A Phase II Open-label Study of Combined Ruxolitinib and Enasidenib in Patients With Accelerated/Blast-phase Myeloproliferative Neoplasm or Chronic-phase Myelofibrosis With an IDH2 Mutation
John Mascarenhas, MD
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CONSENT FORM TO VOLUNTEER IN A RESEARCH STUDY
AND AUTHORIZATION FOR USE AND DISCLOSURE OF MEDICAL INFORMATION

Form Version Date: 11 Nov 2021

STUDY INFORMATION:

Study Title: A Phase II Open-label Study of Combined Ruxolitinib and Enasidenib in Patients with Accelerated/Blast-phase Myeloproliferative Neoplasm or Chronic-phase Myelofibrosis with an IDH2 Mutation (MPN-RC 119)

Principal Investigator: Michal Bar-Natan, MD

Physical Address: Ruttenberg Cancer Center, 1470 Madison Ave., New York, New York 10029

Mailing Address: **Icahn School of Medicine at Mount Sinai, Hematology/Oncology,**

One Gustave L. Levy Place, New York, NY 10029

Phone: 212-241-0481

SUMMARY OF THIS RESEARCH STUDY:

In medicine, there are many unanswered questions. A "research study" is when scientists try to answer a question about something that we don't know enough about. Participation in a research study may or may not directly help you or others. Participation is entirely voluntary. It is completely up to you whether or not you take part. You can also change your mind at any time and it will not affect your ability to get medical care within the Mount Sinai Health System

The purpose of this research study is to test the effectiveness and safety of Enasidenib when used in combination with the standard of care drug Ruxolitinib and to find out how well it works in patients with either accelerated or blast phase myeloproliferative neoplasm or high risk Chronic-phase myelofibrosis and who have an IDH2 mutation.

Myelofibrosis occurs when an enzyme called Janus Kinases (JAKs) affects the ability of blood stem cells to form the normal amounts of red and white blood cells and platelets. It is believed that overactive JAK signaling (with or without a JAK mutation) affects the normal production of blood stem cells from bone marrow. Blood stem cells are formed in the bone marrow. The bone marrow of patients with myelofibrosis and MPN is extensively scarred because mutated blood stem cells produce mature cells that grow too quickly and take over the bone marrow. Scar tissue in the bone marrow affects the body's ability to produce a normal level of blood cells. People who have accelerated phase MPN or myelofibrosis have too few red blood cells and frequently have an enlarged spleen. The spleen is often enlarged because blood cell production may have moved from bone marrow to the spleen.

Standard treatment for people with myelofibrosis is Ruxolitinib. Ruxolitinib is a treatment that targets JAK signaling. Ruxolitinib works by reducing the overactive signaling of the JAK to keep the production of blood cells controlled.

Many patients who have myeloproliferative diseases have an IDH2 mutation. Research indicates that MPN patients with the IDH mutation have a higher risk of their MPN transforming to acute leukemia.

Enasidenib is an FDA approved drug for the treatment of patients with relapsed or refractory acute myeloid leukemia who have an IDH2 gene mutation. Enasidenib works by inhibiting the IDH2, reducing the levels of its product and helping your bone marrow grow normal mature blood cells.

This study proposes that the combination of these two drugs in patients who have MPN and an IDH2 mutation will improve the response to therapy. While many patients have received each of these drugs separately, they have not been given together before.

Response to the combination of these two drugs will be measured based upon by a reduction of scar tissue forming in bone marrow, blood cell levels, reduction of spleen and liver size, recovery of blood cell formation in bone marrow, increase in quality of life, and reduction of other symptoms associated with MPN.

Safety of this study will be measured by collecting data on side effects you may or may not experience. Possible side effects are detailed in another section of this document.

You are being asked to participate in this study because you have either a Myeloproliferative Neoplasm (MPN) in accelerate or blast phase or previously treated high-risk Chronic-phase myelofibrosis. If not already known, you will be tested to see if you have the IDH2 mutation to determine if you qualify for participation.

If you choose to participate, your participation will be as follow. Each cycle is 28 days. Participation may last for 6 cycles and continue for further cycles until you no longer respond to the study regimen, have a side effect that prevents you from continuing the study regimen, you decide to no longer participate, or indefinitely if you have a good response to the study regimen.

Visits during the first two cycles will be weekly and then will be every 4 weeks from cycle 3 and beyond. Visits will include lab work, ECG's, physical exam, and the collection of blood and bone marrow samples. During your participation in this study, you will be asked to maintain a drug diary, take surveys that will tell us about how you are doing and provide information about any side effects you may experience. At the end of your study participation, another visit is required after 30 days to see if you have any lingering side effects.

The main risks to you if you choose to participate are abnormal blood counts, bleeding and bruising, dizziness, headache, urinary tract infections, weight gain, gas, shingles, increased blood pressure, constipation, other infections (including Tuberculosis), nausea, vomiting, decreased appetite, loss of taste, abnormal labs, fast or chaotic heartbeats, and differentiation syndrome (IDH-DS), and possible death. Differentiation Syndrome is a side effect of Enasidenib. IDH-DS is condition that affects your blood cells and should be treated immediately. Symptoms of IDH-DS include fever, cough, shortness of breath, rapid weight gain (more than 10 pounds in a week), swelling in the arms, legs, neck, groin, or underarms, and bone pain. There is more detailed risk information later in this consent.

REPRODUCTIVE RISKS

If you are a woman who is pregnant or planning to get pregnant, you cannot take part in this study because we do not know how the study regimen might affect a developing fetus. We will do a pregnancy test before you start the study regimen to make sure you are not pregnant.

CONCERNS FOR SEXUALLY ACTIVE MEN AND WOMEN: Women should not become pregnant and men should not father a baby while taking part in this study because we do not know how the study regimen/ procedures could affect a man's sperm (for some regimens/procedures, the concern may be that the sperm might be affected and in some cases, could be carried by the semen into the vagina and cause harm) or a fetus, if a woman becomes pregnant during the study.

