to the updated Expedited Adverse Event Reporting Table in Section 9.3.1.
- The remaining sub-section has been renumbered.

Section 9.4.1 (Comprehensive Adverse Events and Potential Risks list (CAEPR) for XL184 (Cabozantinib ~~s-malate~~, NSC 761968)
This section has been revised to include the updated cabozantinib CAEPR (Version 2.5~~-4~~, ~~December 17, 2018~~ August 29, 2024) provided by NCI CTEP. Changes from Version 2.4 to Version 2.5 include the following:
- Added New Risk:
    - Less Likely: Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)
- Rare but Serious: Endocrine disorders - Other (thyroid dysfunction)
- Deleted:
    - Also Reported on XL184 Trials but With Insufficient Evidence for Attribution: Aspiration

Section 10.1.1 (NCI Supplied Agents)
- In the third paragraph the second and third sentences have been updated to "Access to AURORA requires the establishment of credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems, ~~a CTEP Identity and Access Management (IAM) account and the~~ maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time or use the dialog function in AURORA to communicate with PMB staff."
- "Agent Shortage" and "Material Safety Data Sheets" have been added as two subsequent new subsections.

Section 10.1.2 (Agent Inventory Records)
- The first paragraph, first sentence has been updated to, "The investigator, or a responsible party designated by the investigator, must maintain a ~~careful record~~ complete accountability of the receipt, dispensing …"
- A new second paragraph regarding Product Quality Complaint (PQC) has been added.

Section 10.1.3 (Investigator Brochure Availability)
The second sentence has been updated to, "Access to AURORA requires the establishment of credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems, ~~a CTEP IAM account and the~~ maintenance of an "active" account status…"

Section 10.2 (Cabozantinib (Cabozantinib ~~s-malate~~, XL184, NSC# 761968, IND #, IND holder: DCTD, NCI)
In subsection "Preparation, Storage and Stability" the first and third paragraphs have been completely replaced to reflect CTEP requested current drug information.

Appendix II (Toxicity Algorithms)
All Version 4 CTCAE Toxicity Algorithms have been replaced with Version 5 CTCAE Toxicity Algorithms.

UPDATES TO THE MODEL CONSENT FORM:

What risks can I expect from taking part in the treatment study?

- In Drug Risks, the table under the "Possible Side Effects of Cabozantinib" heading has been updated per CAEPR Version 2.~~4~~5 with the following risk list changes:
- Added New Risk:
    - Occasional: In children or adolescents: may interfere with growth

A replacement protocol document and model consent form have been issued.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

Research Study Informed Consent Document

Study Title for Participants: Testing the Addition of Nivolumab to chemotherapy in Treatment of Soft Tissue Sarcoma

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: A Multicenter Phase II Trial of Paclitaxel With and Without Nivolumab in Taxane Naïve, and Nivolumab and Cabozantinib in Taxane Pretreated Subjects with Angiosarcoma (NCT04339738)

Overview and Key Information

This study is being conducted by the Alliance for Clinical Trials in Oncology (Alliance), a national clinical research group supported by the National Cancer Institute (NCI). The Alliance is made up of cancer doctors, health professionals, and laboratory researchers, whose goal is to develop better treatments for cancer, to prevent cancer, to reduce side effects from cancer, and to improve the quality of life of cancer patients.

What am I being asked to do?

We are asking you to take part in a research study. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer. We are asking you to take part in this research study because you have a type of cancer called angiosarcoma.

Taking part in this study is your choice.

You can choose to take part or you can choose not to take part in this study. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. You also 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 has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

Why is this study being done?

The purpose of this study is to:

1. Compare treatment with chemotherapy (paclitaxel) alone to using a combination of nivolumab plus chemotherapy (paclitaxel) treatment in patients with angiosarcoma who have not been treated with paclitaxel chemotherapy alone.
2. Evaluate the effect of nivolumab in combination with cabozantinib on angiosarcoma (cancer) in patients who have either received paclitaxel or similar chemotherapy previously, or whose cancer has grown previously while getting paclitaxel chemotherapy on this study.

