Appendix B

A Phase I Study of Intra-arterial Onyx-015 for Squamous Cell Cancer of the Head and Neck

RESEARCH CONSENT FORM
[Name of Medical Institution] [Patient ID Number]
Protocol Title: A Phase I Study of Intra-arterial Onyx-015 for Squamous Cell Cancer of the Head and Neck
Principal/Overall Investigator: [Name]
Site-Responsible Investigator(s)/Institution: [Name(s)/Institution]
Co-investigator(s)/Study Staff: [Name(s)]
Description of Subject Population: Adult
For Patients Receiving Onyx 015 Plus PF

INTRODUCTION

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to participate. Please take your time to make your decision, and discuss it with your friends and family.

You are being asked to take part in this study because you have squamous cell cancer of the head and neck that has grown or come back after the use of standard drugs and therapies used to treat your disease (such as chemotherapy, surgery, or radiation).

Subject Population: Adult patients with Squamous Cell Carcinoma of the Head and Neck Receiving Onyx-15 Plus PF
IRB Protocol Number: ________ Sponsor Protocol Number: ________
Consent Form Approval Date: ________ Amendment Number Approved: ________
IRB Expiration Date: ________ Amendment Approval Date: ________

With this treatment you will be receiving a genetically modified virus, related to the common cold virus, called Onyx-015. Onyx-015 has been designed to enter your tumor cells and cause the cells to die. Onyx-015 should only work in cells that have mutated (your cancer cells) because it does not have the right structure to work in healthy cells. Onyx-015 has undergone testing for humans in both head and neck cancer and ovarian cancer.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find the highest dose of Onyx-015 that can be given into an artery feeding your head and neck tumor without causing severe side effects, then to test the safety and usefulness of PF (cisplatin and 5-fluorouracil, types of chemotherapy) when given with Onyx-015, and to see what effects (good and bad) these treatments have on you and your head and neck cancer when combined.

This research is being done to learn more about the use of Onyx-015 in the treatment of your type of cancer.
HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?
About 24–35 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?
[Figure B.1 is a flow chart that depicts the course of the study.—eds.]

*Medical tests:* If you take part in this study, you will have the following tests and procedures:
Medical tests that are part of regular cancer care and may be done even if you do not join the study:

- A single injection of Onyx-015 the first day of treatment, followed by 1 course of PF chemotherapy on Days 1 through 4 of treatment
- Blood tests on Day 1 or 2.
- Biopsy of your tumor and normal tissue on Day 4.

3 to 4 weeks after Day 1

- **If your tumor is not growing,** you will receive a second injection of Onyx-015 and a second course of PF chemotherapy.
- **If your tumor grows to greater than 25% larger,** you will be taken off Protocol and move on to the Best Alternative therapy available.

6 to 8 weeks after Day 1

- **If your tumor is still not growing,** you will continue to receive PF chemotherapy every 3–4 weeks until your doctor thinks it is no longer helping you. We will want to see you every 4 weeks for up to 4 months if your tumor continues to not grow.
- **If your tumor grows to greater than 25% larger,** you will be taken off Protocol and move on to the Best Alternative therapy available.

*Figure B.1*
• Complete physical exam
• Chest x-ray
• CT or MRI scan (uses sophisticated computers and magnetic fields or radio waves to take pictures of your body)
• Blood tests

Many of the tests which are part of regular cancer care are done more frequently because you are on this study.

**Standard procedures being done because you are in this study:**
• Porta-cath (a device placed under the skin of your chest, giving access to a major vein in your chest and into which a needle can be inserted to deliver chemotherapy)
• Photographs of tumor
• Biopsy of the tumor and normal tissue before and 4 days after treatment
• Arterial catheterization (a needle is placed in an artery in the groin which allows the radiologist to view the blood supply to the tumor using an injected contrast dye called angiography. Local anesthesia will be used, and the procedure will take up to four hours. Your x-ray exposure during this procedure is estimated as about one-half (50%) of the maximum annual exposure that a person who works with radiation is allowed to receive).

**Procedures (treatment):**
If you are eligible and agree to take part in this study, you will receive an investigational drug called Onyx-015 and two standard chemotherapy drugs: cisplatin and 5-fluorouracil (5-FU). Onyx-015 is a genetically modified virus, similar to what spreads the common cold, that attacks cancer cells and causes them to die.

Onyx-015 will be injected in a small volume of fluid into the arteries in your head and neck near the location of your tumor using arterial catheterization, a process which takes up to four hours. A biopsy will be taken of both your tumor and normal tissues before and after your injection and later looked at to see how well the virus is getting into your tumor and your normal cells. A blood sample will also be taken before and after treatment and stored so that we can later look at how the virus affects you.

