To: CTEP Protocol and Information Office

From: [redacted], MD, DTC, NCI

Date: January 7, 2020

Re: Amendment to Protocol 9149: Molecular Profiling-based Assignment of Cancer Therapy for Patients With Advanced Solid Tumors (MPACT)

With this amendment, we would like to update the Treatment consent form to allow the sole patient who continues to receive randomized Trametinib DMSO treatment (22+ cycles) to consent to having her mutational status and arm assignment (i.e., experimental or control) disclosed to herself and/or her treating physician now, rather than wait until disease progression, given the new non-randomized study design and statistical analysis plan. We would also like to allow this patient to consent to sample unlinking while she remains on study, in order to enable research-use analysis of the sample in parallel with the other results from the randomized phase of the study. Thank you for your consideration.

#	Section	Comments
1.	Header	Updated the protocol version date.
2.	How long will I be in this study? My choices if I joined the study before 2019	Given the new non-randomized study design and statistical analysis plan, we would like to revise and update the protocol to allow the sole patient who continues to receive randomized Trametinib DMSO treatment (22+ cycles to consent to having her mutational status and arm assignment (i.e., experimental or control) disclosed to herself and/or her treating physician now, rather than wait until disease progression to find out per the original study plan. The patient, in discussion with the treating physician, will have the same on-study treatment options at progression as before, but because she is unblinded we think she will have better information sooner about her future treatment options.
3.	My choices if I joined the study before 2019	Revised document to allow the sole remaining randomized patient to give her consent for sample unlinking to occur while the patient remains on study, in order to enable research analysis of the sample in parallel with the other results from the randomized phase of the study.

Consent Form

Study Title for Study Participants: MPACT study to compare effects of targeted drugs on tumor gene variations

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: P9149, Molecular Profiling-based Assignment of Cancer Therapy for Patients With Advanced Solid Tumors (MPACT)

What is the usual approach to my cancer?

You are being asked to take part in this research study because standard medical treatments such as chemotherapy, surgery, and/or radiotherapy have not been very effective for the type of advanced cancer that you have.

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:

- your doctor will discuss possible treatment options for your cancer
- you may choose to take part in a different research 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?

Blood, tissue, and tumor cells contain genes which are made up of DNA and which serve as the "instruction book" for each cell in the body. We know that variations in some tumor genes play an important role in how cancers grow. Identifying these tumor variations and selecting drugs that work against them is one way scientists are trying to treat cancer. However, we do not know whether patients treated with a drug designed to target their tumor variation actually get benefit from the treatment (that is, show tumor shrinkage or tumor stability over time). In this research study, we are studying four different investigational treatments:

- **AZD1775 with carboplatin**
- **Trametinib DMSO**
- **Everolimus**
- **Veliparib with temozolomide**

The study drugs on this trial are all investigational and are not approved by the Food and Drug Administration (FDA) for your type of cancer. Some of these drugs are approved by the FDA to treat other types of cancer. Please ask your study doctor for more information about this.

To do this research study, we first needed to find out if your tumor had one of the gene variations we are studying. Our results show that you **do** have one of these variations. Up to 100 patients will participate in this research study at several cancer research centers in North America.

What are the study groups?

The design of this study has changed since we first opened it in 2014. At that time, patients were randomized (like flipping a coin) to receive **either** a study drug thought to work on their tumor gene variation (group 1), **or** a study drug thought not to work on their tumor gene variation (group 2). The study drugs were one of the four treatments on the previous page. We have since completed enrolling patients on 3 of the 4 treatment groups. Some patients are still receiving these study treatments. We learned that these 3 treatments did not work better in patients who had that tumor variation than in patients who did not. We have not yet learned if the 4th treatment, veliparib with temozolomide, works better in patients with your tumor variation. New patients who agree to take part in this study will be given the study drugs veliparib and temozolomide. After the first 12 patients have taken part, we will stop adding new patients if the drugs are not working. Please feel free to ask your study team for more information about this.

If your cancer gets worse, we may ask you for a tumor biopsy to find out if your tumor gene variations have changed since you began taking study drugs. This biopsy is optional and for research.

All of the study drugs are taken by mouth except for carboplatin, which is administered by IV (through a vein in your arm). Your study doctor will explain how often you will take the drugs and when you will need to come to the Clinical Center for study tests and procedures. The treatment is given over cycles, which are either 3 or 4 weeks long depending on which drug you are given. The drugs used in this study have known side effects that we will discuss with you before you sign this consent form.

How long will I be in this study?

You will receive study drugs for as long as you are tolerating them and your cancer is either stable or getting better. After you finish this research study, we would like to look in more detail at your tumor to find out if it had other gene variations. We will only do this once you have finished taking study drugs and we have deleted all your personally identifiable information (such as your name and medical record number) from each sample so that we cannot "link" your personal information with the genetic results.

Your doctor will continue to watch you for side effects and follow your condition for 30 days after you finish the study, or until any drug-related side effects you may have had have stabilized or resolved.

