ECOG-ACRIN
cancer research group
Reshaping the future of patient care

November 10, 2022

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 #31 to EAY131-Z1K, *MATCH Treatment Subprotocol Z1K: Ipatasertib in Patients with Tumors with AKT Mutations.*

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 Sites are not permitted to conduct the study utilizing outdated versions of any MATCH protocol documents after the activation date of this addendum.

Re: Review of **Amendment #42** of Protocol #**EAY131-Z1K:** "MATCH Treatment Subprotocol Z1K: Ipatasertib in Patients with Tumors with AKT Mutations"

I. Recommendations:

#	Section	Comments
1.	Appendix V	On page 1 of the patient handout, please remove "BVD-523B (ulixertinib)" and replace with "Ipatasertib." **PI Response:** This change has been made.

The following revisions to the EAY131-Z1K protocol have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Version Date and addendum number.
2.	Appendix V	Study drug listed on page 1 of patient handout updated to Ipatasertib.

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The following revisions to the EAY131-Z1K Informed Consent Document have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Version Date.

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

We request review and approval of this addendum to EAY131-Z1K so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Senior Director of Protocol Development

Study Title for Study Participants: Testing Ipatasertib as Potentially Targeted Treatment in Cancers with AKT Genetic Changes

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Molecular Analysis for Therapy Choice (MATCH): MATCH Treatment Subprotocol Z1K: EAY131-Z1K: Ipatasertib in Patients with Tumors with AKT Mutations

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 ipatasertib. There is currently no standard approach for treating cancers with the genetic changes that you have (AKT mutation). People who are not in a study are usually treated with either surgery, radiation or with drugs. Sometimes, combinations of these could be used, and your doctor can explain which of these standard therapies may be best for you. These standard therapies could reduce symptoms and 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.

Why is this study being done?

The purpose of this study is to test any good and bad effects of the study drug ipatasertib in patients whose cancer has an AKT mutation. The effects of ipatasertib on your cancer is unknown and it may 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. Ipatasertib is an AKT inhibitor which is investigational and is not approved by the Food and Drug Administration (FDA). There will be about 35 people taking part in this part of the study.

What are the study groups?

All study participants will get the same study intervention, which consists of the study drug ipatasertib. You will take ipatasertib by mouth once a day continuously, with or without

food. You will receive ipatasertib once daily for the entire time you are enrolled in the study. Metastatic breast cancer patients (ER/PR positive and HER2 negative) will be allowed to continue fulvestrant or an aromatase inhibitor while receiving the study drug. Participants with castration resistant prostate cancer should maintain castrate levels of testosterone while receiving the study drug.

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 not too bad and you agree to stay on study. After you finish taking ipatasertib, 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 extra tests and procedures will I have if I take part in this study?

Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there are some extra tests and procedures that you will need to have if you take part in this study.

If the tests and procedures show that you can take part in this study, and you choose to take part, then you will need the following extra tests. They may not be part of the usual approach for your type of cancer.

During the study:

- A repeat blood test in the third week after you start ipatasertib (approximately 15 days after the first dose).

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.

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 ipatasertib may not be as good as the usual approach for your cancer or condition 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 ipatasertib 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 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.

Here are important things to know 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, and 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.
- 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.

The tables below show the most common and the 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 Ipatasertib

(Table Version Date: September 16, 2021)

COMMON, SOME MAY BE SERIOUS In 100 people receiving ipatasertib, more than 20 and up to 100 may have:
• Diarrhea, nausea

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving ipatasertib, from 4 to 20 may have:
• Anemia which may require blood transfusion • Pain • Heartburn, vomiting • Tiredness • Loss of appetite • Changes in taste • Rash

RARE, AND SERIOUS In 100 people receiving ipatasertib, 3 or fewer may have:
• Sores in the mouth, which may cause difficulty swallowing • Liver damage which may cause yellowing of the eyes and skin • Bruising, bleeding • Damage to the lungs, which may cause shortness of breath

Rarely, patients have been noted to have abnormal liver tests (related to how well the liver is working). Let your study doctor know if you are experiencing belly pain or swelling, or, if severe, yellow eyes and skin. Inflammation of the lung (i.e. pneumonitis) has also been reported. Let your study doctor know if you have worsening cough or shortness of breath. It is unclear whether these symptoms were related to taking the ipatasertib or not.