A member of the research team is available to answer any questions you may have about this study. Please feel free to ask questions that you may have before you decide to participate. You may also take home an unsigned copy of this form to think about or discuss with family or friends before deciding. If you choose to participate, any new information that develops during this research study such as new risks or benefits will be given to you promptly. If you participate, you will be given a copy of this signed and dated form.

If you are interested in learning more about participating in this study, please continue to read below.

PARTICIPATION IN THIS RESEARCH STUDY:

This research study will be fully explained to you by a member of the study team. Feel free to ask all the questions you want before you make a decision about whether or not to participate. Any new information that develops during this research study that might make you change your mind about participating will be given to you promptly.

You may qualify to take part in this research study because you have an IDH2 gene mutation and you have a diagnosis of one of the following: accelerated-phase myelofibrosis, blast phase myelofibrosis or chronic phase myelofibrosis with high-risk features. Myelofibrosis (MF) is an uncommon type of leukemia that affects your body's normal production of blood cells. The production of blood cells normally occurs in your body's bone marrow, however, people with MF's bone marrow is often scarred which leads to a lack of red blood cells which result in anemia, weakness, fatigue and an enlarged spleen. A gene mutation named JAK2 is thought to be the reason why people develop myelofibrosis.

DISCLOSURE OF FINANCIAL INTERESTS:

Funds for conducting this research are provided to the Myeloproliferative Neoplasms Research Consortium (MPN-RC) through a grant provided by the National Cancer Institute (NCI). Additional funds are being provided by Celgene and Incyte. Celgene will provide the study drug Enasidenib. Celgene will be providing Enasidenib to study participants. Incyte, the manufacturer of ruxolitinib or Jakafi, will also provide funds. Celgene and Incyte have a financial interest that could be affected by the outcome of the results of this research study.

Dr. John Mascarenhas (a Sub-Investigator in this study) receives financial compensation as an advisory board member for Celgene (provider of funds for this study and manufacturer of Enasidenib, a drug being investigated in this study).

In addition, Dr. Mascarenhas receives financial compensation as a consultant for the Incyte Corporation (provider of funds for this study and manufacturer of Ruxolitinib, a drug being investigated in this study).

If you have questions regarding paid relationships that your physician/researcher may have with industry, we encourage you to talk with him or her, or check for industry relationships posted on individual faculty pages on our website at http://icahn.mssm.edu/.

LENGTH OF TIME AND NUMBER OF PEOPLE EXPECTED TO PARTICIPATE:

Your participation in this research study is expected to last at least six months unless you have a bad reaction to the study drug. If you respond well, then you can remain on the study regimen until either you decide you want to stop, or the physician decides that it is no longer safe or effective for you to receive the study drug, or the study closes.

The number of people expected to take part in this research study at this site, the Icahn School of Medicine at Mount Sinai is 7. This study will also be conducted at 9 other sites. The total number of people expected to take part in this multi-site research study is 32.

DESCRIPTION OF WHAT'S INVOLVED:

If you agree to participate in this research study, the following information describes what may be involved.

No procedures may take place until you have agreed to participate in this study and signed this form. All procedures will take place at Ruttenberg Cancer Center unless otherwise specified.

Screening:

- *Medical History and Physical Exam: A complete history and physical exam and manual measurement (in cm) of your liver and spleen, if palpable. Your study doctor will ask you a series of questions. He or she will use a stethoscope (a device placed on your skin to allow the doctor to hear inside your body) to listen to your heart, lungs, and belly. He or she will feel your entire body, including your neck, trunk, arms, and legs.*
- *Measurements of your vital signs: heart rate, breathing rate, blood pressure, temperature, weight, and height.*
- *You will be asked to provide information about your age, race, gender, and ethnicity.*
- *You will be asked to provide information about your prior medical history including all active conditions and conditions you have been told you have within the last 10 years. You will also be asked to provide information about what treatment, if any you have had for these conditions.*
- *Current medications will also be reviewed. It is important that you tell your study doctor about any medications you are currently taking or have taken within the last 30 days. Please tell your study doctor about all medications including over-the-counter medications, vitamins, herbal medications, and alternative medicines. You may need to stop some of your medicines in order to be able to take part in this study.*
- *You will be asked about any transfusion history you have had within the last 3 months.*
- *Bone marrow aspiration/biopsy/cytogenetics/molecular genetic profiling. Bone marrow aspiration, also called bone marrow sampling, is the removal be suction (through a needle placed into the bone) of fluid from the soft, spongy materials that lines the inside of most bones (marrow). (Approx. 1 ½ tsp). During a bone marrow aspiration/biopsy, an area of the hip is numbed and a needle is placed through the skin and into the hip bone. A small sample of the bone marrow and bone is withdrawn. The bone marrow will be examined to see if it is abnormal. (If you have had a bone marrow biopsy within the last 90 days and we are able to get the results, you will not have to repeat one at*

screening.) Your genes are in the cells of your body. Genes make you different from anyone else. Some genes are responsible for inherited traits like hair and eye color. Some genes affect the chances that a person will get a certain disease or how their body responds to drugs. The purpose of testing for specific molecular profiling is to determine if you qualify for this research. The bone marrow testing is normally done for patients with MPN.

- *Blood samples (approximately 9 tsp blood) will be drawn from your vein for clinical and research purposes*
- *Urine* will be collected for standard of care urinalysis
- *Pregnancy test (1 tsp of blood): Serum HCG for women of childbearing potential. Women will not be allowed to participate if they are pregnant or nursing.*
- *Both men and women who are able to have children must agree to use 2 effective forms of birth control (hormonal or barrier method of birth control, or abstinence) from the time of screening through their participation in the study.*
- *Spleen volume assessment by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI).*
- *Electrocardiogram (ECG): will be done to measure the electrical activity of your heart. For this test, you will be asked to lie down while 12 sticky pads are applied to each of your arms, legs, and to your chest. The ECG will last about five minutes. The ECG is being done for research purposes.*
- *Cardiac function assessment for research purposes will be done by having an ECHO or MUGA scan.*
- *Nail clippings: 2 clippings will only be gathered once (at screening visit) for research. Your nail clippings will provide normal material, like DNA, for comparison with the abnormal material from your blood and/or bone marrow.*

If the screening exams, tests, and procedures show that you can continue in the study, and you choose to take part, then you will need the following tests and procedures during the study period outlined below.

