Protocol Title:

A Phase 2 Study of lamivudine in patients with p53 mutant metastatic colorectal cancer

DF/HCC Principal Research Doctor / Institution:

Aparna Raj Parikh, MD / Massachusetts General Hospital

Phase II Consent

A. INTRODUCTION

You are invited to take part in a clinical trial, a type of research study, because you have p53 mutant metastatic colorectal cancer. This research study is studying a drug as a possible treatment for this diagnosis.

The name of the study drug involved in this study is:

- Lamivudine

For purposes of this research, you will be referred to as a "participant".

It is expected that about 32 people will take part in this research study.

An Internal Fund at MGH, is supporting this research study by providing funding for the research study.

This research consent form explains why this research study is being done, what is involved in participating in the research study, the possible risks and benefits of participation, alternatives to participation, and your rights as a research participant. The decision to participate is yours. If you decide to participate, please sign and date at the end of this form. We will give you a copy so that you can refer to it while you are involved in this research study. If you choose not to participate in this research study, the research doctors will discuss other treatment options with you and/or refer you back to your primary doctor.

We encourage you to take some time to think this over, to discuss it with other people and your primary doctor, and to ask questions now and at any time in the future.

B. WHY IS THIS RESEARCH STUDY BEING DONE?

This research study is a Phase II clinical trial. Phase II clinical trials test the safety and effectiveness of an investigational drug to learn whether the drug works in treating a specific disease. "Investigational" means that the drug is being studied.

The FDA (the U.S. Food and Drug Administration) has not approved lamivudine for your specific disease but it has been approved for other uses.

In this research study, we are studying the effects of lamivudine on your type of cancer. This drug may help prevent the growth and spread of the cancer cells to other parts of your body. We have discovered that your particular type of colon cancer, which has a p53 mutation may be sensitive to treatment with lamivudine by impairing the ability of the cancer cells to grow.

C. WHAT OTHER OPTIONS ARE THERE?

Taking part in this research study is voluntary. Instead of being in this research study, you have other options which may include the following

- Receive standard treatment including TAS-102 or Regorafenib
- Take part in another research study.
- Receive no therapy specific to your cancer.
- Comfort care, also called palliative care. This type of care may help to reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to treat the symptoms.

Please talk to the research doctor about your options before you decide whether you will take part in this research study.

D. WHAT IS INVOLVED IN THE RESEARCH STUDY?

Sometimes it is hard to keep track of all of the details and procedures that are part of a research study. We will describe them in this consent form and you can refer to this at any time during the research study.

Before the research starts (screening):
After signing this consent form, you will be asked to undergo some screening tests or procedures to find out if you can be in the research study. Many of these

tests and procedures are likely to be part of regular cancer care and may be done even if it turns out that you do not take part in the research study. If you have had some of these tests or procedures recently, they may or may not have to be repeated.

- **A medical history,** which includes questions about your health, current medications, and any allergies.
- **Physical exam,** Including your height and weight measurements and your vital signs.
- **Performance status,** which evaluates how you are able to carry on with your usual activities.
- **Blood Tests.** You will have 15-20 ml of blood drawn to see how your body is reacting to this treatment.
- **Electrocardiogram (EKG),** which measures your heart's electrical activity
- **An assessment of your tumor** by one or more of the following standard assessment tools: X-ray, CT (Computerized Tomography) scan, MRI (Magnetic Resonance Imaging) or PET (Positron Emission Tomography) scans
- **Your previously collected and stored tissue (archival tissue) will be obtained for tests**. No additional tissue will be collected.
- **Tumor Biopsies.** A pre study biopsy will be required if a biopsy was not done after the most recent treatment received. The tumor biopsy should be collected, if medically feasible, in the opinion of the investigator**. There will also be a biopsy** at cycle 2 day 1 of treatment or prior if participants come off study prior. This biopsy should be +/- 1 week of treatment and of same lesion as pre-study biopsy if safe to do. These biopsies will help us understand the tumor at the time of starting treatment and the effect of the drug on the tumor. We do what we call sequencing of the tumor and we will look at the DNA and RNA of the tumor which can help us understand how the tumor reacts to the treatment. We also will look at how the immune system is working in the tumor based on the effect of the lamivudine.

