APPROVAL WITH MODIFICATIONS

DATE:	1 Nov 2024
TO:	Ekaterina Galanzha, PhD
PROTOCOL:	CytoAstra, LLC, In vivo liquid biopsy for early detection of metastatic melanoma (Pro00075507)
APPROVAL DATE:	29 Oct 2024

IRB APPROVED:

Documentation:	• Protocol (Not Dated)
Consent Form(s):	• Main Informed Consent Form (Advarra IRB Approved Version 29 Oct 2024, Revised 29 Oct 2024)

The IRB has reviewed the above referenced documentation submitted on your behalf. The IRB granted approval with the modifications listed below:

- **Modifications to the Informed Consent Form template**

The Consent Form(s) referenced above are now available on your Advarra CIRBI Platform workspace. **The IRB determined new subjects need to sign the above referenced Consent Form(s).**

Audio/visual recruitment or subject material approved in script format only must be submitted in final format for the IRB to review what potential subjects will see or hear. The IRB does not review the content found in embedded links or QR codes, therefore this content must be submitted for review and approval separately, prior to use.

If you wish to appeal the IRB's determinations and/or imposed modifications, please submit supporting documentation to address the IRB's concerns by creating an Appeal Modification in CIRBI.

Compliance Statement/REB Attestation (Applicable for research conducted in Canada):

The IRB attests that this submission has been approved by an IRB whose membership complies with the requirements defined in Health Canada regulations, ICH GCP guidelines, FDA regulations at 21 CFR part 56, and HHS regulations at 45 CFR part 46. The IRB carries out its functions in accordance with FDA regulations at 21 CFR parts 50, 56, 312, and 812; HHS regulations at 45 CFR part 46, subparts A-E; good clinical practices; Health Canada regulations; and the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, as appropriate to the research.

Advarra IRB is registered with OHRP and FDA under IRB#00000971.

Please review the IRB Handbook located in the "Reference Materials" section of the Advarra CIRBI™ Platform (www.cirbi.net). A copy of the most recent IRB roster is also available.

Thank you for continuing to use Advarra IRB to provide oversight for your research project.

Sincerely,

Luke Gelinas, PhD
Executive Board Chair

Informed Consent form for Subject and Authorization to Use and Disclose Personal Health Information

Sponsor / Study Title:	**CytoAstra LLC / "In vivo liquid biopsy for early detection of metastatic melanoma"**
Principal Investigator: (Study Doctor)	**Ekaterina Galanzha, PhD**
Telephone:	**501-940-6155 (24-Hour)**
Address:	**CytoAstra, LLC 11912 Kanis Road Suite F6 Little Rock, AR 72211**

This Informed Consent Form is for men and women who we are invited to participate in research on early diagnosis of melanoma progression. Your study doctor will explain the clinical study to you. Clinical studies include only people who choose to take part in the study. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. The device that will be used in this study is not cleared by the United States Food and Drug Administration (FDA) for general public use.

Financial Disclosure: An investigator on this study owns the patent to the study device. As a result, the investigator may benefit financially from a successful study. Additional steps have been taken to manage the potential conflict of interest that this financial arrangement may. Please speak with your study doctor if you have questions about this.

You will be given a copy of the full Informed Consent Form.

Key Information

We are asking if you want to volunteer for a research study. The purpose of this study is to test if the Cytophone study device can be used to identify melanoma cells in blood that can potentially initiate metastases, the secondary tumors. Our newly developed clinical Cytophone study device will analyze your blood using sound and light to determine if your blood has melanoma cells and to count these cells. The diagnostic study procedure is non-invasive. It means that there are no incisions, no injections, no blood draws, no radiation, and no chemotherapy. To link the results gathered during previous studies of our Cytophone study device, we will also ask you to provide a 25-mL (about 5 teaspoons) blood sample. By doing this study, we hope to diagnose the early spreading of melanoma cells and find out a link between early melanoma progression and melanoma cells in blood with a goal to develop a new diagnostic test to improve survival. This study device has not been cleared by the United States Food and Drug Administration (FDA) and

is, therefore, considered an investigational device. You will not receive the results of the Cytophone device in this research.

