To: CTEP Protocol and Information Office

From: Alice Chen, MD, DTC, NCI

Date: November 10, 2022

Re: Amendment to NCI Protocol 10398: A Phase 2 Study of Anti-PD-L1 Antibody (Atezolizumab) in Chondrosarcoma and Clear Cell Sarcoma

This amendment is in response to Matt Boron's notice regarding atezolizumab drug information updates. The only change to the consent forms is the version date.

Thank you for your consideration.

I. ICD Changes:

#	Section	Comments
1.	Footer	Updated the version date.

Research Study Informed Consent Document

Study Title for Participants: Testing Atezolizumab in People 2-17 Years Old with Clear Cell Sarcoma or Advanced Chondrosarcoma

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: NCI Protocol 10398 "A Phase 2 Study of Anti-PD-L1 Antibody (Atezolizumab) in Chondrosarcoma and Clear Cell Sarcoma"

If the individual being asked to participate in this research study is a minor**,** the term "you" refers to "you and/or your child" throughout the remainder of this document; "we" means the doctors and other staff.

Overview and Key Information

What am I being asked to do?

We are asking you to take part in a research study. A research study is a way to learn more about a new drug and its uses. 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 advanced clear cell sarcoma or chondrosarcoma that is not curable by surgery and for which there is no standard treatment. People with your type of advanced cancer usually don't have effective treatment options, including radiation and chemotherapy.

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. 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 main reason this study is being done is to answer the following question:

- Does the study drug, atezolizumab (MPDL3280A), cause your cancer to shrink by at least one-quarter compared to the size it is now?

We are doing this study because we want to find out if this approach is better or worse than the usual approach for your chondrosarcoma or clear cell sarcoma. The usual approach is defined as care most people get for chondrosarcoma or clear cell sarcoma that is not curable by surgery. Atezolizumab has not been approved by the FDA for your type of cancer.

What is the usual approach to my clear cell sarcoma or chondrosarcoma?

The usual approach for patients with your type of cancer who are not in a study is treatment with radiation, kinase inhibitor drugs, immunotherapy drugs, or chemotherapy drugs. There are no treatments that are FDA-approved for your health condition or proven to help patients with your health condition live longer. That includes radiation and chemotherapy.

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

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

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

If you decide to take part in this study, you will get atezolizumab through a vein in your arm (IV) once every 3 weeks (21 days). The Study Team will monitor your cancer and your safety. You will continue to get doses of atezolizumab for as long as your cancer does not get worse, the side effects are tolerable, you agree to stay on study, and the study doctor agrees it is still in your best interest to take part in the study.

After you stop atezolizumab treatment, your doctor will continue to follow your condition for 90 days from your last treatment date or until you start a new treatment. This follow up will consist of three telephone calls from the Study Team: one call between Day 27 and Day 30 after the last dose of atezolizumab, one call between Day 57 and Day 60 after the last dose of atezolizumab, and one call between Day 87 and Day 90 after the last dose of atezolizumab.

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 atezolizumab may not be as good as the usual approach at shrinking or stabilizing your cancer.

There is also a risk that you could have side effects from the atezolizumab. 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:

- Tiredness
- Infection
- Anemia (tiredness from low red blood cell counts)
- Diarrhea, nausea, vomiting
- Difficulty swallowing
- Fever
- Flu-like symptoms including body aches
- Allergic reaction
- Loss of appetite
- Pain in back
- Cough, shortness of breath, stuffy nose
- Itching, acne, rash

Atezolizumab 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:

- Hormone gland problems (e.g., problems with control of metabolism, growth, stress response, blood pressure, sexual organs, pain, temperature, and blood sugar)
- Pain in belly
- Pain or swelling of the joints
- Rash that develops on skin, nails, scalp and inside of mouth or vagina that may be painful

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

Benefits

There is some evidence that drugs like atezolizumab that affect your immune system might shrink your type of cancer. It is not possible to know now if atezolizumab will shrink your cancer compared to the usual approach. This study will help the study doctors learn things that will help people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop at any time.

If you decide to stop, let your study doctor know as soon as possible. It's important that you stop safely. Your doctor can help you with this. 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.

Once you have turned 18, we will contact you to find out if you would still like to participate 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 Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor (the National Cancer Institute). The study sponsor is the organization who oversees the study. The study may be stopped by the sponsor if they determine the drug is not working.

You may be able to continue treatment with atezolizumab if it is helping you feel better, even if tests suggest that your cancer is getting worse. If you meet the rules for continuing treatment, your doctor will discuss with you the possible risks and benefits of continuing.

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 test the good and bad effects of the drug called atezolizumab. Atezolizumab could shrink your cancer, but it could also cause side effects, which are described in the risks section below. The study doctors hope to learn if the study drug will shrink your cancer by at least one quarter compared to its size. We also plan to test the effect of the study drug on immune cells in your blood.

Atezolizumab has already been approved by the FDA to treat other cancers but not for clear cell sarcoma or advanced chondrosarcoma.