These screening procedures may be repeated at each study visit.

If these tests show that you are eligible to participate in the research study, you may begin the study treatment. If you do not meet the eligibility criteria, you will not be able to participate in this research study.

Study Treatment Overview:

- **Oral Study Drug(s):** Each study treatment cycle lasts 28 days during which time you will be taking the study drug Lamivudine 2 times per day. This will continue until disease progression or you are taken off of the study.

You will come into the clinic once a week for all cycles and once again at the off-study appointment. You will be followed for up to 4 months after you have completed the study, or once you are taken off of the study.
If you take part in this research study you will be given a drug diary. You will be asked to document information in the drug diary about the study treatment you are being asked to take.

Research Study Plan:

	Pre-Study	Cycle 1*				Cycle 2+*		2 months	Off Study
		Day1	Day 8	Day 15	Day 22	Day1	Cycle 2 Day15§		
Medical history*	X	X	X	X	X	X	X		
Physical exam*	X	X	X	X	X	X	X		X
Performance status*	X	X	X	X	X	X	X		X
Blood Tests*	X	X	X	X	X	X	X		X
EKG (as indicated)*	X								
Tumor Assessment**	X	Tumor measurements are repeated every **8** weeks. Documentation (radiologic) must be provided for participants removed from study for progressive disease.							X
Archival Tissue	X								
Tumor Biopsy	X****					X***			
Lamivudine		X	X	X	X	X	X		
Surveys¶	X							X	
HIV test	X								

HBV test	X								
CEA		X				X			

*All Assessment will occur +/- 3 days
**Tumor Assessments will occur every 8 weeks
***On treatment biopsy will occur at cycle 2 day 1 or prior should treatment be stopped prior. This biopsy should be +/- 1 week of treatment and of same lesion as pre-study biopsy if safe to do.
****A pre study biopsy will be required if a biopsy was not done after the most recent treatment received. The tumor biopsy should be collected, if medically feasible, in the opinion of the investigator
§ Cycle2 Day15 visit will only be done at the discretion of the provider.
¶ Surveys will be administered at baseline on the date of enrollment or prior to start and then at every 2 months at the time of scans

Planned Follow-up:
We would like to keep track of your medical condition. We would like to do this by having you come into the clinic for a follow-up visit. Keeping in touch with you and checking your condition helps us look at the long-term effects of the research study.

E. HOW LONG WILL I BE IN THIS RESEARCH STUDY?

You will be on the study treatment until the time of disease progression or if you are taken off of the protocol. You will be followed for an additional 4 months.

You may be taken off the research study drug for many reasons including if:

- It is considered to be in your best interest
- The study treatment or procedures are found to be unsafe or ineffective
- There is any problem with following study treatments and procedures
- You are a female and become pregnant or plan to become pregnant
- Your condition worsens
- A decision is made to close the study
- Or for other unforeseen reasons that make it necessary to stop your participation in the research study

If you are removed from the research study, the research doctor will explain to you why you were removed.

In addition, you can stop participating in the research study at any time, however, the FDA requires that any information collected up to the point of your withdrawal cannot be removed from the study. If you decide to stop participating in this research study, we encourage you to talk to the research doctor and your primary doctor first.

F. WHAT ARE THE RISKS OR DISCOMFORTS OF THE RESEARCH STUDY?

There are risks to taking part in any research study. One risk is that you may get a study drug that does not help treat your disease or that makes your condition or disease worse. Another risk is that there may be side effects.