You are to start the first day of the study within 30 days of completing the screening procedures. For the first two cycles that you are on the study, you will return to the clinical at least once a week for tests and to be seen by your study doctor. You will be given study drugs and a drug diary at the beginning of each cycle. Each cycle is 28 days. During these visits, do not forget to tell your study doctor if you start taking any new medicines, feel unwell or want to stop participation in this study for any reason. After the first two cycles, you will come in for visits once a month until you stop the study regimen for whatever reason. A mandatory safety follow up visit will be done within 30 days after the end of the study regimen or before you start a new regimen, whichever comes first.

Your study medications are both taken orally at home every day unless you are being seen in the clinic for a study visit. If you are being seen in the clinic for a study visit, you will need to bring the study drugs with you to take in the clinic. You should fast 2 hours before and 1 hour after taking Enasidenib. You do not need to fast when taking Ruxolitinib and you may take it at the same time you take Enasidenib.

<u>Days 1 and 8 of Cycles 1 and 2</u>

- *A physical exam including a review of current medical conditions and medications you are taking.*
- *A pregnancy test for women of child-bearing potential.*
- *Blood samples (approximately 5 tsp blood) will be drawn from your vein for clinical and research purposes.*

    - *NOTE: Research blood samples will drawn on day 1 only.*
- Electrocardiogram (ECG): will be done to measure the electrical activity of your heart.
- *You will be asked to complete a brief survey about your symptoms.*

Days 8 and 22 of Cycles 1 and 2
- *A pregnancy test for women of child-bearing potential.*
- *Blood samples will be drawn from your vein for clinical purposes only.*
- Electrocardiogram (ECG): will be done to measure the electrical activity of your heart.
- *You will be asked to complete a brief survey about your symptoms.*

Day 1 of Cycles 3 through 6
- *A physical exam including a review of current medical conditions and medications you are taking.*
- *You will be asked to provide updated transfusion history.*
- *A pregnancy test for women of child-bearing potential.*
- *Blood samples (approximately 5 tsp blood) will be drawn from your vein for clinical and research purposes*
- Electrocardiogram (ECG): will be done to measure the electrical activity of your heart.
- Bone marrow aspirate and biopsy is done at C4 D1 (for accelerated phase patients, may be done at the discretion of the Investigator for chronic phase patients).
- Study drug will be dispensed
- You will complete a drug diary and return to your study doctor
- You will return all unused medication and the bottles
- *You will be asked to complete a brief survey about your symptoms.*

Day 1 of Cycle 7 and Beyond
- *A physical exam including a review of current medical conditions and medications you are taking.*
- *You will be asked to provide updated transfusion history.*
- *A pregnancy test for women of child-bearing potential.*
- *Blood samples (approximately 5 tsp blood) will be drawn from your vein for clinical and research purposes*
- *Bone marrow aspirate and biopsy*
    - *NOTE: This will be done* at C7 D1 (for all patients), C10 D1 (for accelerated phase patients, may be done at the discretion of the Investigator for chronic phase patients), and every 6 cycles, thereafter (for all patients).
- Electrocardiogram (ECG): will be done to measure the electrical activity of your heart.
- Spleen volume assessment by CT or MRI.
    - NOTE: This will be done at cycle 7 day1, cycle 10 day 1 and every 6 cycles afterward.
- Study drug will be dispensed
- You will complete a drug diary and return to your study doctor
- You will return all unused medication and the bottles. *You will be asked to complete a brief survey about your symptoms*

Response to the study regimen will be done after 6 cycles of the study regimen and every 3-6 cycles afterwards for the remainder of participation on the study. The response to the study regimen will be determined based upon exams, tests, and/or procedures to determine whether you will be allowed to

continue in the study. If you are not allowed to continue in the study, the study doctor will discuss the reasons with you.

End of Study Regimen

- *A physical exam including a review of current medical conditions and medications you are taking.*
- *You will be asked to provide updated transfusion history.*
- *A pregnancy test for women of child-bearing potential.*
- *Blood samples will be drawn from your vein for clinical purposes only.*
- Electrocardiogram (ECG): will be done to measure the electrical activity of your heart.
- Spleen volume assessment by CT or MRI.
- You will return a completed drug diary to your study doctor
- You will return all unused medication and the bottles
- *You will be asked to complete a brief survey about your symptoms*

End of Study

- *A physical exam including a review of current medical conditions and medications you are taking.*
- *You will be asked to provide updated transfusion history.*
- *A pregnancy test for women of child-bearing potential.*
- *Blood samples (approximately 5 tsp blood) will be drawn from your vein for clinical and research purposes*
- *Bone marrow aspirate and biopsy NOTE: This will be done at cycle 6, cycle 9 and every 6 months afterward.*
- Electrocardiogram (ECG): will be done to measure the electrical activity of your heart.
- Spleen volume assessment by CT or MRI. NOTE: This will be done at cycle 6, cycle 9 and every 6 months afterward.
- Response assessment
- *You will be asked to complete a brief survey about your symptoms*

Survival Follow Up

After your End of Study visit, you will be asked to continue follow-up with your study doctor or the study coordinator every 3 months for up to 1-year. This period may be conducted by record review (including public records) and/or telephone contact with you, your family, or your treating physician (if appropriate). During the follow up, your doctor or the study coordinator will collect further data related to your health, for example, if you are taking any therapies following the clinical trial for your MPN-associated disease.

Early Termination Visit:

If you are withdrawn from the study, or choose to withdraw from the study, you will be required to meet with your study doctor for a final evaluation of your symptoms and general health. The procedures will be the same at the End of Study Visit procedures.

