

November 10, 2022

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Dear Ms. Kruhm:

Enclosed is Addendum #31 to EAY131-Z1E, *Molecular Analysis for Therapy Choice (MATCH): MATCH Treatment Subprotocol Z1E: LOXO-101 in Patients with Tumors with NTRK Fusions*.

This addendum is in response to Dr. John Wright, Dr. Jeffrey Moscow, and Dr. Meg Mooney September 22, 2022 Request for Rapid Amendment for LOXO-101.

The following revisions to EAY131-Z1E protocol have been made in this addendum:

|    | Section    | Change                                                          |
|----|------------|-----------------------------------------------------------------|
| 1. | Cover Page | Updated Version Date.                                           |
| 2. | 3.3        | Updated the LOXO-101 CAEPR list with version 2.3, May 12, 2022. |

The following revisions to EAY131-Z1E Informed Consent Document have been made in this addendum:

|    | Section                                                                          | Change                                                                                         |
|----|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| 1. | <a href="#">Cover Page</a>                                                       | Updated Version Date.                                                                          |
| 2. | <a href="#">What possible risks can I expect from taking part in this study?</a> | Updated the possible risks language and the LOXO-101 risk list with version 2.3, May 12, 2022. |

If you have any questions regarding this addendum, please contact [eradomyshelesky@ecog-acrin.org](mailto:eradomyshelesky@ecog-acrin.org) or 857-504-2900.

We request review and approval of this addendum to EAY131-Z1E so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Senior Director of Protocol Development

## **Study Title for Study Participants: Testing LOXO-101 as potentially targeted treatment in cancers with NTRK genetic changes**

**Official Study Title for Internet Search on**  
<http://www.ClinicalTrials.gov>: Molecular Analysis for Therapy Choice (MATCH): MATCH Treatment Subprotocol Z1E: EAY131-Z1E: Larotrectinib (LOXO-101) in Patients with Tumors with NTRK Fusions

Version Date: November 10, 2022

### **What is the usual approach to my cancer?**

You are being asked to take part in this part of the study because you have genetic changes in your tumor that are potentially targeted by LOXO-101. There is currently no standard approach for treating cancers with the genetic changes that you have (NTRK fusions). People who are not in a study are usually treated with either surgery, radiation, or with drugs. Sometimes combinations of these are used and your doctor can explain which may be best for you. These treatments can reduce symptoms and may stop the tumor from growing for several months or more.

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

If you decide not to continue on this study, you have other choices for your care. For example:

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

### **Why is this study being done?**

The purpose of this study is to test any good and bad effects of the study drug LOXO-101 in patients whose cancer has NTRK fusions, involving a gene called NTRK1, NTRK2, or NTRK3. LOXO-101 could shrink your cancer but it could also cause side effects. Researchers hope to learn if the study drug will shrink the cancer by at least one-quarter compared to its present size. LOXO-101 is designed to block the activity of the proteins made by these genes as a way to treat the cancer. LOXO-101 is not approved by the Food and Drug Administration (FDA) so its use is considered investigational. LOXO-101 has been tested already in a separate phase 1 study designed to determine the optimal dose and possible side effects. In some patients with NTRK1, NTRK2 or NTRK3 gene fusions, LOXO-101 caused tumors to shrink. There will be about 35 people taking part in this study.

## What are the study groups?

All study participants will get the same study intervention which consists of the study drug LOXO-101. You will take LOXO-101 by mouth two times daily every day, about 12 hours apart. You will receive LOXO-101 for the entire time you are enrolled in the study.

You will be required to maintain a patient pill calendar and bring it with you to every clinic visit.

A study calendar that shows how often these tests will be done is attached.

## How long will I be in this study?

You will receive the study drug as long as your cancer does not get worse, the side effects are tolerable and you agree to stay on study. When you finish taking LOXO-101, your doctor will continue to watch you for side effects and follow your condition with visits to the office for follow-up exams every 3 months for 2 years, and every 6 months for the third year from your enrollment in the study.

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

If you choose to take part in this study, there is a risk that the LOXO 101 (Larotrectinib sulfate) may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss
- You may not be able to take part in future studies.

The LOXO-101 used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may make it hard for you to have children.
- 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.

- The study doctor will work with you to treat your side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

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

Rev. Add12 **Possible Side Effects of LOXO-101:**

Rev. Add17

Rev. Add23

Rev. Add31

(Table Version Date: **Version 2.3, May 12, 2022**)

| <b>OCCASIONAL, SOME MAY BE SERIOUS</b>                                                                                                                                                                                                                                                                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| In 100 people receiving LOXO-101 (Larotrectinib sulfate), from 4 to 20 may have:                                                                                                                                                                                                                          |
| <ul style="list-style-type: none"><li>• Anemia which may require blood transfusion</li><li>• Pain</li><li>• Constipation, diarrhea, nausea, vomiting</li><li>• Swelling of arms, legs</li><li>• Tiredness, fever</li><li>• Weight gain</li><li>• Dizziness</li><li>• Cough, shortness of breath</li></ul> |

| <b>RARE, AND SERIOUS</b>                                                                                                      |
|-------------------------------------------------------------------------------------------------------------------------------|
| In 100 people receiving LOXO-101 (Larotrectinib sulfate), 3 or fewer may have:                                                |
| <ul style="list-style-type: none"><li>• Difficulty walking</li><li>• Feeling of "pins and needles" in arms and legs</li></ul> |

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

You should report and discuss with the study doctor any other medication(s) you are taking while you are treated with the study drug(s), so that he/she can take action to prevent any potential drug interactions.