All cancer treatments can have side effects, which can range from mild and reversible to severe, long lasting and possibly life-threatening. There is a great deal of variability among side effects of different cancer treatments and between individuals. In a research study, all of the risks or side effects may not be known before you start the study. **You need to tell your doctor or a member of the study team immediately if you experience any side effects.**
Everyone in the research study will be watched carefully for side effects. You will be monitored during the administration of study drugs to keep track of your blood counts and organ function, particularly your kidney and liver function. If you experience side effects, they may go away after you stop taking the study drug. Some side effects can be mild; but others can be long lasting and may never go away. Some may be life-threatening or fatal.

Since the effect of the study drug taken with other medications may not be known, it is important that you tell the research doctor about all prescription and non-prescription drugs, herbal preparations and nutritional supplements that you are taking or planning to take. There may also be some foods that you should avoid while on this research study and your research doctor will review this information with you.

During the research study, you will be notified of newly discovered side effects or significant findings, which may affect your health or willingness to participate. You may be asked to sign a new consent form that shows that you have been informed of new information relating to this research study.

Risks Associated with Lamivudine:

You will be given a higher dose of lamivudine that what is currently approved but the dose was studied and deemed to be safe in HIV patients. We will also plan to

enroll a few patients and ensure they are safe on the higher dose before accruing the rest of the study. In HIV patients, mild diarrhea, headache, fatigue, nausea and abdominal pain were most commonly reported events.

Frequent (Between a 10-50% chance that this will happen)

- Diarrhea
- Nausea
- Headache
- Cough
- Your nasal cavity may fill with a significant amount of mucus fluid which may lead to a runny nose (rhinorrhea)
- Fever
- Pain in your abdomen, muscles, and bones
- Fatigue

Occasional (Between a 1-10% chance that this will happen)

- Inflammation of the pancreas (Pancreatitis) which may cause upper abdominal pain, abdominal pain that radiates to your back, abdominal pain that feels worse after eating, fever, rapid pulse, nausea, vomiting, and tenderness when touching the abdomen.

Rare (Less than a 1% chance that this will happen)

- Fat in your body will not be distributed evenly (fat maldistribution)
- Lactic acid build up in your body (lactic acidosis) which may cause stomach discomfort, decreased appetite, diarrhea, fast, shallow breathing, discomfort, muscle pain, fatigue (tiredness), and weakness.
- Enlarged liver (Hepatomegaly) which may cause yellowing of the skin or eyes, muscle aches, fatigue, itching, nausea, vomiting, abdominal pain, and poor appetite.
- Relapsing (return of) Type B Viral Hepatitis which may cause dark urine, stomach pain, yellowing of the skin or eyes, pale/clay-colored stool, low-grad fever, loss of appetite, fatigue, feeling sick to the stomach and a lack of nutrition.

Cancer research often includes biopsies, scans, x-rays that are also provided as routine care. The following describes the side effects of procedures done only for the purposes of research.

Risks Associated with Biopsies:

Biopsies are normally performed under the guidance of an imaging technique. Each procedure requires a separate consent prior to the biopsy. The risks may include:

- Pain and discomfort. The amount of pain and discomfort will vary, depending on the location of the biopsy site. These risks can be discussed with the study doctor.
- Minor bleeding at the biopsy site.
- Tenderness at the biopsy site.
- Scarring at the biopsy site.
- Rarely, an infection at the biopsy site.

Uncommonly, complications from biopsies can be life threatening. As with any interventional procedure, other potentially serious complications from bleeding or organ damage may occur. These might require additional surgical intervention.

Risks Associated with MRI Scans:
When having an MRI (Magnetic Resonance Imaging) scan, you will lie still on a table that slides into a tunnel slightly wider than your body. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow cylinder. If you feel uncomfortable in confined spaces, please tell your research doctor. Your doctor may give you a medication to make you feel more comfortable. As images are taken, a loud banging noise will be produced. Earplugs or headphones will be available if needed. The MRI can be stopped at any time at your request, but the scan may not be complete.

The MRI has the potential, during normal routine use, to cause localized warming of your skin and the underlying tissues. You should immediately inform us if you experience discomfort due to warming and the procedure will be stopped.