Because this project involves the use of medications, it is necessary that we make a note of your participation in the electronic medical record. That way anyone treating you will be aware of your participation and may be able to avoid any unfortunate outcomes that could arise if your research participation were unknown.

For Women:

Since you are participating in a research study that involves drugs or an experimental regimen with potential risks to a developing fetus, it is recommended, for your protection, that you not become pregnant for the duration of the study and for at least 4 months after the study. You should not participate if you are breastfeeding. You will be counseled on the risks of becoming pregnant at least once every 28 days about pregnancy precautions and risks of fetal exposure.

A blood pregnancy test will be done before you begin the study and will be repeated weekly for cycles 1 and 2, then will be repeated at the beginning of each study cycle. Women of child bearing potential (WCBP), **must have a negative serum (blood) pregnancy test at each of these tests** and must agree to use adequate methods of birth control throughout the study. Therefore, practicing two forms of effective birth control at the same time is important at least 4 weeks before you begin taking the study medications and for 4 months after you stop taking Enasidenib and Ruxolitinib. No individual birth control is 100% effective.

Recommended methods of birth control are:

- The consistent use of an approved hormonal birth control (pill/patches, rings),
- An intrauterine device (IUD),
- Contraceptive injection (Depo-Provera),
- Double barrier methods (Diaphragm with spermicidal gel or condoms with contraceptive foam),
- Sexual abstinence (no sexual intercourse) or
- Sterilization.

If you are unsure whether the method of birth control you use is acceptable to use while participating in this study, you should ask your study doctor before you begin the study. If you are less than one year post-menopausal, there is the potential that you could become pregnant. If you or your partner becomes pregnant, or may be pregnant, at any time during the trial and up to 4 months after you stop taking the study drugs, it is important that you tell your study doctor immediately. The trial drug may be stopped, and a referral may be made to an obstetrician/gynecologist for follow-up. If you plan to become pregnant in the year following a clinical trial, speak with your study doctor.

Should you become pregnant, regardless of the outcome, the sponsor may ask for information on your pregnancy, even if you are withdrawn from the study, your written consent will be obtained separately in the case that this happens.

For Men:

Since you are participating in a study that involves experimental drugs or an experimental regimen with potential risks to a developing fetus, it is you must use a condom and not impregnate a woman or donate sperm while you are taking the study drug, and for an additional 4 months after you stop taking the study This is because levels of the study drug may be present in the sperm and/or seminal fluid even after you stop taking the study drug. You are encouraged to tell your female partner(s) and/or their doctor(s) that you are participating in a clinical trial.

Should a female partner of yours become pregnant while you are on the study regimen or in the 4 months following the study regimen, you should notify the study doctor, and the pregnant female partner should be advised to call her healthcare provider immediately.

Clinically Relevant Research Results

Results of clinical tests performed during the study will be shared with the subject. Results of biomarker testing done on blood/tissues collected for research purposes will not be shared.

USE OF YOUR DATA AND/OR SPECIMENS:

Your participation in genetic testing is a mandatory part of this study and may help to better understand which MF patients may benefit from the study drug in the future. If you do not want to participate in the genetic testing part of this study, then you cannot participate in this study.

Segments of the DNA called genes are responsible for passing particular traits such as eye color from parents to children. The genes which pass along your traits direct cells in your body to make proteins. Your genes are in the cells in your body. Genes make you different from anyone else. Some genes are responsible for inherited traits like hair and eye color. Some genes affect the chances that a person will get a certain disease or how their body responds to drugs. The research on your biospecimens will/might include whole genome sequencing, which is genetic testing that looks at all of your genes (DNA). This study is being done to help researchers understand why people may react differently to the study drug and how the body uses the study drug.

The researchers would like to ask your permission to keep the data and specimens (like blood, tissue, hair, or any other body matter) collected from you during this study to use them in future research studies. Please tell us how we may use this material in future research studies. You should also know that it is possible that products may someday be developed with the help of your specimens and data, and there are no plans to share any profits from such products with you.

Some of which may play a role in the development of disease such as MF. The study of gene mutations and variations in genes may help scientist to predict which patients with MF are most likely to respond to specific regimens. In this study, genetic testing will be performed in order to learn more about factors which may predict response to the study drug. The doctors at Mount Sinai are working with other cancer researchers, are attempting to better understand the causes of myeloproliferative neoplasms and to develop improved methods for the diagnosis and treatment of these diseases.

As part of this research study, a small sample of your blood will be taken to look for these certain molecules in the blood called “biomarkers.” Because these extra blood and bone marrow samples will be collected at the same time as regularly scheduled blood and bone marrow tests, you will not undergo any additional procedures. These blood and bone marrow samples will be collected for research purposes only. You are also being asked to provide nail clippings. These samples will be used to test and analyze the behavior and activity of molecules (the smallest unit of a substance that can exist alone and retain the character of that substance) and genes (the basic biological unit of hereditary) that may change as by- products of the disease itself. Your nail clippings will provide normal material like DNA for comparison with the abnormal material from your blood and/or bone marrow. This information may provide us with a better understanding of what causes the disease and how to develop better

treatments. You will not receive the results from research on your sample. That study will only collect blood, bone marrow, and nail samples to determine genetic characteristics.

These samples will be sent to special laboratories at the New York Blood Center for careful study and analysis. Your samples will be sent to these laboratories using a unique code that does not identify you by name, address or social security number. Researchers with access to your samples will not be able to identify you. The code linking the sample to your name would be stored at Mount Sinai and known only to your doctor and a limited number of research personnel at Mount Sinai. The research will not have any effect on your care; therefore, the results of the genetic testing will not be placed into your medical records. If you discontinue from the trial, regardless of the reason (patient, investigator or sponsor decision), no further genetic samples will be collected. However, we will continue to use data previously generated from the genetic samples collected prior to the date of discontinuation.