There will be about 68 people taking part in this study.

What are the study groups?

The trial will test three groups of patients based on tumor types. One group will be people with a tumor that is clear cell sarcoma or has an *EWSR1/ATF1* or *EWSR1/CREB1* translocation. The second group will be people with grade 2 or 3 conventional chondrosarcoma. The third group will be people with dedifferentiated chondrosarcoma. All study participants will get the same study drug. However, the amount of study drug you are given will depend on your size. You will be able to receive additional doses of the drug for as long as you remain in the study.

Atezolizumab will be given in the outpatient setting. You won't have to stay overnight in the hospital or clinic. The drug will be given by vein into your arm (IV). The first time you get the drug, it will take about 1 hour to give it to you. You will need to stay at the hospital for 2-3 hours after the first time you get the drug so that your doctor can monitor you. Later in the study, the study drug may be given to you over a period of 30 minutes instead. The study drug is given in cycles. Each cycle involves one dose of study drug every 21 days (on same day of each cycle) until you experience unacceptable side effects or your tumor grows. You will not receive any atezolizumab on the 20 other days of each.

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.

Listed below are exams, tests, and procedures that need to be done as part of this study to monitor your safety and health, but may not be included in the usual care. We will use them to carefully follow the effects of the study treatment, including preventing and managing side effects.

- An electrocardiogram (EKG) and an echocardiogram (ECHO) to test your heart
- A pregnancy test in women who are able to become pregnant
- A CT scan or other imaging test such as ultrasound (an examination using sound waves) or MRI (an examination using magnetic field and radio waves) that detects your tumor

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

- If you are 12 years of age or older, you will need to have blood samples collected for the study. These samples will be collected for genetic sequencing. The researchers will use the samples to learn more about how atezolizumab works and which patients in the future might be most likely to respond to atezolizumab. They might also use some of your blood to learn which genes are only in your tumor and not in your normal blood. Each sample will be approximately 3 teaspoons of blood.

- One sample will be collected at the start of the study, before you begin atezolizumab treatment.
- One sample will be collected before your second dose of atezolizumab (the first day of Cycle 2).
- One sample will be collected before your third dose of atezolizumab. This might happen sooner if your doctor sees that the drug is making your cancer get better.
- One sample will be collected at the end of Cycle 3 and one more at the end of Cycle 5.
- One sample will be collected every 12 weeks after Cycle 5 for the rest of your first year. Then, every 18 weeks during your second year and every 24 weeks in the years after that.
- One sample will be collected if your cancer gets worse.

- If you are 12 years old or older **and are at the NCI,** we will collect extra blood samples to study your immune system.
  - One sample will be collected after two weeks of treatment (if you and your doctor agree to this collection).
  - One sample will be collected at the start of every cycle, beginning with Cycle 2.
  - One sample will be collected if your cancer gets worse.

    Your study doctor can tell you if these blood collections are required for you. Each of these samples will be about 1 teaspoon of blood.

A participant study calendar is attached at the end of this document. It shows how often these exams, tests, and procedures will be done.

If you are 12 years of age or older, the genetic sequencing research tests used in this study will look at genes in your blood samples. Genes are like instruction books inside the normal cells and the cancer cells in your body. These genes are made up of "chemical letters" called DNA (**d**eoxy**r**ibonucleic **a**cid). Genetic sequencing of the DNA in your normal blood cells and of small pieces of tumor DNA that can be found in your blood, will tell the researchers the exact order of the DNA in your tumor cells.

Genetic changes found in your normal blood may be passed down in families. For example, these genetic changes may come from your parents in the same way that eye and hair color are passed down. Genetic tests of normal tissue can reveal information about you and about your relatives. We will not tell you or your parents anything we learn about your genes from research done on this study.

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 atezolizumab may not be as good as the usual approach for your cancer at shrinking or stabilizing your cancer.

You also may have the following discomforts:

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

The atezolizumab 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 your last atezolizumab dose.

Genetic Testing Risks

As part of the research study, you might learn that you have genetic risks for another disease or disability. This might make you upset and it might mean that you and your family need to make hard decisions about how to respond.

You are the only one with your exact genomic information. But some of your genomic information is shared by your blood relatives like your parents, brothers, and sisters. Learning your research results could mean something about your family members and might make you or your family worry. Before joining the study, it may be good to talk with your family members. Ask them if they want you to share your results with them and how they want to you to do that.

Blood Sample Risks

Possible side effects from drawing blood for safety test or research include mild pain, bleeding, bruising, and infection where the needle went in. Fainting or light-headedness can sometimes happen, but they usually last for only a few minutes.

Side Effect Risks

The atezolizumab 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 drug.

Here are important things to know about side effects:

1. The study doctors do not know who will or will not have side effects. **If you experience diarrhea, it is important that you contact the study doctor immediately, even if the diarrhea is mild.**
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.