It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at clinic(s) will continue and nothing will change. If you choose not to participate in this research project, you will be offered the treatment that is routinely offered in this clinic/hospital for melanoma. You may change your mind any time and stop participating even if you agreed earlier.

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study such as:

- Whom to contact in the case of a research-related injury or illness;
- Payment or compensation for being in the study, if any;
- Your responsibilities as a research participant;
- Eligibility to participate in the study;
- The Study Doctor's or study site's decision to withdraw you from participation;
- Results of tests and/or procedures;

Please contact the Study Doctor at the telephone number listed on the first page of this consent document.

If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, contact:

- By **mail**:
  Study Subject Adviser
  Advarra IRB
  6100 Merriweather Dr., Suite 600
  Columbia, MD 21044
- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00075507.

How many people will be studied?

We estimate that 180 participants will be enrolled in this study: 30 healthy participants and 150 participants with diagnosed melanoma at any stage.

Healthy participants aged 18–80 years must be free of current or previous malignancies, as deemed by the study doctor, and must be able to provide informed consent and sit for up to 60 minutes.

Participants with melanoma aged 18–80 years must have histological documented diagnosis of melanoma and must be able to provide informed consent and sit for up to 60 minutes.

All participants must NOT have:

- Clinically relevant cardiovascular (heart), hepatic (liver), neurological (e.g., evidence of organic brain syndrome), endocrine (hormonal), or other major systemic disease making the implementation of the study difficult or putting the participant at risk
- Persistent significant or severe infection, either acute or chronic
- Any known history of severe preexisting constipation

Participants should not be or become pregnant or breast-feeding or plan to become pregnant while on this research study. Women of childbearing potential not protected by effective contraceptive method of birth control and/or who are unwilling or unable to be tested for pregnancy are not eligible to participate in the study.

Please inform the study staff if you have experienced photo-toxicity or have taken medications which cause photosensitization.

What happens if I say "Yes, I want to be in this research"?

You will be tested in an outpatient setting.

Before you begin the study…

The following tests and information will be collected to determine if you qualify to take part in this study:

- Demographics (age, sex, race)
- Melanoma disease staging
- Medical History
- Urine pregnancy test if you are able to have children

You will be also asked to read and sign this consent document. The first Cytophone study procedure must be conducted within 90 days of consent. Participants who do not have the study procedure within 90 days will be removed from the study and must be re-consented for future participation.

During the study:

If you are a healthy participant (i.e., no melanoma), you will receive one diagnostic study procedure with Cytophone. The detection will be done by examination of your hand and/or wrist, and/or forearm. At the beginning, for approximately a few minutes, the study doctor will adjust the position of the laser beam on the blood vessel. The study doctor will use a near-infrared viewer and skin marker to mark the vessel position. Optical or ultrasound imaging may be used to estimate the vessels' diameter. Then, water or ultrasound gel will be applied between the study device and skin surface to ensure a good reading. The study device position will be

adjusted if necessary with a customized three-dimensional stage to obtain maximum signals from the vessel. The real-time detection will be conducted for about 30 minutes and up to one hour if needed.

If you are a melanoma participant, you will receive four Cytophone study procedures:

- 1st study procedure after signing Consent form
- 2nd study procedure in about 3 months after 1st study procedure
- 3rd study procedure in about 3 months after 2nd study procedure
- 4th study procedure in about 3 months after 3rd study procedure

Prior to the first Cytophone study procedure, you will need to have a routine blood test by taking blood sample from your arm. In total, we will take 25 mL (about 5 teaspoons) of blood. At the end of the research any left-over blood sample will be destroyed.

The study staff will be looking after you and the other participants very carefully during the study. If there is anything you are concerned about or that is bothering you about the study, please talk to our study staff or your study doctor.

We will also observe your medical records for one year after the last study procedure. NO additional visit is needed.

Are there benefits to taking part in the study?

There will not be any benefit as a result of your participation in this study but your participation is likely to help us develop new advanced diagnostic methods that would benefit other melanoma patients in the future.

How long will I be in the study?

If you are a healthy participant, you will have one (1) visit, about 90 minutes in length, that will involve checking eligibility, signing a Consent Form, measuring vital signs (temperature, pulse, blood pressure), pregnancy test if you are a female of childbearing potential, and PAFC test including ultrasound imaging, adjustment laser beam on the vessel, and 30-minute PAFC monitoring.