<u>These samples will be obtained at the following times:</u>

- Bone marrow biopsy and aspirate – before starting the study, at cycle 4 day 1, cycle 7 day1, cycle 10 day 1, every 6 cycles afterwards and at the end of study.
- Research blood samples- before starting the study drug, on day 1 of cycles 1 through 7, then every 3 cycles afterwards and at the end of study.
- Nail clippings-at screening, before starting the study drug

The blood and bone marrow samples we collect would normally be obtained at these times while taking the study drug and/or routine follow-up. Blood and bone marrow samples, described in the "Description of What's Involved" section, for this study will be drawn only when these samples are being obtained for clinical purposes. Therefore, you will not have to undergo any additional procedures to participate in this study.

Nail clippings will be obtained only before starting the study drug.

Any information derived directly or indirectly from the future research, as well as any patents, diagnostic tests, drugs, or biological products developed directly or indirectly as a result of this research, are the sole property of the Sponsor (and its successors, licensees, and assigns) and may be used for commercial purposes. You have no right to this property or to any share of the profits that may be earned directly or indirectly as a result of this research. However, in signing this form and donating a blood sample or tumor tissue specimen for future research, you do not give up any rights that you would otherwise have.

To do more powerful research, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. Researchers can then study the combined information to learn even more about health and disease. If you agree to take part in this study, some of your genetic and health information might be placed into one or more scientific databases. There are many different kinds of scientific databases; some are maintained by Mount Sinai or another institution, some are maintained by the federal government, and some are maintained by private companies. For example, the National Institutes of Health (an agency of the federal government) maintains a database called "dbGaP." A researcher who wants to study the information must apply for permission to use the database. Different databases may have different ways of reviewing such requests. Researchers with an approved study may be able to see and use your information, along with that from many other people. Researchers will always have a duty to protect your privacy and to keep your information confidential, but there are risks associated with data collection and sharing. They are described in more detail in the risks section.

YOUR RESPONSIBILITIES IF YOU TAKE PART IN THIS RESEARCH:

If you decide to take part in this research study, you will be responsible for the following things: complying with requirements of the study, maintaining a study drug log, taking prescribed medications, reporting side effects, use of two effective birth control (condom, taking the pill, or barrier methods), and regular attendance at study visits.

COSTS THAT MAY RESULT FROM PARTICIPATION:

Taking part in this research study may lead to added costs to you.

Your or your insurance company will be responsible for the costs of all items and services during the research study that you would have received for your condition if you were not enrolled in this research study. You or your insurance company will also be responsible for the costs of all services that occur during the research study that your physician believes are medically necessary to treat you.

You will receive the study drug Enasidenib at no cost. Ruxolitinib will be charged to you or your insurance since this is medication you would most likely be treated with for your MPN.

PAYMENTS THAT MAY RESULT FROM PARTICIPATION

You will not be paid for taking part in this study.

You have the choice of participating in our travel reimbursement program. You will be reimbursed up to $50 for your travel expenses for study visits from Screening through the core study period ending in cycle 6 and including the End of Study Regimen and End of Study visits. This will potentially include 15 visits in total. You will not be reimbursed for travel and time if you remain on the study drug beyond cycle 6.

This reimbursement will be by check and you should receive it within 3 months of receipts submission. The following information will be required from you to receive the reimbursement:

- *Receipt of travel expenses*
- *Mailing address*
- *Social security number*

Tax law may require Mount Sinai's finance department to report the amount of payment you receive from your participation in this research to the Internal Revenue Service (IRS) or other agencies, as applicable. Generally, this reporting would take place if you receive payments that equal $600 or more from Mount Sinai in a calendar year. You would be responsible for the payment of any tax that may be due.

POSSIBLE BENEFITS:

It is important to know that you may not get any benefit from taking part in this research. Others may not benefit either. You may or may not benefit from participation in this research based upon if the treatment combination is effective for you. Your condition may not get better or may get worse during your participation in this study. The knowledge learned from this research study may be helpful to other people with myeloproliferative disorders. However, no benefit, to you or others, can be promised because of your participation in this research.

REASONABLY FORESEEABLE RISKS AND DISCOMFORTS:

While on this research study, you are at risk for certain side effects associated with the study medication you will be taking. There may also be side effects that we can't predict or that are unknown at this time which could be serious, permanent, or in some cases, result in death. Therefore, it is important that you communicate any and all symptoms that you experience to your study doctor. Medications can be given to you to make side effects less serious and less uncomfortable. If you do experience side effects, we can withhold or stop your study drug. Many side effects go away shortly after the drug is stopped, but in some cases, side effects can be serious, long lasting or permanent. You should also tell your study doctor about any other medications or supplements that you are taking.

Risks from the research

The investigators have designed this study learn about the safety and efficacy of the combination of Ruxolitinib and Enasidenib. The combination may have side effects that are worse than previously observed or that have not been previously observed in animals or humans. The new regimen may not improve your condition or disease, or it may make your condition or disease worse.

Risks from the specific research procedures (drug(s), interventions, or procedures)

The following section will describe the risks related to each your participation in this research study. You should talk to your study doctor about any side effects or other problems that you have while taking part in the study.

Side effects can range from mild to serious. Serious side effects are those that may require hospitalization, are life threatening or fatal (could cause death). The frequency that people experience a certain side effect can range from many (likely), few (less likely) or only one or two (rarely).

