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

December 5, 2025

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 #39 to EAY131-H, *MATCH Treatment Subprotocol H: Phase II Study of Dabrafenib and Trametinib in Patients with Tumors with BRAF V600E or V600K Mutations (Excluding Melanoma, Thyroid Cancer, Colorectal Adenocarcinoma, and Non-Small Cell Lung Cancer).*

This addendum is in response to the Trametinib Rapid Request for Amendment (RRA) from Dr. Helen Chen dated November 14, 2025.

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.

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

	Section	Change
1.	Cover Page	Updated Version Date and addendum number.
2.	Global	Updated CTEP site throughout.
3.	3.3	Updated CAEPR for Trametinib to Version 2.7, July 25, 2025. Inserted note to match the Trametinib CAEPR, which states, “Any event listed in the EAY131-H specific expedited reporting requirements in Section 3.2.1 must be reported in CTEP-AERS, even if the event is listed as an exception in the green column below.”

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

	Section	Change
1.	Cover Page	Updated Version Date.

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

	Section	Change
2.	Possible Side Effects of Trametinib	Updated Risk List for Trametinib to version dated July 25, 2025.

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

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

Thank you.

Sincerely,

Pamela Cogliano

Senior Director of Protocol Development

Study Title for Study Participants: Testing Trametinib and Dabrafenib as potentially targeted treatment in cancers with genetic changes.

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:

Molecular Analysis for Therapy Choice (MATCH)

MATCH Treatment Subprotocol H: EAY131-H: Phase II Study of Dabrafenib and Trametinib in Patients with Tumors with BRAF V600E or V600K Mutations (Excluding Melanoma, Thyroid Cancer, Colorectal Adenocarcinoma, and Non-Small Cell Lung Cancer)

Version Date: December 5, 2025

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 trametinib and dabrafenib. There is currently no agreed upon approach for treating cancers with the genetic changes that you have ($BRAF^{V600}$ mutation). People who are not in a study are usually treated with either surgery, radiation, or with drugs that have been FDA approved. 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.

Rev.2/16

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.

Rev.2/16

Why is this study being done?

Rev. Add13
Rev. Add25

The purpose of this part of the study is to test any good and bad effects of the study drugs, trametinib and dabrafenib, in patients whose cancer has genetic changes called $BRAF^{V600}$ mutations. Trametinib and dabrafenib could shrink your cancer but the drugs could also cause side effects. Researchers hope to learn if giving trametinib with dabrafenib will shrink the cancer by at least one-quarter compared to its present size. Trametinib and dabrafenib are FDA-approved to treat advanced melanoma and non-small cell lung cancer with a $BRAF^{V600}$

mutation but are considered experimental for the treatment of other cancers with this mutation. There will be about 85 people taking part in this study.

Rev.2/16

Rev. 3/17

What are the study groups?

All study participants will get the same study drugs, trametinib and dabrafenib. All study participants will take dabrafenib by mouth twice daily in the morning and evening, with trametinib by mouth once daily, with either the morning or evening dose of dabrafenib. The evening dose of dabrafenib should be taken approximately 12 hours after the morning dose. The study drugs should be taken either 1 hour before or 2 hours after a meal. If a dose of dabrafenib is missed, it should not be taken if within 6 hours of the next scheduled dose. If a dose of trametinib is missed, it should not be taken if it within 12 hours of the next scheduled dose. Swallow dabrafenib capsules whole. Do not crush, chew, or open capsules. Swallow trametinib tablets whole. Do not crush or chew tables.

How long will I be in this study?

You will receive trametinib and dabrafenib as long as your cancer does not get worse, the side effects are tolerable and you agree to stay on study. After you finish trametinib and dabrafenib, 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.

Rev.2/16

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 exams that you will need to have if you take part in this study.

Rev. 8/15, 2/16

Before you begin the study:

You will need to have the following extra procedures at the beginning of this study to find out if you can receive the trametinib and dabrafenib:

- Echocardiogram (ECHO) or nuclear study (multigated acquisition [MUGA] or similar scan), which are used to assess your heart function
- Eye exam by an ophthalmologist

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

Rev. 8/15, 2/16, 3/17

During the study:

- Electrocardiogram (ECG), at week 5, week 13, and every 12 weeks thereafter, to see whether there are any abnormalities in the rhythm of your heart that might be caused by the drug or if you have symptoms that might suggest an abnormality.

- Echocardiogram (ECHO) or nuclear study (multigated acquisition [MUGA] or similar scan), at week 5, week 13, and every 12 weeks thereafter, to see how your heart is working

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.

Rev. 8/15

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 drugs (trametinib and dabrafenib) 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. These risks are described in more detail below.

There is also a risk that you could have other 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.

Rev. 12/16
Rev. Add21
Rev. Add25
Rev. Add34

Possible Side Effects of Dabrafenib

(Table Version Date: January 17, 2025)

COMMON, SOME MAY BE SERIOUS In 100 people receiving dabrafenib (GSK2118436B), more than 20 and up to 100 may have:
• Nausea • Tiredness • Fever (Fever and complications of fever are more frequent and severe when dabrafenib (GSK2118436B) is used together with trametinib dimethyl sulfoxide.) • Pain • Headache • Hair loss • Skin changes including rash

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving dabrafenib (GSK2118436B), from 4 to 20 may have:
• Anemia which may require blood transfusion. • Constipation, diarrhea, vomiting • Chills • Swelling of arms, legs • Flu-like symptoms including body aches • Cold symptoms such as stuffy nose, sneezing, sore throat • Bleeding (The risk is increased when dabrafenib (GSK2118436B) is used together with trametinib dimethyl sulfoxide.) • Infection, especially when white blood cell count is low • Loss of appetite • A new skin cancer resulting from treatment of earlier cancer • Wart • Dizziness • Cough • Dry skin • Change in hair • Increased sweating • Redness, pain or peeling of palms and soles • Itching • High blood pressure which may cause headaches, dizziness, blurred vision • Blood clot which may cause swelling, pain, shortness of breath (The risk is increased when dabrafenib (GSK2118436B) is used together with trametinib dimethyl sulfoxide.)