Risks Associated with Contrast Agents Used During Scans:
There is a small risk with using a contrast agent that is injected into a vein during the PET-CT. The contrast agent is a special dye that highlights organs, blood vessels or tissue to make them more visible. Depending on the type of contrast agent that is used, it may cause decreased kidney function or worsen kidney function in people who already have decreased kidney function. Therefore, we will monitor your kidney function closely while you participate in this study. If there is any change in your kidney function, we may have to remove you from the study.

Uncommonly, some people have allergic reactions (such as hives and itching) to the contrast agent. Serious reactions (for example, drop in blood pressure, difficulty breathing or severe allergic reaction and death) are rare.

Reproductive Risks:
The drugs used in this research study may affect a fetus. While participating in this research study and for 4 months after, you should not become pregnant or father a baby, and should not nurse a baby. We can provide counseling about preventing pregnancy for either male or female study participants. Let your doctor know immediately if you become pregnant or find out that you are going to be the father of a child.

In the event that your partner becomes pregnant, it may be critical to share information regarding your participation in this research study with that person. Your research doctor should also be told if this happens.

Non-Physical Risks:
Because of side effects or the time required for tests and clinic visits while you are on this research study, you may be unable to keep up with your normal daily activities.

G. WHAT ARE THE BENEFITS OF THE RESEARCH STUDY?

We do not know if taking part in this study will help you. This study may help researchers learn information that could help people in the future.

H. CAN I STOP BEING IN THE RESEARCH STUDY AND WHAT ARE MY RIGHTS?

You have the right to choose not to sign this form. If you decide not to sign this form, you cannot participate in this research study.

You can stop being in the research study at any time. Tell the research doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop. Leaving the research study will not affect your medical care outside of the research study.

If you choose not to participate, are not eligible to participate, or withdraw from this research study, this will not affect your present or future care and will not cause any penalty or loss of benefits to which you are otherwise entitled.

It is important to tell the research doctor if you are thinking about stopping so your research doctor can evaluate the risks from stopping the drug.

I. WILL I BE PAID TO TAKE PART IN THIS RESEARCH STUDY?

You will not be paid for participating in this study.

We may use your samples and information to develop a new product or medical test to be sold. The sponsor and hospital may benefit if this happens. There are no plans to pay you if your samples are used for this purpose.

J. WHAT ARE THE COSTS?

Taking part in this research study might lead to added costs to you or your insurance company.

You will not be charged for lamivudine. It is possible that lamivudine may not continue to be supplied free for some reason. If this would occur, your research doctor will talk with you about your options.

You or your insurance company will be charged for portions of your care during this research study that are considered standard care. You may be responsible for co-payments and deductibles that are typical for your insurance coverage.

If you have questions about your insurance coverage, or the items you might be required to pay for, please call financial services for information. The contact information for financial services are:

- Massachusetts General Hospital: (617) 726-2191

The National Cancer Institute provides an online resource to help people participating in cancer clinical trials understand which services their insurance company is required by law to pay. This can be found at the website below or can be provided by the study team:

www.cancer.gov or 1-800-4-CANCER (1-800-422-6237)

K. WHAT HAPPENS IF I AM INJURED OR BECOME SICK BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

If you think you have been injured as a result of taking part in this research study, tell the person in charge of this research study as soon as possible. The research doctor's name and phone number are listed in this consent form.

The treating hospital will offer you the care needed to treat injuries directly resulting from taking part in this research. These treatments will be billed to your insurance company. You will be responsible for deductibles and co-payments. There are no plans to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

We will need to collect certain personal information about you for insurance or payment reporting purposes, such as your name, date of birth, gender, social security number or Medicare identification number and information related to this research study. We may be required to report this information to the Centers for Medicare & Medicaid Services. We will not use this information for any other purpose.

L. Future use of data and Specimens

Your personal information and/or biospecimens collected during this study may be stored and used for future research. Any personal identifiers will be removed, before they are shared, so that the information or samples cannot be linked back to you.