The chemotherapy drugs, paclitaxel and cabozantinib, work to prevent cells from growing. Nivolumab is a drug that works through your body's immune system to help the immune system act against cancer cells. Nivolumab has been studied and found to shrink tumors in some people with cancer. Researchers hope to learn if the combination of nivolumab and chemotherapy could shrink your type of tumor, and possibly prevent it from coming back. The cabozantinib and nivolumab chemotherapy drugs are both study medications because they are FDA approved for treatment of other kinds of cancers but have not been tested in this kind of cancer, while the paclitaxel chemotherapy drug is considered non-experimental (non-study medication) because it is a standard chemotherapy used to treat this kind of cancer. This combination treatment may also cause side effects. They are described in detail in the risks sections below.

There will be 90 participants in this study.

What is the usual approach to my Angiosarcoma?

The usual approach for patients who are not in a study is treatment with surgery, radiation therapy, or chemotherapy. There are several chemotherapy drugs approved by the Food and Drug Administration (FDA) for treatment of different cancers. These are commonly used, sometimes with surgery or radiation therapy. Your cancer may not be well suited to surgery or radiation therapy, or you may have decided against these options. Your doctor can explain which treatment may be best for you. These treatments can reduce symptoms and may stop the tumor from growing for a few months or longer.

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

- You may choose to have one of the usual approaches described above. If you decide against these usual approach options, you may be missing or delaying benefit you could receive from these treatments.
- 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 to only get comfort care to help relieve your symptoms and not get treated for your cancer.

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

If you have never received "taxane" type chemotherapy before, you will be given one of two treatment: combination chemotherapy with paclitaxel and nivolumab or chemotherapy with

paclitaxel alone. You will receive either of these treatments until your cancer gets worse or the side effects become too severe, for a maximum of 2 years. The decision about which treatment you will receive is not made by you or the study team. It is made by a computer in a process called randomization. You will have a 50:50 chance to be assigned either of these two treatments.

The previously treated with "taxane" group described below closed to new patient participation on 10/28/2021:
If you have received "taxane" chemotherapy before, you will be given combination of chemotherapy with cabozantinib and nivolumab, until your cancer gets worse or the side effects become too severe, for a maximum of 2 years.

The paclitaxel and nivolumab chemotherapy medicines will be given intravenously (through the vein). Paclitaxel will be given once per week for three weeks followed by a one week break. The nivolumab will be administered once every four weeks. The cabozantinib is a pill that is taken by mouth once per day. Do not take cabozantinib with food. Do not eat for at least 2 hours before and 1 hour after taking cabozantinib. Swallow tablets whole with a full glass (8 ounces) of water. Do not crush or chew tablets.

If you are taking cabozantinib, you will be required to record when you take the study drug in a medication diary. The medication diary should be returned to your treating physician, along with any leftover pills that you did not take.

After you finish your assigned treatment, your doctor and study team will watch you for side effects. They will check you every 3 months for 3 years after treatment. This means you will keep seeing your doctor for 3 years after 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 for you to think carefully about these as you make your decision.

Risks
We want to make sure you know about a few key risks right now. We give you more information in the "What risks can I expect from taking part in this study?" section.
If you choose to take part in this study, there is a risk that the study treatments may not work for you and your angiosarcoma might get worse. If this happens the study doctor will take you off the study and discuss other treatment options with you.

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

Some of the most common side effects that the study doctors know about are:
- Diarrhea, nausea, vomiting
- Tiredness
- Weight loss, loss of appetite

- Hair loss

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

Benefits
There is some evidence in people with other types of cancer that were treated with nivolumab and chemotherapy that these drugs helped in stopping cancer cells from growing. However, we do not know if this will happen in people with your type of cancer. It is possible that the study drugs/study approach will extend your life or extend your time without disease; however, this is not guaranteed. This study will help the study doctors learn things that 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 taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It's important that you stop safely. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

Your 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.

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: You become pregnant while on the study.
- The study is stopped by The Alliance Cooperative Group / National Cancer Institute (NCI), Institutional Review Board (IRB), or Food and Drug Administration (FDA).