RARE, AND SERIOUS In 100 people receiving dabrafenib (GSK2118436B), 3 or fewer may have:
• Damage to the heart which may cause shortness of breath, swelling of ankles, and tiredness • Heart failure which may cause shortness of breath, swelling of ankles, and tiredness. • Swelling and redness of the eye with a chance of blindness • Visual loss • A tear or hole in the bowels that may require surgery • Pain in belly (pancreas) that may require hospitalization • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat. • Production of too many white cells that may cause failure of multiple organs • Fainting • Kidney damage which may require dialysis (The risk is increased when dabrafenib (GSK2118436B) is used together with trametinib dimethyl sulfoxide.) • Skin rash developing 1-8 weeks after a drug is given which may be accompanied by fever, lymph node swelling and organ failure. • Swelling and redness of the skin • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body

Rev. 2/16, 1/17
Rev. Add19
Rev. Add25

Possible Side Effects of Trametinib

(Table Version Date: July 25, 2025)

COMMON, SOME MAY BE SERIOUS In 100 people receiving trametinib, more than 20 and up to 100 may have:
• Diarrhea, nausea • Tiredness • Swelling of the body • Skin changes including rash, acne

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving trametinib, from 4 to 20 may have:
• Anemia which may require blood transfusion • Abnormal heartbeat which may cause fainting • Blurred vision or other visual disturbances • Dry eye, mouth, skin • Swelling of the eye • Pain • Constipation, heartburn, vomiting

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving trametinib, from 4 to 20 may have:
• Sores in the mouth which may cause difficulty swallowing • Chills, fever • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Infection • Swollen or broken skin around the nail which may cause redness or infection • Change in heart function • Loss of appetite, dehydration • Dizziness, headache • Muscle weakness • Numbness, tingling or pain of the arms and legs • Cough, shortness of breath • Hair loss, itching • Change in or loss of some or all of the finger or toenails • High blood pressure which may cause headaches, dizziness, blurred vision • Bleeding

RARE, AND SERIOUS In 100 people receiving trametinib, 3 or fewer may have:
• Heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Change in the eyes (blood clot or retinal detachment) which may cause blindness • Blood clot which may cause swelling, pain, shortness of breath • A tear or hole in the bowels that may require surgery • Life threatening disorder where the immune system attacks the cells/organs of the body which may cause fever, rash, yellow eyes and skin, shortness of breath, headache, weakness, swollen lymph nodes • Kidney damage which may require dialysis • Damage to muscle which may cause muscle pain, dark red urine • Damage to the lungs which may cause shortness of breath • Redness, pain or peeling of palms and soles • Skin rash developing 1-8 weeks after a drug is given which may be accompanied by fever, lymph node swelling and organ failure • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body

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 drugs, so that he/she can take action to prevent any potential drug interactions.

Rev.2/16 Please refer to the drug interaction handout and wallet card for additional information.

Rev. 3/17 **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 for 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 drugs:

- 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?

Trametinib and dabrafenib will be supplied at no charge while you take part in this study. It is possible that trametinib and dabrafenib 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.

Rev.2/16

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 or any 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).

Rev. 8/15

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 _____

Rev. 8/15, 2/16, 3/17

Study Calendar:

Visit	Patient Activities
Before starting study drugs (within four to six weeks of start of treatment)	• Routine blood tests • Electrocardiogram (ECG) • Pregnancy test (if you are a woman who could become pregnant) • History and physical examination • Imaging (CT or MRI; same method to be used at future visits) • Eye exam by an ophthalmologist • Echocardiogram (ECHO) or nuclear study (Multigated Acquisition [MUGA] or similar scan) to assess your heart function • Dermatologic exam
Week 1: Day 1	• Routine blood tests • History and physical examination • Begin taking the study drugs, Dabrafenib and Trametinib.
Week 5: Day 1	• Routine blood tests • History and physical examination • Electrocardiogram (ECG) • Echocardiogram (ECHO) or nuclear study (Multigated Acquisition [MUGA] or similar scan) to assess your heart function • Eye exam by an ophthalmologist, if clinically necessary • Return pills and patient pill calendar
Week 9 (and onwards): Day 1	• Every 4 weeks: Routine blood tests, a history of how you feel, a physical examination, and an eye exam (if clinically necessary) • Every 8 weeks: Imaging (CT or MRI; by same method as screening), and a dermatologic exam • Week 13 and every 12 weeks thereafter: An electrocardiogram (ECG) and an echocardiogram (ECHO) or a nuclear study (multigated acquisition [MUGA] or similar scan) of your heart • Return pills and patient pill calendar at each clinic visit
End of treatment	• Side effects assessment • Return pills and patient pill calendar • Dermatologic exam
Follow up: Every three months for two years and every six month 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 • Dermatologic exam