August 19, 2020

Martha Kruhm, MS RAC
Head, Protocol and Information Office
Quality Assurance Section
CTEP, DCT, NCI
6130 Executive Blvd, EPN Room 7000
Bethesda, MD 20892

Dear Ms. Kruhm:

Enclosed is Addendum #25 to EAY131-C2, *Crizotinib in Patients with Tumors with MET Exon 14 Deletion*

This addendum is in response to Dr. Tali Johnson's Amendment Request for updates to specific protocol language for Crizotinib dated June 5, 2020.

Please replace your current copy of the protocol and Informed Consent document with these updated versions. We recommend that each institution maintain a file containing the original protocol, Informed Consent, and all subsequent revisions/versions.

IRB Review Requirements:

This addendum has been reviewed and approved by the Central IRB, which is the sole IRB of record for this study. Local IRB review and approval is unnecessary.

Implementation of this addendum must occur on the activation date. Sites are not permitted to conduct the study utilizing outdated versions of any MATCH protocol documents after the activation date of this addendum.

The following revisions to EAY131-C2 protocol have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Version Date and addendum number.
2.	Appendix III	Updated patient drug information template format.

The following revisions to EAY131-C2 Informed Consent Document have been made in this addendum:

	Section	Change
1.	Page 1	Updated Version Date.

If you have any questions regarding this addendum, please contact aagu@ecog-acrin.org or 857-504-2900.

28 State Street, Suite 1100, Boston, MA 02109 p: 857.504.2900 f: 617. 589.0914 ecog-acrin.org

We request review and approval of this addendum to EAY131-C2 so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Senior Director of Protocol Development

Study Title for Study Participants: Testing Crizotinib as potentially targeted treatment in cancers with MET Exon 14 Deletion genetic changes

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Molecular Analysis for Therapy Choice (MATCH): MATCH Treatment Subprotocol C2: EAY131-C2: Crizotinib in Patients with Tumors with MET Exon 14 Deletion

Version Date: August 19, 2020

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 (MET exon 14 deletion) that are potentially targeted by crizotinib. There is currently no agreed upon approach for treating cancers with the genetic changes that you have. 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 take part in this study, you have other choices. 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.

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Why is this study being done?

The purpose of this study is to test any good and bad effects of the study drug called crizotinib. Crizotinib 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. Crizotinib is FDA approved for the treatment of patients with metastatic non-small cell lung cancer with anaplastic lymphoma kinase (ALK) or ROS1-positive tumors. For this study, crizotinib is considered experimental. 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 crizotinib. You will take crizotinib by mouth twice daily. Crizotinib should be taken

approximately 12 hours apart and without regard to meals. Crizotinib capsules should be taken whole (do not crush, dissolve, or open capsules). Any missed dose may be taken up to 6 hours prior to the next scheduled dose. Otherwise, the missed dose should be skipped, and you will resume taking crizotinib with the next scheduled dose. If you vomit after a study dose, another dose should not be taken; instead, wait and resume drug dosing at your next scheduled dose.

Rev. 3/17 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 exams, tests, and/or procedures 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. After you finish taking crizotinib, 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:

- 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

The crizotinib 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.

Rev. 8/17 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 interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some 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 that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

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Possible Side Effects of Crizotinib:

(Table Version Date: October 30, 2018)

COMMON, SOME MAY BE SERIOUS In 100 people receiving crizotinib (PF-02341066), more than 20 and up to 100 may have:
• Visual disturbances • Swelling of the eye • Constipation, diarrhea, nausea, vomiting • Swelling of the body • Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving crizotinib (PF-02341066), from 4 to 20 may have:
• Anemia which may require blood transfusion • Abnormal heartbeat • Pain • Heartburn • Sores in the mouth • Cold symptoms such as stuffy nose, sneezing, sore throat • Infection, especially when white blood cell count is low • Loss of appetite • Dizziness, headache • Changes in taste • Damage to nerves that may interfere with walking or organ function which may cause numbness, tingling, weakness • Rash, itching

RARE, AND SERIOUS In 100 people receiving crizotinib (PF-02341066), 3 or fewer may have:
• Heart failure which may cause shortness of breath, swelling of ankles, and tiredness • A tear or hole in the bowels that may require surgery • Sores in the throat • Difficulty swallowing • Liver damage which may cause yellowing of eyes and skin, swelling • Change in the heart rhythm

RARE, AND SERIOUS In 100 people receiving crizotinib (PF-02341066), 3 or fewer may have:
• Fainting • A sac in the kidney that is filled with fluid • Damage to the lungs which may cause shortness of breath

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.

If you have increased shortness of breath, cough or fever, contact your doctor immediately.

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

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.

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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.

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.)*

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 the costs of taking part in this study?

Crizotinib will be supplied at no charge while you take part in this study. It is possible that crizotinib 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 conducting 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.

Participant's signature

_____

Date of signature _____

Signature of person(s) conducting the informed consent discussion

_____

Date of signature _____

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Study Calendar:

Visit	Patient Activities
Visit 1: Screening (within four to six weeks of start of treatment)	History and physical examination Routine blood tests Imaging (CT or MRI; same method to be used at future visits) to look at your cancer Pregnancy test (if you are a woman who could become pregnant) ECG
Visit 2: Start of treatment	History and physical examination Routine blood tests
Visits 3 and beyond: Ongoing treatment evaluations about every 28 days	History and physical examination Routine blood tests Collection of patient pill calendar Imaging (CT or MRI; by same method as screening) every other visit, or more frequent if clinically necessary ECG (if clinically necessary)
End of treatment	Side effects assessment Collection of patient pill calendar
Follow up: Every three months for two years, then every six months for the third year	History and physical examination Side effects assessment, if clinically necessary Routine blood tests, if clinically necessary Imaging (CT or MRI; by same method as screening), if clinically necessary