The cisplatin is given one to two days after the injection. The 5-FU will be given over four days through a portable pump starting the same day as the cisplatin.

You will be monitored both by clinic visits and by blood tests for 3 to 4 weeks. If your tumor is getting smaller then you will receive a second injection of Onyx-015, another dose of cisplatin and 5-FU, and monitored for another 3 to 4 weeks. If your tumor is still responding after two cycles, you will continue to be treated with cisplatin and 5-FU only.

**HOW LONG WILL I BE IN THE STUDY?**
We think you will be in the study for a total of between 5 and 6 months minimum, or for as long as your tumor continues to respond (gets smaller). This involves between 4 to 8 weeks of treatment with Onyx-015, continued treatment with chemotherapy alone, followed by once-a-month visits to the outpatient clinic for four months.

The investigator and/or your doctor may decide to take you off this study if:
• You are unable to tolerate treatment
• The treatment does not work on your cancer
• You are unable to meet the requirements of the study (for example, you do not return for follow-up visits)

• Your doctor no longer believes further treatment would be beneficial

You can stop participating at any time. Your decision to withdraw from the study will not affect in any way your medical care and/or benefits. If you decide to stop participating in the study, we encourage you to discuss your decision with your doctor.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for the side effects described below. You should discuss these with the researcher and/or your doctor. There may also be other side effects that we cannot predict. You may receive other drugs to make side effects less serious and uncomfortable. Many side effects go away shortly after the drugs are stopped, but in some cases side effects can be serious or long-lasting or permanent.

Reproductive risks
Because the drugs in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. You should also not nurse your baby while on this study. If you have any questions about the reproductive issues or about preventing pregnancy, please discuss them with the investigator or your doctor.

Risks and side effects related to the Onyx-015 we are studying include:

Very likely:
• Flulike symptoms (fever, chills, fatigue, muscle aches, weakness)
• Pain in the tumor area

Less likely:
• Infection at the tumor site (if the tumor dies rapidly, tissue could break off that would raise the risk of infection)
• Breathing problems (you may have breathing problems if the tumor is located in your mouth and pieces break off, lodging in your airways. You may also have breathing problems if there is an inflammation or swelling around your tumor near your breathing passage, which makes the passage smaller).
• Infection of “normal” (noncancer) cells from Onyx-015 that could cause coughing, fever, shortness of breath, upset stomach, diarrhea, nausea, and vomiting (slight chance)
• Irregular heartbeat (observed in only one previous patient)
• Death (very rare; in a separate study, one patient died after an injection into an artery in the liver of a similar virus at a higher dosage than you will receive in this study)

Risks and side effects related to the standard chemotherapy Cisplatin and 5-Fluorouracil include:

Very likely:
• Nausea
• Vomiting
• Mucositis (mouth sores)
Less likely:

- Kidney damage (rare and potentially permanent)
- Nerve damage (most commonly in arms or legs, or high-frequency hearing loss, potentially permanent)
- Hair loss (rare and temporary)
- Diarrhea
- Skin rashes
- Phlebitis (irritation of the veins)
- Infection at the tumor site (if the tumor dies rapidly, tissue could break off which would raise the risk of infection)
- Breathing problems (if the tumor is located in your mouth and pieces break off, the tissue could lodge in your airways)
- Irregular heartbeat (observed in only one previous patient)
- Chest pain
- Blindness (rare and permanent)
- Death (very rare)

Risks and side effects related to the standard angiography (arterial catheterization) procedure include:

Very likely:

- Pain in the tumor area
- Discomfort from needles for blood draw and tumor injections

Less likely:

- Stroke (rare and permanent)
- Blindness (rare and permanent)
- Nerve injury (rare and permanent)
- Reaction to the injected contrast dye (very rare)
- Death (very rare)

Risks and side effects related to the standard biopsy procedure include:

Very likely:

- Pain in the tumor area
- Discomfort from needles for blood draw and tumor biopsies

For more information about risks and side effects, ask the investigator.
ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
If you agree to take part in this study, there may or may not be direct medical benefit to you. This study may even be harmful. We hope the information learned from this study will benefit other patients with your type of cancer in the future.

WHAT OTHER OPTIONS ARE THERE?
Instead of being in this study, you have these options:

- Other chemotherapy drugs and drug combinations
- Chemotherapy with radiation
- Other studies of new anticancer therapeutics
- No therapy at this time with supportive care to help you feel more comfortable

Please discuss these and other options with your doctor.

WHAT ABOUT CONFIDENTIALITY?
Please refer to the last two pages of this form for information about confidentiality issues.

WHAT ARE THE COSTS?
Taking part in this study may lead to added costs to you or your insurance company. Please ask the investigator and/or your doctor about any expected added costs or insurance problems.