It is important that you understand the information in the informed consent before making your decision. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

What is the purpose of this study?

The purpose of this study is to compare chemotherapy treatment alone to using a combination of nivolumab plus chemotherapy treatment. The chemotherapy drugs, paclitaxel and cabozantinib, could work to prevent cells from growing. Nivolumab is a drug that works through your body's immune system to help the immune system act against cancer cells. There will be 90 people participating in this study.

What are the study groups?

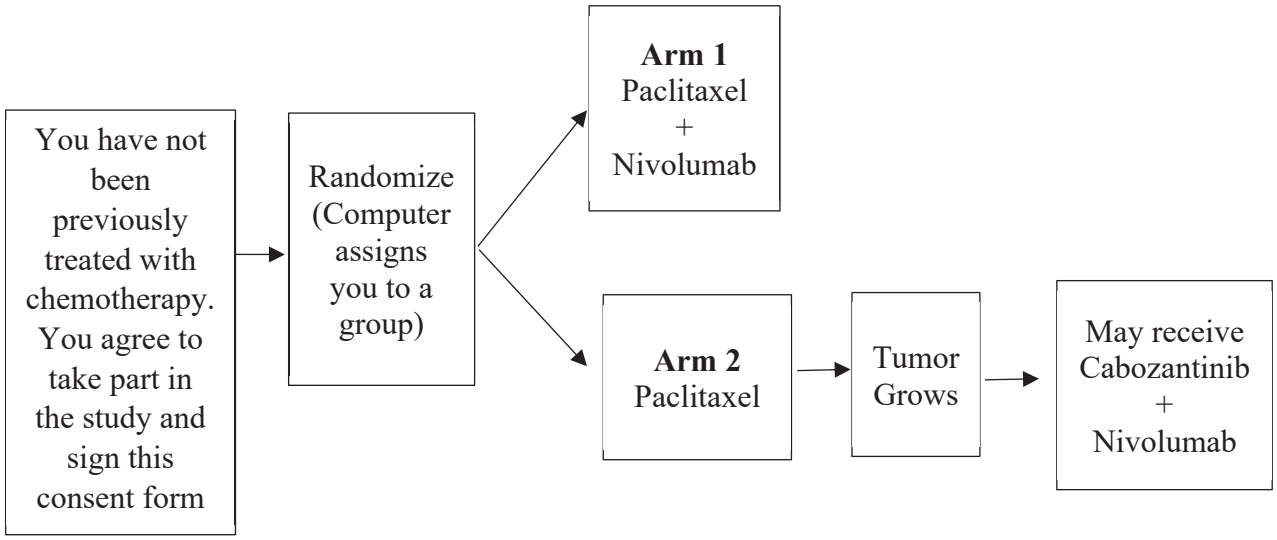
This study has 2 study groups.

Group 1: Participants in this group will be patients that have not received prior chemotherapy treatment with paclitaxel or similar "taxane" chemotherapy. In this group, participants will be assigned to one of two arms. In Arm 1, participants will receive combination of paclitaxel and nivolumab. Participants assigned to Arm 2, will only receive paclitaxel.

We will use a computer to assign you to one of the study arms. This process is called "randomization." It means that your doctor will not choose and you cannot choose which study arm you are in. You will be put into a study arm by chance. You will have a 50:50 chance of being in Arm 1 or Arm 2.

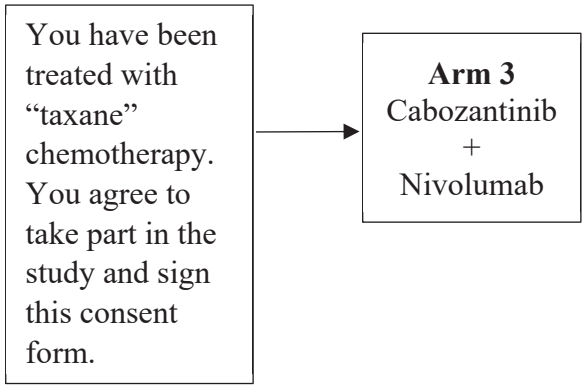
If you are assigned to Arm 2 and your cancer gets worse you will have the choice to receive cabozantinib and nivolumab if your doctor feels it would benefit you.