If you are a participant with melanoma, you will have four (4) visits over about 9 months. The first visit will take about 90 minutes and involve checking eligibility, signing a Consent Form, measuring vital signs (temperature, pulse, blood pressure), pregnancy test if you are a female of childbearing potential, blood draw, and PAFC test including ultrasound imaging, adjustment laser beam on the vessel, and 30-minute PAFC monitoring.

Visits 2, 3 and 4 will take about 60 minutes each and involve measuring vital signs (temperature, pulse, blood pressure), pregnancy test if you are a female of childbearing potential, and PAFC test including ultrasound imaging, adjustment laser beam on the vessel, and 30-minute PAFC monitoring.

After you are finished with the study procedures the study doctor will follow-up your medical records for about 12 months.

Can I stop being in the study?

YES.

Participation in research study is completely voluntary. You do not have to take part in this research study if you do not wish to do so. You can decide to stop at any time. If you are thinking about stopping or decide to stop, tell your study doctor. Leaving the study will not affect your medical care. All of your rights will still be respected.

On other hand, the study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

Is there any way being in this study could be bad for me?

You may have side effects while on the study. Risks and side effects related to the Cytophone study procedure are expected to be no greater than what might be encountered in daily life or during routine physical examinations. However, the Cytophone study device is new for humans and may include risks that are currently unforeseeable. The possible risks and side effects of Cytophone study procedure include:

Likely:

- Local soft warming sensation
- Local redness
- Local tingling sensation
- Experiencing discomfort from sitting for the time required to complete the study procedure

Less Likely:

- Needle like pain (tingling sensation)
- Twinges (a sudden, sharp localized pain)
- Burning of the skin
- Itching of the hand
- Feeling warm all over your body

Rare:

- Thermal injury (burn) to the skin exposed to the laser
- Laser-induced eye injury if you accidentally do not put on the laser safety goggles

Many side effects go away soon after the Cytophone study procedure is over. In rare cases, side effects can be long lasting. To minimize any risks, careful monitoring of skin changes will be provided during the study procedure and local treatment will be provided as needed including ice pack, skin lotion or topical steroid. Your study staff may give you medicines to help lessen side effects. Eye protection will be required for anyone in the room during the operation of the lasers.

The blood draw procedure is routine; its risks are considered as minimal and may include pain and bruising at the site from where blood was taken and rarely infection. Experienced study staff will collect the blood using approved techniques. Pressure and dressings will be used to minimize pain, bruising and infection.

As with any research study, a possible breach of participant confidentiality is a risk. To minimize this risk, participants will be assigned a study number unrelated to their medical record number or other personally identifying information. Data from this study will be only associated with the participant's number.

In addition to these risks, this research study may hurt you in ways that are unknown. If you see/feel any side effect while taking part in the study let the study doctor know right away by calling the phone number listed on the first page of this consent form.

What are the alternatives to participation?
This research study is for research purposes only. The only alternative is to not participate in this study.

Will I receive any type on compensation?
There could be compensation for participating in this study. The compensation would be paid on a per visit basis, and only paid, once each visit is completed for the study. The amount of compensation would be $50 per completed visit.

Will it cost me anything to participate in this research study?
Taking part in this research study will not lead to any costs to you.

Will my medical information be kept private?
If you decide to be in this study, the study doctor and study staff will use and share health data about you to conduct the study. Health data may include:

- Your name
- Address
- Phone number
- Date of birth
- Medical history
- Information from your study visits, including all test results

Health data may come from your study records or from existing records kept by your doctor or other health care workers.

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. We may share some of

this information with the following offices or entities: the Institutional Review Board Office, the US Office of Research Integrity; the US Office for Human Research Protections; the US Food and Drug Administration. Any research information shared with outside entities will not contain your name, address, telephone or social security number or any other personal identifier unless disclosure of the identifier is necessary for review by such parties or is required by law.