*Risks and side effects related to **Ruxolitinib***

- *Laboratory abnormalities (decrease in red blood cells, decrease in platelet counts, decrease in white blood cells, increase in cholesterol levels, increase in liver enzymes) up to 90%*
- *Bruising 23%,*
- *Dizziness and headache 15-18%,*
- *Urinary tract infections <9%,*
- *Weight gain <7%,*
- *Gas and constipation 5-8%,*
- *Shingles 2-6%,*
- *Elevated blood pressure <6%,*
- *Infection – including Tuberculosis up to 10% and rare*

Risks and side effects related to **Enasidenib**

- *Isocitrate Dehydrogenase – Differentiation Syndrome (IDH-DS). IDH-DS is a life-threating side effect that has occurred in about 19% of AML patients treated with Enasidenib with 5% of these cases as causing death. Reports of symptoms from IDH-DS have occurred as early as 10 days and up to 5 months after starting Enasidenib. Patients should call your study doctor and go to the emergency room right away if any of the following symptoms occur while taking Enasidenib:*
  - *Fever*
  - *Cough*
  - *Shortness of breath*
  - *Swelling of arms and legs*
  - *Swelling around the neck, groin, or underarm area,*
  - *Fast weight gain of more than 10 pounds within a week*
  - *Bone pain*
  - *Dizziness of feeling lightheaded*

- *Common side effect of Enasidenib include:*
  - *Nausea and vomiting 34-50%*
  - *Diarrhea 43%*
  - *Yellowing of the skin or whites of the eyes 81%*
  - *Decreased appetite 34%*

Risks and Side Effects related to **MRI Scans**:

- Claustrophobia
- Allergic reaction to contrast
- Serious allergic reactions that can be life-threatening may occur
- Death or serious injury due to movement of metals in the body.

Other risks that can be seen with participating in any clinical trial include:

- Risk of loss of private information; this risk always exists, but there are procedures in place to minimize the risk.
- Since the study drug combination is for research, when taken alone or in combination with other medications (including alcohol or illegal substances), there may be other risks that are unknown.
- All drugs have a potential risk for allergic reaction, which if not treated promptly, could become life threatening.
- There may be other side effects or risks that are not known at this time. Should information become available that may affect your participation in this research study, you will be informed. You can then decide if you wish to continue with your participation in the study. To limit the risks as much as possible you will be subject to medical supervision. It is your responsibility to report to the study doctor and staff all changes in your physical condition during the study. This is important for your safety.
- The risks of a blood draw include pain, bruising, and the slight possibility of infection at the place where the needle goes in. Some people feel dizzy or may faint during or after a blood draw.

- In addition to these risks, this research may hurt you in ways that are not known. The unknown risks might be minor or might be major (death).

Risks of Bone Marrow Aspirates

- Severe pain, swelling, and infection

Risks and Side Effects related to **CT Scans**:

The level of risk depends on the number of scans performed, whether contrast dye is used, and the amount of radiation used for the specific scans. Contrast dye is not being used in this study. The radiation received from CT scans may increase your lifetime chance of getting cancer. Ask the study doctor or study staff about the risk from CT scans in this study.

This research study includes exposure to radiation from x-rays or gamma rays. This radiation exposure is for research purposes only and is in addition to any radiation needed for your medical care. X-rays and gamma rays from natural or medical sources can damage the genetic material (DNA) in your cells. At low radiation exposures, the body is usually able to repair the damage. Radiation risk is believed to be related to the total lifetime exposure. You should think about your own history of radiation exposure from tests (like x-rays or CT scans) in deciding about the radiation in this study. If you have questions about the total amount of radiation exposure you will be receiving, you should ask your doctor.

The estimated radiation exposure that you will get for this research study will be 22.55 mSv (an mSv is the scientific unit of measurement for whole body radiation dose). The greatest annual exposure (22.55 mSv) is projected to be in year(s) 1. This exceeds the 6.2 mSv that the average person in the United States gets each year from both natural sources like the sun, outer space, air, food and soil, as well as from medical procedures. It is less than the 50 mSv of radiation that is allowed each year for people who are exposed to radiation in their jobs.

Other risks that can be seen with participating in any clinical trial include:

- Risk of loss of private information; this risk always exists, but there are procedures in place to minimize the risk.
- Since the study drug combination is for research, when taken alone or in combination with other medications (including alcohol or illegal substances), there may be other risks that are unknown.
- All drugs have a potential risk for allergic reaction, which if not treated promptly, could become life threatening.
- There may be other side effects or risks that are not known at this time. Should information become available that may affect your participation in this research study, you will be informed. You can then decide if you wish to continue with your participation in the study.
- To limit the risks as much as possible you will be subject to medical supervision. It is your responsibility to report to the study doctor and staff all changes in your physical condition during the study. This is important for your safety.
- The risks of a blood draw include pain, bruising, and the slight possibility of infection at the place where the needle goes in. Some people feel dizzy or may faint during or after a blood draw.

In addition to these risks, this research may hurt you in ways that are not known. The unknown risks might be minor or might be major (death).

- If you are or become pregnant, this research may hurt your baby or your pregnancy in ways that are unknown. The unknown risks might be minor or might be major (death) for the pregnancy. You should not become pregnant or impregnate a woman while on this research study. Please read the acceptable methods of birth control found under the Description of What's Involved section of this document.
- Group Risks - Although we will not give researchers your name, we will give them basic information such as your race, ethnic group, and sex. This information helps researchers learn whether the factors that lead to health problems are the same in different groups of people. It is possible that such findings could one day help people of the same race, ethnic group, or sex as you. However, they could also be used to support harmful stereotypes or even promote discrimination.
- Privacy Risks - Your name and other information that could directly identify you (such as address, date of birth or social security number) will never be placed into a scientific database. However, because your genetic information is unique to you, there is a small chance that someone could trace it back to you. The risk of this happening is very small but may grow in the future. Since the database includes genetic information, a break in security may also pose a potential risk to blood relatives as well as yourself. For example, it could be used to make it harder for you (or a relative) to get or keep a job or insurance. If your private information was misused it is possible you would also experience other harms, such as stress, anxiety, stigmatization, or embarrassment from revealing information about your family relationships, ethnic heritage, or health conditions.

Side effects from this study will likely go away soon after you stop the study regimen. In some cases, side effects can be long lasting or may never go away.

Everyone taking part in the study will be watched carefully for any side effects. However, the study doctors don't know all the side effects that may happen. Be sure to tell your study doctor immediately, about any side effect that you have while taking part in the study.