Investigators, including investigators from collaborating institutions, can request this data and samples for new research. Samples and data may also be shared with outside non-profit academic investigators as well as with for-profit pharmaceutical investigators or commercial entities, with whom we collaborate.

You will not be asked to provide additional informed consent for the use of your identifiable information or samples in future research.

Future research studies may include genetic research. Your genes are unique to you. At this time, you cannot be identified through this research, if the samples and specimens are anonymized. There is a risk that you might be reidentified in the future as genetic research progresses

M. GENETIC RESEARCH

This research will involve genomic and germline testing.

The Genetic Information Nondiscrimination Act of 2008 (GINA) is a federal law that protects Americans from being treated unfairly because of differences in their DNA that may affect their health, and may prevent discrimination by health insurers and employers based on genetic information. GINA is intended to ease concerns about discrimination that might keep some people from getting genetic tests that could benefit their health, and enable people to take part in research studies such as this without fear that their DNA information might be used against them by health insurers or their workplace. This protection does not extend to disability or life insurance. Additional information can be found at http://www.genome.gov/10002328.

As part of this study, your anonymized specimens or genetic data may be placed into one or more publicly-accessible scientific databases, such as the National Institutes of Health's Database for Genotypes and Phenotypes (dbGaP). Through such databases, researchers from around the world will have access to anonymized samples or data for future research.

N. WHAT ABOUT CONFIDENTIALITY?

We will take measures to protect the privacy and security of all your personal information, but we cannot guarantee complete confidentiality of study data.

Medical information created by this research study may become part of your hospital medical record and may be forwarded to your primary doctor. Information that does not become part of your medical record will be stored in your study file. It may also become part of a DF/HCC research database.

The results of this research study may be published. You will not be identified in publications without your permission.

As participation in this study involves providing a specimen of your tissue, please know that if the research doctor leaves the institution, the research and the tissue might remain at the DF/HCC or might be transferred to another institution.

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.

O. WHOM DO I CONTACT IF I HAVE QUESTIONS ABOUT THE RESEARCH STUDY?

If you have questions about the study, please contact the research doctor or study staff as listed below:

Massachusetts General Hospital
- Aparna Raj Parikh, MD: (617) 724-4000

24-hour contact: Please contact Massachusetts General Hospital at 617-724-4000 and ask that your doctor be paged.

For questions about your rights as a research participant, please contact a representative of the Office for Human Research Studies at DFCI (617) 632-3029. This can include questions about your participation in the study, concerns about the study, a research related injury, or if you feel/felt under pressure to enroll in this research study or to continue to participate in this research study.

P. PRIVACY OF PROTECTED HEALTH INFORMATION

Federal law requires Dana-Farber/Harvard Cancer Center (DF/HCC) and its affiliated research doctors, health care providers, and physician network to protect the privacy of information that identifies you and relates to your past, present, and future physical and mental health conditions ("protected health information"). If you enroll in this research study, your "protected health information" will be used and shared with others as explained below.

1. What protected health information about me will be used or shared with others during this research?

- Existing medical records, including mental health records.
- New health information created from study-related tests, procedures, visits, and/or questionnaires

2. Why will protected information about me be used or shared with others?

The main reasons include the following:
- To conduct and oversee the research described earlier in this form;
- To ensure the research meets legal, institutional, and accreditation requirements;

- To conduct public health activities (including reporting of adverse events or situations where you or others may be at risk of harm); and
- To provide the study sponsor with information arising from an adverse event or other event that relates to the safety or toxicity of the drug(s) used in the study and for the purpose of this or other research relating the study drug(s) and their use in cancer;
- To better understand the diseases being studied and to improve the design of future studies; and,
- Other reasons may include for treatment, payment, or health care operations. For example, some medical information produced by this research study may become part of your hospital medical record because the information may be necessary for your medical care. (You will also be given a notice for use and sharing of protected health information.)

3. Who will use or share protected health information about me?

- DF/HCC and its affiliated research doctors and entities participating in the research will use and share your protected health information. In addition, other DF/HCC offices that deal with research oversight, billing or quality assurance will be able to use and share your protected health information.