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, 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.

Diarrhea Prevention:

During the first 4 weeks, it is recommended that you take loperamide (2 mg oral twice a day or 4 mg once a day) to prevent diarrhea. Depending on how you tolerate the study medication and experience diarrhea, your treating physician may recommend you continue taking the loperamide for the rest of the study.

Vomiting:

If you vomit within 30 minutes of taking your ipatasertib, you should take another dose to replace it. If you vomit more than 30 minutes after taking your ipatasertib, you should wait until the next day to take your dose at your regular time.

If you miss a dose, you may take the dose up to a maximum of 8 hours after the scheduled dose time. If greater than 8 hours after the scheduled dose time, the missed dose should not be made up. If you need to take the dose earlier for whatever reason, you can take the dose up to 8 hours earlier than the scheduled dose time.

Hormone Therapy:

Some prostate and breast cancer patients with a certain genetic change (ER/PR positive and HER2 negative) who have been receiving hormone therapy may continue the hormone therapy (except for tamoxifen or toremifene) following the same schedule as previously administered.

Blood Draw Risks:

Risks of having blood drawn are soreness and/or a black and blue mark at the site from where the blood is drawn. Sometimes, people feel uncomfortable at the time of the blood draw. Occasionally people feel lightheaded or faint. There is also a small risk of infection

whenever blood is drawn.

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. Also, male patients must agree to not donate sperm for the duration of study participation, and for 4 months after completion of study.

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, Institutional Review Board (IRB) or Food and Drug Administration (FDA).

If your cancer becomes worse during treatment with the study drug:

- You may be asked to take part in another MATCH study treatment. Your study doctor will discuss this with you.
- If you decide to take part in another MATCH study arm, a new biopsy will 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?

Ipatasertib will be supplied at no charge while you take part in this study. It is possible that ipatasertib 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 office visits, 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.

Participant's signature

_____

Date of signature _____

Signature of person(s) conducting the informed consent discussion

_____

Date of signature _____

Study Calendar

Visit	Patient Activities
Visit 1: Before starting study (within 4 to 6 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) Electrocardiogram (ECG) If applicable, continue hormone therapy before receiving ipatasertib. Hormone (or endocrine) therapy is treatment that blocks the body's natural hormones, such as estrogen. Anastrazole, Letrozole, Exemestane, and Fulvestrant are allowable hormone therapies for this study.
Visit 2: Start of treatment Cycle 1, Day 1	History and physical examination Fasting routine blood tests If applicable, continue hormone therapy before receiving

Visit	Patient Activities
	ipatasertib. Hormone (or endocrine) therapy is treatment that blocks the body's natural hormones, such as estrogen. Anastrazole, Letrozole, Exemestane, and Fulvestrant are allowable hormone therapies for this study.
Visit 3: Cycle 1, Day 15	History and physical examination Fasting repeat blood test on the third week that you start ipatasertib (approximately 15 days after the first dose). Side effects assessment
Visit 4: Cycle 2, Day 1	History and physical examination Fasting routine blood tests Side effects assessment
Visit 5: Cycle 2, Day 15	History and physical examination Fasting routine blood tests Side effects assessment
Visits 6 and beyond: Ongoing treatment evaluations about every 28 days	History and physical examination Routine blood tests (fasting at the beginning of the second cycle; for subsequent cycles, fasting blood tests are recommended but not required) Collection of patient pill calendar Imaging (CT or MRI; by same method as screening) every other visit, or more frequent if clinically necessary If applicable, continue hormone therapy before receiving ipatasertib. Hormone (or endocrine) therapy is treatment that blocks the body's natural hormones, such as estrogen. Anastrazole, Letrozole, Exemestane, and Fulvestrant are allowable hormone therapies for this study. Side effects assessment
End of treatment	Side effects assessment Collection of patient pill calendar
Follow up: Every 3 months for 2 years and every 6 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