The Sponsor has taken steps to safeguard your genetic testing information, so the risk of loss of confidentiality is small, however, if confidentiality is broken, results of genetic testing may become available to insurance carriers or employers. The knowledge of this information has the potential to lead to discrimination in employment or insurance. Someone with a known genetic condition indicating a susceptibility to develop a disease or condition might be denied a job or a promotion, or denied health or life insurance, because they are regarded as a health risks and therefore an economic risk. Carriers for a genetic disorder might be discriminated against and viewed as having the potential to have a child with a genetic condition.

There is a Federal law called the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans, and most employers of over 15 people to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

OTHER POSSIBLE OPTIONS TO CONSIDER:

Your other choices may include:

• Getting treatment or care without being in a study
• Taking part in another study, and
• Getting no treatment

If you decide that you don't want any more active regimen, one of your options is called "comfort care." Comfort care includes pain medication and other support. It aims to maintain your comfort and dignity rather than cure disease. Usually this care can be provided at home.

If you think you might prefer comfort care, please discuss this with your family, friends and your doctor. Not participating in this research is an option. The researcher will discuss all your options with you.

IN CASE OF INJURY DURING THIS RESEARCH STUDY:

For medical emergencies, call 911. If you are injured or made sick from taking part in this research study, medical care will be provided. Generally, this care will be billed to you or your insurance in the ordinary manner and you will be responsible for all treatment costs not covered by your insurance, including deductibles, co-payments and coinsurance. This does not prevent you from seeking payment for injury related to malpractice or negligence. Contact the investigator for more information.

For more information on clinical trials and medical insurance coverage, you can visit the National Cancer Institute's website at: http://cancer.gov/clinicaltrials/understanding/insurance-coverage. Another way to get this information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

No other compensation will be offered by the sponsors of this study, the Mount Sinai Health System Hospitals, or the Biomedical Research Alliance of New York.

You are not waiving any legal right to seek additional compensation through the courts by signing this form.

ENDING PARTICIPATION IN THE RESEARCH STUDY:

Your participation in this study is voluntary. You may refuse to take part in this study or once in the study you may stop at any time without any penalty. This will not affect your ability to receive medical care at any of the Mount Sinai hospitals or to receive any benefits to which you are otherwise entitled.

If you decide to stop being in the research study, please contact the Principal Investigator or the research staff and tell them if you want to leave the study. If you do decide to stop participation, please do not stop taking Ruxolitinib without consulting with your physician. Your physician may either prescribe a tapering dose of Ruxolitinib over 4-7 days to reduce a sudden increase in symptoms or prednisone to ensure you can safely stop taking this medication. Additionally, for your safety, if you leave the study early, you may be asked to return to the study doctor's office for a final study visit.

If you stop being in the research study, already collected information may not be removed from the research study database and will continue to be used to complete the research analysis. You may be asked whether the study doctor can collect information from your routine medical care. If you agree, this data will be handled the same as research data.

If you decide you don't want your samples and/or data to be used for research anymore, you can contact the researcher and ask to have your samples and/or data removed from future use. If any samples or data have already been shared without your identity, it won't be possible to retrieve them because no one will know who you are. Samples and data that have already been used will not be affected by your decision. Any samples and/or data that are still linked to your identity by a code the researcher has will be withdrawn so that no future sharing of your samples and/or data will take place. If your samples have already been deposited in an external repository, the study team will request that your samples be removed.

Withdrawal without your consent: The study doctor, the sponsor or the institution may stop your involvement in this research study at any time without your consent. This may be because the research study is being stopped, the instructions of the study team have not been followed, the investigator believes it is in your best interest, or for any other reason. If specimens or data have been stored as part of the research study, they too can be destroyed without your consent. More possible reasons for removal from the study include: you become ineligible for continued participation, side effects that warrant discontinuation of the study drug combination, you become pregnant, or your condition changes and you need treatment that is not allowed while you are taking part in the study

If you leave the study before the planned final visit, you may be asked by the study doctor to have some tests or procedures done so that you can leave the study safely.

CONTACT INFORMATION:

If you have any questions, concerns, or complaints at any time about this research, or you think the research has harmed you, please contact the office of the research team and/or the Principal Investigator (PI), John Mascarenhas, MD at phone number (212) 241-6756.

If you experience an emergency during your participation in this research, contact the PI and call 911 or go to the emergency room.

If you have any questions about your rights as a research subject or complaints regarding this research study, or you are unable to reach the research staff, you may contact a person independent of the research team at the Biomedical Research Alliance of New York Institutional Review Board at 516-318-6877. Questions, concerns or complaints about research can also be registered with the Biomedical Research Alliance of New York Institutional Review Board at www.branyirb.com/concerns-about-research.

MAINTAINING CONFIDENTIALITY – HIPAA AUTHORIZATION:

To the extent allowed by law, every effort will be made to keep your personal information confidential. However, information from this study will be submitted to the study sponsor and to the U.S. Food and Drug Administration. It may be submitted to governmental agencies in other countries where the study product may be considered for approval. Medical records, which identify you and the consent form signed by you, will be looked at by the sponsor or the sponsor's representatives and may be looked at by the FDA and other regulatory agencies, the Institutional Review Board, and the Biomedical Research Alliance of New York. While these parties are aware of the need to keep your information confidential,

total confidentiality cannot be guaranteed. The results of this research project may be presented at meetings or in publications; however, you will not be identified in these presentations and/ or publications.