Another way to find out what will happen to you during this study if you are in **Group 1** is to read the chart below. Start reading at the left side and read across to the right.



The group described below closed to new patient participation on 10/28/2021:
Group 2: Participants in this group will either be patients that have received prior chemotherapy treatment with paclitaxel or a similar "taxane" chemotherapy or participants who progress while in Group 1. In this group, participants will receive a combination of cabozantinib and nivolumab.

Another way to find out what will happen to you during this study if you are in Group 2 is to read the chart below. Start reading at the left side and read across to the right.



What exams, tests, and procedures are involved in this study?

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.

Some exams, tests, and procedures are a necessary part of the research study, but would not be included in usual care. Listed below are procedures that will be done for research purposes only.

<u>During the Study:</u>

- Review of Medication Diary (if taking cabozantinib)

Questionnaires

Electronic surveys: For this study, you will be asked to complete the questionnaires on your personal smartphone or electronic device, which can be used to enter your answers to the questions. If you need help installing and/or using the questionnaire application (or "app") on your phone or tablet, ask for help at your study site. Someone may help you enter your answers in the device if you need.

The use of your own electronic device on a cellular network may result in a small cost to your data plan. You will not be reimbursed for any costs to your data plan. Regardless of the device you use, your answers and personal information will not be stored on the device.

Your survey answers will be sent to the research database and will be kept private as described in the section below called, "Who will see my medical information?" Your e-mail address will only be used for this survey and will not be used for mail or marketing purposes. The Alliance will not keep your email address.

Paper Surveys: If using your phone or a tablet is not possible or if you prefer to complete the questionnaires on paper, a paper survey will be provided.

In addition to your doctor's usual safety review, you will be asked to complete two questionnaires electronically or on paper as stated above. The questionnaires you will be asked to

fill out are questions about your physical and emotional well-being. Researchers will use this information to learn more about how you feel during cancer treatment and what the effect of the treatment may be.

You will be asked to complete questionnaires at the following times:
- After registration, and within 7 days prior to the start of treatment
- Day 15 of Cycle 1 of your treatment
- Day 1 and 15 of Cycle 2 of your treatment
- During your clinical visits on day 1 of each cycle (starting with cycle 3 of your treatment)

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

General Risks

If you choose to take part in this study, there is a risk that the study drugs may not be as good as the usual approach for your angiosarcoma at managing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office than usual
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The medications used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use during the study and for 5 months after you have completed the study.

This study will use a sample of your tissue. Generally, your hospital will keep some of your tissue. This tissue may be needed to guide your treatment decisions in the future. Because this study will need to use some of this tissue, there is a small risk that it could be used up.

Blood Collections Risks

Blood collection is usually a very low risk procedure. There is a small risk of bleeding, bruising, infection, inflammation, blood clot or discomfort at the site of the blood collection. Attention will be taken to apply pressure following the procedure to reduce bleeding. You may feel dizzy or faint when blood is being drawn. We will ask you to lie down for a few minutes until any dizziness passes.

Side Effect Risks

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 test your blood and let you know if changes occur that may affect your health.

There is also a risk that you could have other side effects from the study drugs/study approach.

Here are important things to know about side effects:

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

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

This study is looking at a combination of the usual drugs used to treat this type of cancer plus a study drug. This different combination of drugs may increase your side effects or may cause new side effects.

Drug Risks

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

Possible side effects of Paclitaxel

COMMON, SOME MAY BE SERIOUS In 100 people receiving Paclitaxel, more than 20 and up to 100 may have:
• Anemia which may cause tiredness, or may require blood transfusions • Infection, especially when white blood cell count is low • Diarrhea, nausea, vomiting • Sores in mouth which may cause difficulty swallowing • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Bruising, bleeding • Pain • Muscle weakness • Numbness, tingling or pain of the arms and legs • Hair loss

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Paclitaxel, from 4 to 20 may have:
• Abnormal heartbeat • Damage to the lungs which may cause shortness of breath • Blood clot which may cause swelling, pain, shortness of breath