4. With whom outside of DF/HCC may my protected health information be shared?

While all reasonable efforts will be made to protect the confidentiality of your protected health information, it may also be shared with the following entities:

- Outside individuals or entities that have a need to access this information to perform functions relating to the conduct of this research such as analysis by outside laboratories on behalf of DF/HCC and its affiliates (for example, data storage companies, insurers, or legal advisors).
- The sponsor(s) of the study, its subcontractors, representatives, business partners, and its agent(s): DF/HCC
- The funder(s) of the study, its subcontractors, representatives, business partners, and its agent(s): Sundry
- Other research doctors and medical centers participating in this research, if applicable

- Federal and state agencies (for example, the Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and/or the Office for Human Research Protections), or other domestic or foreign government bodies if required by law and/or necessary for oversight purposes. A qualified representative of the FDA and the National Cancer Institute may review your medical records.
- Hospital accrediting agencies
- A data safety monitoring board organized to oversee this research, if applicable

Some who may receive your protected health information may not have to satisfy the privacy rules and requirements. They, in fact, may share your information with others without your permission.

5. For how long will protected health information about me be used or shared with others?

- There is no scheduled date at which your protected health information that is being used or shared for this research will be destroyed, because research is an ongoing process.

6. Statement of privacy rights:

- You have the right to withdraw your permission for the research doctors and participating DF/HCC entities to use or share your protected health information. We will not be able to withdraw all the information that already has been used or shared with others to carry out related activities such as oversight, or that is needed to ensure quality of the study. To withdraw your permission, you must do so in writing by contacting the researcher listed above in the section: “Whom do I contact if I have questions about the research study?”
- You have the right to request access to your protected health information that is used or shared during this research and that is related to your treatment or payment for your treatment, but you may access this information only after the study is completed. To request this information, please contact the researcher listed above in the section: “Whom do I contact if I have questions about the research study?”

Q. DOCUMENTATION OF CONSENT

My signature below indicates:

- I have had enough time to read the consent and think about participating in this study;
- I have had all of my questions answered to my satisfaction;
- I am willing to participate in this study;
- I have been told that my participation is voluntary and I can withdraw at any time

Signature of Participant
or Legally Authorized Representative

Date

Relationship of Legally Authorized Representative to Participant

DFCI Protocol Number: 17-044	Approved Date (DFCI IRB Approval): 08/23/2019
Date Posted for Use: 08/27/2019	

Research Consent Form
for Biomedical Research
Dana-Farber/ Harvard Cancer Center
BIDMC/BCH/BWH/DFCI/MGH/Partners Network Affiliates OHRS 09.23.16a

To be completed by person obtaining consent:

Adult Participant

The consent discussion was initiated on _____ (date).

Signature of individual obtaining consent: _____

Printed name of above: _____

Date: _____

☐ A copy of this signed consent form will be given to the participant or legally authorized representative.

☐ 1) The participant is an adult and provided consent to participate.

☐ 1a) Participant (or legally authorized representative) is a non-English speaker and signed the translated Short Form in lieu of English consent document:

As someone who understands both English and the language spoken by the participant, I interpreted and/or witnessed, in the participant's language, the researcher's presentation of the English consent form. The participant was given the opportunity to ask questions.

Signature of Interpreter/Witness: _____

Printed Name of Interpreter/Witness: _____

Date: _____

☐ 1b) Participant is physically unable to sign the consent form because:

☐ The participant is illiterate.

☐ The participant has a physical disability.

☐ Other (please describe): _____

The consent form was presented to the participant who was given the opportunity to ask questions and who communicated agreement to participate in the research.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

☐ 2) The participant is an adult who lacks capacity to provide consent and his/her legally authorized representative:

☐ 2a) gave permission for the adult participant to participate

☐ 2b) did not give permission for the adult participant to participate

DFCI Protocol Number: 17-044	Approved Date (DFCI IRB Approval): 08/23/2019
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