AUTHORIZATION TO USE AND DISCLOSE PERSONAL HEALTH INFORMATION

Federal regulations give you certain rights related to your health information. These include the right to know who will be able to get the information and why they may be able to get it. The study doctor must get your authorization (permission) to use or give out any health information that might identify you. If you choose to be in this study, the study doctor will get personal information about you. This may include information that might identify you. The study doctor may also get information about your health, including:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits
- Information obtained during this research about laboratory test results
- Results from diagnostic and medical procedures including but not limited to X-rays, physical
- examinations and medical history
- Billing records

Information about your health may be used and given to others by the study doctor and staff. They might see the research information during and after the study. Your information may be given to the sponsor of this research. “Sponsor” includes any persons or companies that are working for or with the sponsor or are owned by the sponsor. Information about you and your health which might identify you may be given to:

- The U.S. Food and Drug Administration
- Department of Health and Human Services agencies
- Governmental agencies in other countries
- Biomedical Research Alliance of New York (BRANY)
- The Institutional Review Board
- Accrediting agencies
- Data safety monitoring boards
- Health insurers and payers
- MPN Research Consortium members for monitoring and analysis

Your personal health information may be further shared by the groups above. If shared by them, the information will no longer be covered by the U.S. federal privacy laws. However, these groups are committed to keeping your personal health information confidential. If you give permission to give your identifiable health information to a person or business, the information may no longer be protected. There is a risk that your information will be released to others without your permission.

Information about you and your health that might identify you may be given to others to carry out the research study. The sponsor will analyze and evaluate the results of the study. In addition, people from the sponsor and its consultants will be visiting the research site. They will follow how the study is done, and they will be reviewing your information for this purpose. The information may be given to the FDA. It may also be given to governmental agencies in other countries. This is done so the sponsor can

receive marketing approval for new products resulting from this research. The information may also be used to meet the reporting requirements of governmental agencies.

In almost all disclosures outside of Mount Sinai, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier. Some records and information disclosed may be identified with a unique code number. The Principal Investigator will ensure that the key to the code will be kept in a locked file or will be securely stored electronically. The code will not be used to link the information back to you without your permission, unless the Institutional Review Board allows it after determining that there would be minimal risk to your privacy. The Certificate of Confidentiality obtained from the Department of Health and Human Services will not be used to prevent disclosure to local authorities of child abuse and neglect, or harm to self or others. It is possible that a sponsor or their representatives, a data coordinating office, or a contract research organization, will come to inspect your records. Even if those records are identifiable when inspected, the information leaving the institution will be stripped of direct identifiers. Additionally, *the Office of Human Subjects Protection (OHRP) of the Department of Health and Human Services as well as the Food and Drug Administration (FDA) will be granted direct access to your medical records for verification of the research procedures and data. They are authorized to remove information with identifiers if necessary to complete their task. By signing this document, you are authorizing this access.* We may publish the results of this research. However, we will keep your name and other identifying information confidential.

This authorization does not have an expiration date. If you do not withdraw this authorization in writing, it will remain in effect indefinitely.

By signing this consent form, you are giving permission to use and give out the health information listed above for the purposes described above. You do not have to sign this consent form. If you choose not to sign this consent form, you will not be able to be in this research study. Your decision not to sign this consent form will not have any effect on your medical care and you will not lose any benefits or legal rights to which you are entitled. You have the right to review and copy your health information. However, if you decide to be in this study and sign this permission form, you may not be allowed to look at or copy your information until after the research is completed.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor at the address on the front of this informed consent form. If you withdraw your permission, you will not be able to continue being in this study, but you will not have any penalty or loss of access to treatment or other benefits to which you are entitled. When you withdraw your permission, no new health information which might identify you will be gathered after that date. Information that has already been gathered may still be used and given to others. This would be done if it were necessary for the research to be reliable.

If you have not already received it, you will also be given The Hospital's Notice of Privacy Practices that contains more information about how The Hospital uses and discloses your protected health information.

It is important for you to understand that once information is disclosed to others outside Mount Sinai, the information may be re-disclosed and will no longer be covered by the federal privacy protection regulations. However, even if your information will no longer be protected by federal regulations, where possible, Mount Sinai has entered into agreements with those who will receive your information to continue to protect your confidentiality.

If as part of this research project your medical records are being reviewed, or a medical history is being taken, it is possible that HIV-related information may be revealed to the researchers. If that is the case, the following information concerns you. If this research does not involve any review of medical records or questions about your medical history or conditions, then the following section may be ignored.

Notice Concerning HIV-Related Information

HIV-related information that either is collected as part of the research or that may already exist in your medical record might be accessed for the research by the research staff and the study sponsor, but will not be shared with others without your authorization, unless federal or state law requires the disclosure. You have a right to request a list of people who may receive or use your HIV-related information without authorization. If you experience discrimination because of the release or disclosure of HIV-related information, you may contact the New York State Division of Human Rights or New York City Commission on Human Rights. These agencies are responsible for protecting your rights.

Collection of Identifiable Private Information or Identifiable Biospecimens

Identifiers might be removed from your identifiable private information or identifiable biospecimens. After such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without your additional informed consent (or consent from your legally authorized representative).

Certificate of Confidentiality:
To further protect your privacy, the researchers have obtained a Certificate of Confidentiality from the Department of Health and Human Services. This is intended to ensure that your identity as a participant in this research study will not have to be disclosed as a result from a subpoena, for the purpose of identifying you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings other than to the FDA or OHRP as identified above.

The research staff will not share any of your research information or biospecimens with anyone who is not a member of the research team, including any family members or friends, other than to those identified above. However, you should know that if we learn that you or someone else is threatened with serious harm, such as a child or an elderly person being abused, the investigators may notify the appropriate authorities if necessary to protect you or others. A Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. This means that you and your family must also actively protect your own privacy. If an insurer or employer learns about your research participation, and you agree that they can have your research information, then the researchers may not use the Certificate of Confidentiality to keep this information from them.

ADULT PARTICIPANT:
Your signature below documents your permission to take part in this research and to the use and disclosure of your protected health information. A signed and dated copy will be given to you.

Signature of subject	Printed Name of Subject	Date	Time

PERSON EXPLAINING STUDY AND OBTAINING CONSENT:

Signature of consent delegate	Printed Name of consent delegate	Date	Time

WITNESS SECTION:
When a witness is required to observe the consent process, it should be documented below (for example, when subject is illiterate, visually impaired, or this document accompanies a short form consent).

My signature below documents that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the subject, and that consent was freely given by the subject.

Signature of Witness	Printed Name of Witness	Date	Time