You will not be charged for Onyx-015, biopsies, arteriography, and special blood tests done for the research part of this study. You or your insurance company will, however, be charged for any other portion of your care that is considered standard care.

In the case of injury or illness from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.
You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?
Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
For questions about the study or a research-related injury, contact [the principal study investigator] at [telephone number and page number], or contact your research nurse at [telephone number]. Patients at the [hospital] can contact Dr. [name] at [telephone number].
For questions about your rights as a research participant, contact the [medical institution's] institutional review board (which is a group of people who review research studies to protect your rights) at [telephone number].

WHERE CAN I GET MORE INFORMATION?

[Study sponsor information omitted—eds.]
You will get a copy of this form. You may also request a copy of the research study.
The following paragraphs contain standard information that generally applies to persons involved in a research study and are required on all consent forms.

CONFIDENTIALITY

Medical information produced by this study will become part of your hospital medical record unless specifically stated otherwise in this consent form. Information that does not become part of your medical record will be stored in the investigator's file and identified by a code number only. The code key connecting your name to specific information about you will be kept in a separate, secure location. Your medical record is available to health care professionals at [the medical institutions involved in the study], and may be reviewed by appropriate [study hospital] staff members in the course of carrying out their duties; however, they are required to maintain confidentiality in accordance with applicable laws and the policies of the [study hospitals]. Information contained in your records may not be given to anyone unaffiliated with the [study hospitals] in a form that could identify you without your written consent, except as described in this consent form or as required by law.

It is possible that your medical and research record, including sensitive information and/or identifying information, may be inspected and/or copied by the study sponsor (and/or its agent), the Food and Drug Administration (FDA), federal or state government agencies, or hospital accrediting agencies, in the course of carrying out their duties. If your record is inspected or copied by the study sponsor (and/or its agents), or by any of these agencies, the [study hospitals] will use reasonable efforts to protect your privacy and the confidentiality of your medical information.

The results of this study may be published in a medical book or journal used for teaching purposes. However, your name or other identifiers will not be used in any publication or teaching materials without your specific permission. In addition, if photographs, audiotapes, or videotapes were taken during the study that could identify you, then you must give special written permission for their use. In that case, you will be given the opportunity to view or listen, as applicable, to the photographs, audiotapes, or videotapes before you give your permission for their use if you so request.

REQUEST FOR MORE INFORMATION

You may ask more questions about the study at any time. The investigator(s) will provide their telephone number(s) so that they are available to answer your questions or concerns about the study. You will be informed of any significant new findings discovered during the course of this study that might influence your continued participation.

If, during the study or later, you wish to discuss your rights as a research subject, your participation in the study and/or concerns about the study, a research-related injury with someone not directly involved in the study, or if you feel under any pressure to enroll in this study or to continue to participate in this study, you are asked to contact a representative of the [institutional review board at one of the study]
hospitals at the following telephone numbers: __________________________. A copy of this consent form will be given to you to keep.

REFUSAL OR WITHDRAWAL OF PARTICIPATION

Participation in this study is voluntary. You do not have to participate in this study. Your present or future care will not be affected should you choose not to participate. If you decide to participate, you can change your mind and drop out of the study at any time without affecting your present or future care in the [study hospitals]. In addition, the doctor in charge of this study may decide to end your participation in this study at any time after he/she has explained the reasons for doing so and has helped arrange for your continued care by your own doctor, if needed.

INJURY STATEMENT

If you are injured during the course of the study and as a direct result of this study, you should contact the investigator at the number provided. You will be offered the necessary care to treat that injury. This care does not imply any fault or wrong-doing on the part of the [study hospitals] or the doctor(s) involved. Where applicable, the [study hospitals] reserve the right to bill third-party payers for services you receive for the injury. The [study hospitals] will not provide you with any additional compensation for such injuries.

SIGNATURE

I confirm that the purpose of the research, the study procedures, and the possible risks and discomforts as well as potential benefits that I may experience have been explained to me. Alternatives to my participation in the study also have been discussed. All my questions have been answered. I have read this consent form. My signature below indicates my willingness to participate in this study.

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<thead>
<tr>
<th>Subject/Patient</th>
<th>Date</th>
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<tbody>
<tr>
<td>Witness/Advocate/Minor/Legal Guardian (if required)</td>
<td>Date</td>
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<tr>
<td>Additional Signature (if required)</td>
<td>Date</td>
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<td>(Identify relationship to subject)</td>
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I have explained the purpose of the research, the study procedures, identifying those that are investigational, the possible risks and discomforts as well as potential benefits, and have answered any questions regarding the study to the best of my ability.

| Study Representative | Date |