The following entities may receive your health information:

- The site research center and site contractors who are working on the study
- Study monitors and auditors who make sure that the study is being done properly
- CytoAstra LLC, who is sponsoring the study, and that company's contractors and partners
- Government agencies and public health authorities, such as the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS)
- Registries or other research-related databases, to which identifiable information will be directly disclosed by the researcher or research staff associated with this research study
- Representatives of Advarra IRB (an Institutional Review Board that reviews this study)

Your health data will be used to conduct and oversee the research, including for instance:

- To see if the study device works and is safe
- To compare the study device to other devices
- For other research activities related to the study device

The unidentified results of this study may also be used for teaching, publications, or for presentation at scientific meetings. If information from this study is published or presented, your name and other personal information will not be used. **By signing this form, you authorize the use of your observations, and findings found during the course of this study for education, publication and/or presentation.**

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.

Unless you revoke your authorization, it will expire in 5 years after the study ends. Although you may revoke consent to participation in this research at any time and in any format, you must revoke authorization for use or disclosure of your health information in writing.

To revoke your authorization, write to the study doctor at the address listed on the first page of this consent form. If you do this, you will not be able to stay in this study. No new health data that identifies you will be gathered after your written request is received. However, health data about you that has already been gathered may still be used and given to others as described in this form.

Once your health data has been shared with authorized users, it may no longer be protected by federal privacy law and could possibly be used or disclosed in ways other than those listed here.

If you decide not to sign this form, you will not be able to take part in the study.

Statement of Authorization

I have read this form and its contents were explained. My questions have been answered. I voluntarily agree to allow study staff to collect, use and share my health data as specified in this form. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing this form:

_____ _____

Your name (please print) Your signature

_____

Date

Use of Genetic Material. After the blood draws, your blood testing may include a genetic component (e.g., RT-PCR (reverse transcription-polymerase chain reaction) and ctDNA, etc.) that will be conducted according to a federal law, called the Genetic Information Nondiscrimination Act (GINA). The results of genetic blood test will be used only for research

purposes, and will not provide us with any genetic information other than that relating to the presence of melanoma-related genes in your blood sample. In addition, the test results will not be linked to any information that would allow them to be identified as belonging to you. Only study staff involved with this research study will have access to these test results. Therefore, this RT-PCR test is not expected to impact your medical care or place you at risk in any way.

Genetic Information Nondiscrimination Act (GINA)

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans and most employers to discriminate against you based on your genetic information.

This law generally will protect you in the following ways:

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

All health insurance companies and group health plans and all employers with 15 or more people must follow this law.

Be aware that this Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance or long-term care insurance.

What else do I need to know?

Injury compensation. If you have an injury or illness from the study device or the study procedures, the reasonable medical expenses required to treat such injury or illness may be paid for by the study sponsor. The coverage for such injury or illness is only available if the study doctor and study sponsor have decided that the injury/illness is directly related to the study device, or study procedures and is not the result of a pre-existing condition or the normal progression of your disease, or because you have not followed the directions of the study doctor.

In the event you are hurt by being in this study research, treatment will be available. This treatment may include: first aid, emergency treatment, and/or follow-up care. This treatment may be billed to you or your insurance company in the normal manner. No special arrangements have been made for payment to you for additional treatment resulting solely because of injuries from your participation in this study.

No payment will be made by CytoAstra for lost wages, expenses, compensation for pain and suffering, discomfort or disability. There are no plans for CytoAstra to be responsible for any injury or illness to you as a result of your being in this study.

To pay medical expenses, the sponsor will need to know some information about you like your name, date of birth, and Medicare Beneficiary Identifier (MBI). This is because the sponsor has to check to see if you receive Medicare and if you do, report the payment it makes to Medicare.

Optional Elements (Photographs)

The research study may take photographs. Your image(s) from this study may be viewable indefinitely in electronic media (such as the internet) and in print media (such as books and journals). There will be no identifying facial pictures taken.

This research activity is optional, meaning that you do not have to agree to it in order to participate in the research study. Please indicate your willingness to participate in this optional activity by placing your initials.

I agree	**I disagree**
_____	_____

Consent

I have read the information in this consent form, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I voluntarily agree to participate in this study:

_____ _____

Your name
(please print)

Your signature

_____

Date

_____ _____

Printed name (person obtaining consent)

Signature (person obtaining consent)

_____

Date

Note: A copy of the signed, dated consent form must be kept by the Study Doctor and a copy must be given to the study participant.