RARE, AND SERIOUS In 100 people receiving Paclitaxel, 3 or fewer may have:
• Heart attack or heart failure which may cause shortness of breath, swelling of ankles, and tiredness • A tear or a hole in the stomach which may cause belly pain or that may require surgery • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body

Possible side effects of cabozantinib

COMMON, SOME MAY BE SERIOUS In 100 people receiving XL184 (cabozantinib), more than 20 and up to 100 may have:
• Diarrhea, nausea, vomiting • Tiredness • Weight loss, loss of appetite • Changes in taste • Redness, pain or peeling of palms and soles • High blood pressure which may cause headaches, dizziness, blurred vision

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving XL184 (cabozantinib), from 4 to 20 may have:

- Anemia which may require blood transfusion
- Pain
- Constipation, heartburn
- Dry mouth, skin
- Sores in the mouth which may cause difficulty swallowing
- Swelling of arms, legs
- Infection
- Bruising, bleeding
- Dehydration
- Muscle weakness
- In children or adolescents: may interfere with growth
- Dizziness, headache
- Cough, shortness of breath
- Internal bleeding which may cause black tarry stool, blood in vomit, coughing up blood, or blood in urine
- Bleeding from multiple sites including the nose
- Changes in voice
- Hair loss, rash
- Change in hair color
- Blood clot which may cause swelling, pain, shortness of breath

RARE, AND SERIOUS

In 100 people receiving XL184 (cabozantinib), 3 or fewer may have:

- A tear or hole in internal organs that may require surgery
- Non-healing surgical site
- Damage to the jawbone which may cause loss of teeth
- Bleeding in the brain which may cause confusion
- Stroke which may cause paralysis, weakness
- Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)
- Lung collapse

Possible side effects of nivolumab

Special precautions

Side effects of Nivolumab may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when Nivolumab is used in combination with ipilimumab. **Call or see your healthcare provider right away if you develop any problems listed below or the symptoms get worse.**

COMMON, SOME MAY BE SERIOUS

In 100 people receiving Nivolumab, more than 20 and up to 100 may have:

- Tiredness

Table Version Date 06/10/2023

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Nivolumab, from 4 to 20 may have:
• Anemia which may require blood transfusion • Swelling and redness of the eye • Pain • Diarrhea, nausea • Dry mouth • Fever • Swelling and redness at the site of the medication injection • Bruising, bleeding • Pain or swelling of the joints • Loss of appetite • Reaction during or following a drug infusion which may cause fever, chills, rash Nivolumab may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to: • Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath. • Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness. • Skin: itching; rash, blisters including inside the mouth; loss of skin pigment • Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly • Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior; decreased sex drive; weight loss or weight gain; excessive thirst or urination; dizziness or fainting.

RARE, AND SERIOUS In 100 people receiving Nivolumab, 3 or fewer may have:
• Swelling of arms and legs which may cause a feeling of heaviness and tightness • Dry eyes • Sores in the mouth which may cause difficulty swallowing • A syndrome starting with flu-like symptoms and followed by swelling, tenderness which may cause blurred vision, ringing in the ears, changes in hair or hair loss • Swelling of the bowels Nivolumab may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to: • Visual disturbances which may cause double vision, blurred vision, or loss of vision with a chance of blindness • A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma • Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling. • Heart problems including swelling and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body. • Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine • Swelling of the brain (meningitis/encephalitis) which may cause: headache, stiff neck confusion, sleepiness, seizures or injury to the brain which may cause headache, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome) • Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut damage), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received Nivolumab therapy, since the risk and severity of transplant-associated complications may be increased.

Additional Drug Risks

The study drug could interact with other drugs and food. For your safety, you must tell the study doctor or nurse about all the prescribed medical foods and drugs, herbal products, over-the-counter (OTC) drugs, vitamins, natural remedies, and alcohol that you are taking before you start the study and before starting to take any of these products while you are on the study. You should not consume grapefruits, grapefruit juice, Seville oranges, or St. John's wort while on this study. Taking or eating these items can raise cabozantinib levels to unsafe levels in your body. Your study doctor will give you patient clinical trial wallet card. Share this information with your family members, caregivers, other health care providers, and pharmacists.