If you joined the study before 2019, you were randomized to treatment group 1 or treatment group 2. You and your doctor were not told which group you were placed in. Now that we are done comparing the two groups, we would like to ask you if you would like to know now which group you are in. The original plan was to wait until your cancer got worse before telling you. You will still be able to switch to a different study treatment that is thought to work on your tumor gene variation if you are not currently being treated with that drug. Please ask your study doctor for more information about this.

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 may need to have if you take part in this study that are not part of the usual approach for your type of cancer.

Before you begin the study:

You will need to have the following extra tests and procedures to find out if you can be in the study:

- a pregnancy test, if you are a woman capable of becoming pregnant. If you are pregnant you will not be eligible to take part in this research study.
- an eye exam for patients taking certain study drugs. This will be explained by your study doctor.
- an echocardiogram (depending on the study treatment)

If the extra tests and procedures show that you can take part in the study, and you choose to take part, then you will have the following extra tests and procedures during the study:

- an optional tumor biopsy, if your cancer gets worse on treatment (we will ask you to sign a separate consent document for this procedure)
- an echocardiogram (depending on the study treatment) may be done every 3 cycles

We will give you a study chart so that you can see when you need to come in to the Clinic to have these tests and procedures done.

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
- There is a risk someone could get access to the personal information in your medical records or other information researchers have kept about you. Someone might be able to trace this information back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job. There are laws against misuse of genetic information, but they may not give full protection. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.
- The study drugs may not be better, and could possibly be worse, than the usual approach for your cancer.
- There can also be a risk in finding out new genetic information about you. New health information about inherited traits that might affect you or your blood relatives could be found during the study.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except that the Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the US Food and Drug Administration (FDA). Please understand that a Certificate of Confidentiality does not prevent you, the researchers, or a member of your family from voluntarily releasing information about yourself or your participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information. **There also may be other privacy risks that we have not foreseen.**

The drugs 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. 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.

Inform your physician and study healthcare team about current medications including over the counter drugs, herbals, or natural medicines. We do not know if taking any of the study drugs will cause other drugs you may be taking to work differently. It is very important that you talk to a member of the research team before beginning any new drugs, over-the-counter medications, vitamins, or alternative therapies.

The tables on the next pages 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.

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

Taking this drug? Yes/No

Possible side effects of AZD1775 in combination with chemotherapy:

COMMON, SOME MAY BE SERIOUS

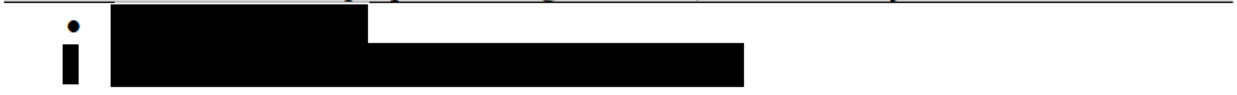
In 100 people receiving AZD1775, more than 20 and up to 100 may have:

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving AZD1775, from 4 to 20 may have:

RARE, AND SERIOUS

In 100 people receiving AZD1775, 3 or fewer may have:



Possible side effects of Carboplatin:

COMMON, SOME MAY BE SERIOUS

In 100 people receiving Carboplatin, more than 20 and up to 100 may have:

- Hair loss
- Vomiting, nausea
- Infection, especially when white blood cell count is low
- Anemia which may cause tiredness, or may require blood transfusions
- Bruising, bleeding
- Belly pain

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving Carboplatin, from 4 to 20 may have:

- Diarrhea, Constipation
- Numbness and tingling in fingers and toes
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

RARE, AND SERIOUS

In 100 people receiving Carboplatin, 3 or fewer may have:

- Changes in vision
- Changes in taste
- Damage to organs which may cause hearing and balance problems

Recommendations when taking this drug:

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with carboplatin.

Possible side effects of Everolimus: Taking this drug? Yes/No

COMMON, SOME MAY BE SERIOUS

In 100 people receiving everolimus, more than 20 and up to 100 may have:

- Anemia, which may require blood transfusion
- Diarrhea
- Sores in the mouth which may cause difficulty swallowing
- Tiredness
- Rash

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving everolimus, from 4 to 20 may have:

- Pain
- Constipation, nausea, vomiting
- Swelling of arms, legs
- Fever
- Infection, especially when white blood cell count is low
- Bruising, bleeding
- Weight loss, loss of appetite
- Changes in taste
- Headache
- Cough, shortness of breath
- Nose bleed
- Damage to the lungs which may cause shortness of breath
- Dry skin
- Itching

RARE, AND SERIOUS

In 100 people receiving everolimus, 3 or fewer may have:

- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Non-healing surgical site
- Kidney damage which may require dialysis

Recommendations when taking this drug:

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with everolimus.