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 Atezolizumab

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

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving atezolizumab, from 4 to 20 may have:
• Anemia which may require blood transfusion • Diarrhea, nausea, vomiting • Difficulty swallowing • Fever • Flu-like symptoms including body aches • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Reaction during or following a drug infusion which may cause fever, chills, rash • Loss of appetite • Pain in back • Cough, shortness of breath, stuffy nose • Itching, acne, rash Atezolizumab (MPDL3280A) 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: • 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 urine; dizziness or fainting. • Pain in belly • Pain or swelling of the joints • Rash that develops on skin, nails, scalp and inside of mouth or vagina that may be painful

RARE, AND SERIOUS In 100 people receiving atezolizumab, or fewer may have:
• Bruising, bleeding

Atezolizumab (MPDL3280A) 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:

- Heart problems including swelling and heart failure. Symptoms and signs of heart problems may include: shortness of breath, swelling of the ankles and body.
- A condition with high blood sugar which leads to tiredness, frequent urination or excessive thirst.
- Swelling and redness of the eye
- 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.
- 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.
- Swelling of the brain (meningitis/encephalitis), which may cause: headache, confusion, sleepiness, seizures, and stiff neck.
- Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine.
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs.
- 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.
- Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath.
- Skin: blisters on the skin, including inside the mouth (can be severe), rash with blisters, skin rash developing 1-8 weeks after a drug is given, which may be accompanied by fever, lymph node swelling and organ failure.

Additional Drug Risks

The study drug could interact with other drugs. Your study doctor will give you a drug information handout and wallet card that lists these possible interactions. 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.

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.

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 clear cell sarcoma or chondrosarcoma. 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 atezolizumab 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.

You and/or your insurance provider will not have to pay for exams, tests, and procedures done for research purposes only or that are covered by the study.

If you are 12 years old or older, we will collect your blood several times for genetic analysis. We explained these blood collections in the "What exams, tests, and procedures are involved in this study?" section. You and/or your insurance provider will not have to pay for these blood collections or tests.

If you are 12 years old or older and you are at the NCI, we will collect your blood to test what the atezolizumab is doing to your immune system. We explained these blood collections in the "What exams, tests, and procedures are involved in this study?" section. You and/or your insurance provider will not have to pay for these blood collections or tests.

You or your insurance provider will not have to pay for the atezolizumab while you take part in this study.

Taking part in this study may mean that you need to make more visits to the clinic or hospital than if you were getting the usual approach to treat your cancer. You may have more travel costs. You may need to take more time off school or work. You may have other additional personal costs.

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 study sponsor and any company supporting the study or the study agent now or in the future. This would include any organization helping the company with the study.
- 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.

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.

There are laws that protect your genetic information. However, there is a risk that someone could get access to your genetic information and identify you by name. In some cases, employers could use your genetic information to decide whether to hire or fire you. The study doctors believe the risk of this happening is very small. However, the risk may increase in the future as people find new ways of tracing information. For more information about the laws that protect you, ask your study doctor.

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

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.

(Note to Local Investigator: The signature requirements for pediatric patients can be adjusted based on local guidelines.)

Participant's signature (written assent of minor)

_____

Date of signature

_____

Parent/Guardian's signature

_____

Date of signature

_____

Signature of person(s) conducting the informed consent discussion

_____

Date of signature

_____

Participant Study Calendar

Day	Participant Activity
Before starting study drug	• Check in at _____ [*name of center*] • Medical history and physical exam, including ECOG Performance Status (an assessment of how you are doing with your daily living activities) • Echocardiogram and EKG to test your heart • Tumor measurements by CT/MRI or PET • Routine blood tests • Required blood draw for genetic research (all patients 12 and older) • Required blood draw for research on the effects of the study drug (some patients only) • Pregnancy test for women who are able to become pregnant
Cycle 1 Day 1	• Go to _____ [*name of center*] • Routine blood tests • Atezolizumab will given through a vein over 1 hour, followed by observation at _____ [*name of center*] for 2-3 hours
Cycle 1 Day 15	• Check in at _____ [*name of center*] • Routine blood tests • Blood draw for research on the effects of the study drug (some patients only; optional)
Cycle 2 Day 1	• Go to _____ [*name of center*] • Medical history and physical exam • Routine blood tests • Required blood draw for genetic research (all patients 12 and older) • Required blood draw for research on the effects of the study drug (some patients only) • Atezolizumab will given through a vein (about 30 minutes to 1 hour)
Cycle 3 and onwards, Day 1	• Go to _____ [*name of center*] • Medical history and physical exam • Routine blood tests • Required blood draw for research on the effects of the study drug (some patients only) • Atezolizumab will given through a vein (about 30 minutes to 1 hour)
Cycle 3 and onwards	• Tumor measurement by CT/MRI or PET to measure any changes in the size of your tumors will be performed at the end of Cycle 3, and at the end of every 2 cycles after that (less often once you have been on study for >1 year) • Required blood draw for genetic research at the end of Cycles 3 and 5 and every 4 cycles after that (less often once you have been study for >1 year)