Rarely, there are problems getting enough supplies of the study drug. If that happens, your doctor will talk with you about your options.

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 your doctor about:
    - all medications and supplements you are taking
    - any side effects
    - any doctors' visits or hospital stays outside of this study
    - if you have been or are currently in another research study.
- Write down in your medication diary when you take the study drug cabozantinib at home (if applicable).

For women: Do not get pregnant or breastfeed while taking part in this study. **For men:** Do not father a baby while taking part in this study. **For all:** Tell your study doctor right away if you think that you or your partner have become pregnant during the study or within 5 months after your last dose of study drug. It is recommended that you do not become pregnant, breast fed, or father a child for at least 5 months after stopping treatment. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

What are the costs of taking part in this study?

You and/or your insurance plan will need to pay for the costs of medical care you get as part of the study, just as you would if you were getting the usual care for your cancer. This includes:

- the costs of tests, exams, procedures, and drugs that you get during the study to monitor your safety, and prevent and treat side effects.
- the costs of getting the nivolumab, paclitaxel, and cabozantinib ready and giving it to you.
- your insurance co-pays and deductibles.

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

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

The NCI will supply nivolumab and cabozantinib at no charge while you take part in this study. Even though it probably won't happen, it is possible that the manufacturer may not continue to provide these medications to the NCI for some reason. If there is no treatment available at all, the study would close.

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

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

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at or receive copies of some of the information in your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- The pharmaceutical companies providing the study drugs, Bristol Myers Squibb (providing nivolumab) and Exelixis (providing cabozantinib).
- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study
- The FDA and the groups it works with to review research.
- The NCI and the groups it works with to review research.
- The NCI's National Clinical Trials Network and the groups it works with to conduct research.

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

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.

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, and email address if appropriate*).

For questions about your rights while in this study, call the (*insert name of organization or center*) Institutional Review Board at (*insert telephone number*).

Optional studies that 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. They are separate from the main study described above. These optional studies will not benefit your health. The researchers leading these optional studies hope the results will help other people with cancer in the future. The results will help other people with cancer in the future. The results will not be added to your medical records and you and your study doctor will not know the results.

Taking part in these optional studies is your choice. You can still take part in the main study even if you say "no" to any or all of these studies. There is no penalty for saying "no." You and your insurance company will not be billed for these optional studies. If you sign up for, but cannot complete any of these optional studies for any reason, you can still take part in the main study.

Optional sample collections for known laboratory studies and/or storage for possible future studies

Researchers are trying to learn more about cancer and other health problems using blood and tissue samples from people who take part in clinical trials. By studying these samples, researchers hope to find new ways to prevent, detect, treat, or cure diseases.

Some of these studies may be about how genes affect health and disease. Other studies may look at how genes affect a person's response to treatment. Genes carry information about traits that are found in you and your family. Examples of traits are the color of your eyes, having curly or straight hair, and certain health conditions that are passed down in families. Some of the studies may lead to new products, such as drugs or tests for diseases.

Unknown future studies

If you choose to take part in this optional study, and tissue samples from previous biopsies will be collected and stored. Storing samples for future studies is called "biobanking." The biobank is being run by the Alliance for Clinical Trials in Oncology and is supported by the NCI. This is a publicly funded study. Samples from publicly funded studies are required to be shared as broadly as possible. However, we will protect your privacy. The goal of this is to make more research possible that may improve people's health.

The biobank is a public research resource. It has controlled access. This means that researchers who want to get samples and data from it must submit a specific research request. The request identifies who they are and what their planned research project is. Before getting the samples and data, the researchers must agree to keep the data private, only use it for their planned research project, and never use it to try to identify you.

We don't know what research may be done in the future using your blood samples. This means that:

- You will not be asked if you agree to take part in the future research studies.
- You and your study doctor will not be told when or what type of research will be done.
- Future research studies may include sequencing of all or part of your DNA called genomic sequencing. All your genetic information makes up your genome. Genomic sequencing is a test that records all or part of the pieces of DNA that are in your genes, piece by piece. This is usually done to look for changes in your genome that may cause health problems.
- You will not get reports or other information about any research that is done using your samples.