Possible side effects of Temozolomide

Taking these drugs? Yes/No

COMMON, SOME MAY BE SERIOUS

In 100 people receiving Temozolomide, more than 20 and up to 100 may have:

- Headache, seizure
- Constipation, nausea, vomiting, diarrhea
- Trouble with memory
- Difficulty sleeping
- Muscle weakness, paralysis, difficulty walking
- Dizziness
- Tiredness
- Hair loss

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving Temozolomide, from 4 to 20 may have:

- Infection, especially when white blood cell count is low
- Bruising, bleeding
- Anemia which may cause tiredness, or may require transfusions
- Severe skin rash with blisters and can involve inside of mouth and other parts of the body
- Rash

RARE, AND SERIOUS

In 100 people receiving Temozolomide, 3 or fewer may have:

- Cough, damage to the lungs which may cause shortness of breath
- Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require blood transfusions
- Liver damage which may cause yellowing of eyes and skin, swelling
- A new cancer including leukemia resulting from treatment of a prior cancer

Possible side effects of Veliparib:

COMMON, SOME MAY BE SERIOUS

In 100 people receiving veliparib, more than 20 and up to 100 may have:

Nausea
Tiredness
Bruising, bleeding

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving veliparib, from 4 to 20 may have:

Anemia which may require blood transfusion
Infection, especially when white blood cell count is low
Belly pain
Constipation, diarrhea, vomiting
Weight loss, loss of appetite
Dehydration

Dizziness, headache
Changes in taste
Rash

RARE, AND SERIOUS

In 100 people receiving veliparib, 3 or fewer may have:

Cancer of bone marrow caused by chemotherapy
Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions
A new cancer resulting from treatment of earlier cancer
Seizure
Blood clot which may cause swelling, pain, shortness of breath

Recommendations when taking this drug:

We recommend that you avoid being in the sun as much as possible because this can make any skin rash you might get from Veliparib worse. You should also use a sun screen.

Possible side effects of Trametinib DMSO:

COMMON, SOME MAY BE SERIOUS

In 100 people receiving trametinib (GSK1120212B), 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 (GSK1120212B), from 4 to 20 may have:

- Anemia which may require blood transfusion
- Abnormal heartbeat
- Blurred vision or other visual disturbances
- Dry eye, mouth, skin
- Swelling of the eye
- Pain
- Constipation, heartburn, vomiting
- 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
- Change in heart function
- Loss of appetite, dehydration
- Dizziness, headache
- 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 (GSK1120212B), 3 or fewer may have:

- Heart failure which may cause shortness of breath, swelling of ankles, and tiredness
- Changes 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
- 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

Recommendations when taking this drug:

Tell your doctor about any changes in your vision; your doctor will send you for eye exam and treatment may need to be interrupted. It is important that you do not drive a car or work with machinery if you are experiencing any visual changes.

You should not get pregnant or breastfeed while on this study or for 3 months after you finish study treatment. The drugs used in this study could be very damaging to an unborn baby or nursing child. It is important that you use a combination of any two of the following (a+b or a+c or b+c):

a. Use of oral, injected, implanted, or other hormonal methods of contraception
b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

As a male participant in the study, you must agree to use a condom during intercourse and not father a child during the study and for the period of 3 months following stopping of study treatment. In addition, it is advised that your female partner uses a highly effective form of birth control method (contraception) if she is sexually active and may become pregnant.

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

We do not know if you will receive personal, medical benefit from taking part in this study. The knowledge gained from this study may help others in the future who have cancer.

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 taking study drugs 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 you become pregnant
- If the study is stopped by the sponsor, the IRB (people who review the research to protect the people taking part in the study), 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) Patient Representatives* _____ *(insert telephone number)*

What are the costs of taking part in this study?

Veliparib, trametinib DMSO, AZD1775, everolimus, temozolomide, and carboplatin will be supplied at no charge while you take part in this study. The cost of getting the study agent ready and giving it to you is not paid by the study sponsor, so you or your insurance company will have to pay for this. It is possible that the study agents 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 caring for your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied 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 and pharmaceutical collaborators 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 secure central database for research. Your name or contact information will not be put in the database.

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, drug companies, and pharmaceutical collaborators supporting the study
- The IRB (Institutional Review Board), 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 (FDA) and the National Cancer Institute (NCI) 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 choices if I joined the study before 2019

Please read each sentence below and think about your choice. After reading each sentence, circle and initial the answer that is right for you. No matter what you decide to do, it will not affect your care. Circle your choice of "yes" or "no" for the following:

1. My doctor can be told the results of my tumor gene variations and my treatment group assignment now, instead of waiting until my cancer gets worse.
Yes_____No_____

2. If my doctor is told the results of my tumor gene variations and my treatment group assignment before my cancer gets worse, I can be told the results at that time too.
Yes_____No_____

3. My tumor samples that were collected during the screening part of this study can be separated from my personally identifiable information and used for research now, instead of when I finish taking study drugs.
Yes_____No_____

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 research study.

Participant's signature_____

Print name: _____

Date of signature_____