Please refer to the drug interaction handout and wallet card for additional information.

**Sunlight Exposure Risks:**

While effects of sun exposure are unknown, you should limit sun exposure while taking LOXO-101 and protect your skin by wearing sunscreen and protective clothing due to the potential for photosensitivity with this drug.

**Reproductive risks:**

You should not become pregnant, breastfeed, or father a baby while in this study. The drugs in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

It is important that you understand that you need to either practice "abstinence" (that is avoiding sexual activity) or use birth control while on this study.

Avoiding sexual activity is the only certain method to prevent pregnancy. However, if you choose to be sexually active, you must agree to use an appropriate double barrier method of birth control (such as female use of a diaphragm, intrauterine device (IUD), sponge and spermicide, in addition to the male use of a condom) or involve female use of prescribed "birth control pills" or a prescribed birth control implant. Both double barrier contraception and birth control pills or implants must be used for at least one week prior to the start of the study and continuing for 16 weeks after the last dose of the study drugs. If you choose to be sexually active during the study, you must accept that pregnancy could still result, exposing you or your sexual partner to potential loss of pregnancy as well as other unknown effects on the developing unborn baby. If a woman becomes pregnant while on this study or within 4 weeks after the last dose of study drug, she will be asked information concerning the outcome of her pregnancy. If a female partner of a male patient becomes pregnant while the male patient is on the study or within 4 weeks after the last dose of study drug, the male patient must notify the investigator.

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

This study has only a small chance of helping you because we do not know if the study drug/study approach is effective. This study may help researchers learn things that may help other people in the future.

### **Can I stop taking part in this study?**

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

### **If your cancer becomes worse during treatment with the study drug(s):**

- You may be asked to take part in another MATCH study treatment. Your study doctor will discuss this with you.

- Another biopsy may be required and will be tested to determine if your tumor has new genetic changes and if there is another MATCH study treatment available for your cancer as described in the MATCH Screening Consent.
- This testing will be similar to the testing for genetic changes that was done in the initial screening step of this study
- Your study doctor will be given the results of these new genetic tests and share them with you.
- There may be some additional exams or procedures required for this next treatment. These will be discussed in a separate Consent Form about the next treatment that you will receive.

### **What are my rights in this study?**

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the \_\_\_\_\_  
(insert name of center) Institutional Review Board at \_\_\_\_\_ (insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)

### **What are the costs of taking part in this study?**

The LOXO-101 will be supplied at no charge while you take part in this study. It is possible that the LOXO-101 may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of study drug preparation and administration (if any), and tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are being done at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

### **What happens if I am injured or hurt because I took part in this study?**

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

## Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

The ECOG-ACRIN Cancer Research Group is carrying out this study. ECOG-ACRIN is a cancer research group that conducts studies for the National Cancer Institute. Your doctor is a member of ECOG-ACRIN or another group that is participating in this study. To help protect your privacy, ECOG-ACRIN has obtained a Confidentiality Certificate from the U.S. Department of Health and Human Services (DHHS). With this Certificate, ECOG-ACRIN cannot be forced (for example, by court subpoena) to disclose information that may identify you in any federal, state or local civil, criminal, administrative, legislative or other proceeding. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The study sponsor and the drug company supporting the study
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

## Where can I get more information?

You may visit the NCI Web site at <http://cancer.gov/> for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov/>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

## Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor \_\_\_\_\_ (insert name of study doctor[s]) at \_\_\_\_\_ (insert telephone number).

## My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and

Participant's signature

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Date of signature \_\_\_\_\_

Signature of person(s) conducting the informed consent discussion

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Date of signature \_\_\_\_\_

## Study Calendar

| Visit                                                                                   | Patient Activities                                                                                                                                                                                                                                                                                                       |
|-----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Visit 1:<br>Screening (within four to six weeks of start of treatment)                  | <ul style="list-style-type: none"> <li>History and physical examination</li> <li>Routine blood tests</li> <li>Imaging (CT or MRI; same method to be used at future visits) to look at your cancer</li> <li>Pregnancy test (if you are a woman who could become pregnant)</li> <li>ECG</li> </ul>                         |
| Visit 2:<br>Start of treatment                                                          | <ul style="list-style-type: none"> <li>History and physical examination</li> <li>Routine blood tests</li> <li>ECG, if clinically necessary</li> </ul>                                                                                                                                                                    |
| Visits 3 and beyond:<br>Ongoing treatment evaluations about every 28 days               | <ul style="list-style-type: none"> <li>History and physical examination</li> <li>Routine blood tests</li> <li>Collection of patient pill calendar</li> <li>Imaging (CT or MRI; by same method as screening) every other visit, or more frequent if clinically necessary</li> <li>ECG, if clinically necessary</li> </ul> |
| End of treatment                                                                        | <ul style="list-style-type: none"> <li>Side effects assessment</li> <li>Collection of patient pill calendar</li> </ul>                                                                                                                                                                                                   |
| Follow up:<br>Every three months up to two years, then every 6 months in the third year | <ul style="list-style-type: none"> <li>History and physical examination</li> <li>Side effects assessment, if clinically necessary</li> <li>Routine blood tests, if clinically necessary</li> <li>Imaging (CT or MRI; by same method as screening), if clinically necessary</li> </ul>                                    |