Unknown future research studies may include sequencing of all or part of your DNA. This is called genomic sequencing. Sequencing allows researchers to identify your genetic code. Changes in your genetic code may be passed down through your family. For example, these

genetic changes may be passed down to your children in the same way that eye and hair color are passed down. These are called germline changes.

What is involved in this optional sample collection?

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

1. About 4 tablespoons of blood will be collected from a vein in your arm after you register to the study, Cycle 4 and when your cancer gets worse.
2. A sample from the tissue that was collected when your cancer was diagnosed will be sent to the biobank.
3. **If you have cutaneous angiosarcoma:** You have also been asked to undergo two new skin biopsies at the time you join this study, and again around Cycle 4 (or your first study scan) just for this study to submit more cancer tissue to the biobank. You may opt not to participate in this portion, but still opt to allow your blood and sample of tissue previously collected to be sent to the biobank.
4. Your sample will be stored in the biobank. There is no limit on the length of time we will keep your samples and research information. The samples will be kept until they are used for research or destroyed.
5. Researchers can only get samples from the biobank after their research has been approved by experts. Researchers will not be given your name or contact information.
6. Some of your genetic and health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

What are the risks in this optional sample collection?

- The most common risks related to drawing blood from your arm are brief pain and maybe a bruise.
- **If you have cutaneous angiosarcoma:** Biopsy risk. You will be asked to consent to undergo two skin biopsies for this study. Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, bruising, and pain at the biopsy site. Pain can be treated with regular pain medications. Rarely, an infection can occur. You may sign a separate consent form for the study biopsy that describes the risks in more detail.
- Generally, hospitals will keep some of your tissue. This tissue may be used to help treat your cancer in the future. There is a small risk that when this tissue sample is submitted to the biobank for this optional sample collection, your tissue could be used up.
- Your medical and genetic information is unique to you. There is a risk that someone outside of the research study could get access to your study records or trace information in a database back to you. They could use that information in a way that could harm you. Researchers believe the chance that someone could access and misuse your information is very small. However, the risk may increase in the future as people find new ways of tracing information.
- In some cases, this information could be used to make it harder for you to get or keep a job and get or keep health insurance. There are laws against the misuse of genetic information, but they may not give full protection. For more information about the laws that protect you, ask your study doctor or visit: https://www.genome.gov/10002328/

How will information about me be kept private?

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

1. They will remove identifiers, such as your initials, from your sample and information. They will replace them with a code number. There will be a master list linking the code numbers to names, but they will keep it separate from the samples and information.
2. Researchers who study your sample and information will not know who you are. They also must agree that they will not try to find out who you are.
3. Your personal information will not be given to anyone unless it is required by law.
4. If research results are published, your name and other personal information will not be used.

What are the benefits to taking part in this optional sample collection?

You will not benefit from taking part.

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 to this optional sample collection?

There are no costs to you or your insurance. You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What if I change my mind about this optional sample collection?

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 biobank know. Then, any sample that remains in the biobank will be destroyed or returned to your study doctor. This will not apply to any samples or related health information that have already been given to or used by researchers.

What if I have questions about this optional sample collection?

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 below to show if you would or would not like to take part in each optional study:

Samples for unknown future studies:

I agree that my samples (blood and existing tissue from my cancer diagnoses) and related health information may be kept in a biobank for use in future health research.

YES NO

For Cutaneous Patients Only
I agree to undergo two new skin biopsies: one when I join this study, second when around Cycle 4 (or my first study scan, whichever comes first). I agree those biopsy tissues and related health information may be kept in a biobank for use in future health research.

YES NO

Contact for Future Research

I agree that my study doctor, or someone on the study team, may contact me or my doctor 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 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 and dated copy of this form. I agree to take part in the main study. I also agree to take part in any additional studies where I circled "yes".

Participant's signature

Date of signature

Signature of person(s) conducting the informed consent discussion

Date of signature