CONSENT FOR CANCER RESEARCH

Project Title: Case 1917; Targeting TET2 mutations in Myelodysplastic Syndromes with Azacitidine and Ascorbic Acid

Sponsor: Cleveland Clinic Foundation

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Cancer research studies are coordinated by physicians and scientists from Cleveland Clinic, Case Western Reserve University (CWRU) through the NIH National Cancer Institute (NCI) designated Case Comprehensive Cancer Center (Case CCC). The goal of this collaboration is to enhance cancer treatment and research in Northeast Ohio. This study is being offered at Cleveland Clinic (CC).

What is the usual approach to my MDS, AML, and MPN?

You have been asked to participate in this study because you have one of these diagnosis: Myelodysplastic syndromes (MDS), or myelodysplastic syndromes/myeloprolifrative disorder (MDS/MPN), or you have genetic alteration in one of the genes called TET2. The purpose of this document is to summarize you discussion with the research team and provide you with written information to help you decide whether you want to participate in research. This form also describes the possible risks connected with being in this study. After reviewing this information with the person responsible for your enrollment, you should know enough to be able to make an informed decision on whether you want to take part in the study. Your decision is completely voluntary.

Your treating doctor may be an investigator on this research study. If so, your doctor will have

an interest in both your welfare and in the research study. You are not required to take part in this research offered by your doctor. You may ask for a second opinion from another doctor who is not linked to this study. If you choose not to be in this study, the quality of your regular medical care will not be affected.

The standard treatment approach for myelodysplastic syndromes is single agent Azacitidine as this is a Food and Drug Administration (FDA) approved drug for your condition. The study is investigating whether adding ascorbic acid to Azacitidine will improve your chance of responding to the treatment and delay your chance of progression to acute myeloid leukemia.

The standard treatment approach for acute myeloid leukemia (AML) would include other clinical trials or different combinations of chemotherapy or combinations of hypomethylating agents with other novel agents. However, these approaches would depend on the type of treatment you have received previously, your previous responses, and your other underlying medical problems. Your doctor will discuss your other options with you

The standard treatment approach to the treatment of myelofibrosis for many patients is with a Janus kinase (JAK) inhibitor. There is one JAK inhibitor that has been approved for the treatment of patients with myelofibrosis, called ruxolitinb (may be sold as Jakafi ®). However, one of the side effects of treatment with ruxolitinb is anemia, and it may make treatment more difficult. Other treatments include, chemotherapy, blood transfusions, participation in clinical trials, as well as stem cell transplant.

What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated for cancer. For example: comfort/palliative care

Why is this study being done?

The purpose of this study is to evaluate the efficacy of treatment with Azacitidine (an FDA approved drug for the treatment of various hematologic malignancies to include MDS, AML, and certain types of MPN) and high dose ascorbic acid in patients with TET2 mutations. This approach is intended to enhance the enzymatic activity of TET2 protein, which in turn may help to improve your counts and symptoms, related to your disease. This combination is specific to individuals who carry this mutation.

What are the study groups?

This is an open-label, phase II study that will be conducted at Cleveland Clinic, Taussig Cancer Institute. All study participants will get the same study intervention. It will include the usual chemotherapy, Azacitidine. All study participants will also get the study drug, Ascorbic acid.

Azacitidine will be administered intravenously or subcutaneously at a fixed dose of 75mg/m2/day for 7 days, (allowing for weekends, holidays and institutional standards) of each 28-day cycle. Ascorbic acid will be administered orally daily at 1 g/day three days prior to start Azacitidine and then continues daily for a total of 28 days of each 28 day cycle.

How long will I be in this study?

The treatment will be continued up to 6 cycles depending upon toxicities. If there is no response to treatment by 6 months, you will be taken off the study. If you respond to the treatment, you may continue as long as you are responding and you do not have any side effects that prevent you from continuing the treatment. After you finish your treatment, your doctor will continue to watch you for side effects and follow your condition for 1 year (12 months) after your end of treatment visit.

What extra tests and procedures will I have if I take part in this study?

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

Biomarkers: At specified time points (Screening and Cycle 6 Day 14), blood and marrow samples will be collected to see whether the study drug is producing changes to the genes and proteins related to your cancer. These samples will be used for this research as well stored for future research.

Methylation Profile: At specific time points (Cycle 1) a sample from your blood will be taken to evaluate the methylation profile of your cancer cells. This profile will help the researchers to understand how the changes in this profile will affect your response to the treatment.

Before you begin the study:
Before any testing is done, you must read and sign this consent form. You will need to have the following tests and procedures to find out if you can be in the study:

1. Physical exam, questions about how you are feeling and treatments you have received and review of your blood transfusions.
2. Blood tests (about 2 tablespoons) will be drawn for routine tests.
3. Bone marrow biopsies and aspirations will be done to check the status of your disease and for cytogenetic testing.
    a. Bone Marrow Biopsies: A bone marrow sample will be taken for the study for cytogenetic testing before you begin study drug, if this procedure occurred within 30 days prior to signing the consent those results from the pathology report will be used.

Additionally the specimen will be stored for biobanking. The results of the sample for biobanking will remain confidential and not be shared with you. Your privacy is very important and the researchers will take efforts to protect it. Your test results will be identified by a unique code and the list that links the code to your name will be kept separate from your sample and health information.

Neither you nor your health care plan/insurance carrier will be billed for the collection of the bone marrow sample that will be used for this study.

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

During the study the following will be additional research procedures:

- Methylation profile (Cycle 1 only)
- Mutational Analysis (Cycle 6 Day 28)

Study Calendar

Period	Screening Period (Day-17 to Day -3)	Treatment Period															Extended Treatment Period Cycles		End Of Treat-ment (EOT)	Follow up[k]
		Cycle 1				Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6						
Day		-3	1	7[c]	14[n]	1	7[c]	1	7[c]	1	7[c]	1	7[c]	1	7[c]	28[g]	1	7[c]		
Administration of Azacitidine			X	X[b]		X	X[b]	X	X[b]	X	X[b]	X	X[b]	X	X[b]		X	X[b]		
Ascorbic Acid Dispensement		X[a]				X		X		X		X		X			X			
disease history and prior therapies	X																			
Record RBC/ platelets transfusion	X	X				X		X		X		X		X		X	X			
History and physical exam[dm]	X	X				X		X		X		X		X		X	X			X[j]
Vital signs[d]	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X[j]
ECOG performance status[em]	X	X				X		X		X		X		X		X	X		X	
Hematology[d m]	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[j]
Serum Chemistry[d m]	X	X				X		X		X		X		X		X	X		X	
Pregnancy test	X															X				
Disease response assessment[f]	X															X	X		X	
Bone marrow biopsy and aspiration[L]	X															X[h]			X[i]	
Mutational analysis blood draw[/L]	X[l]															X				
Methylation profile blood draw[L]	X		X	X	X															
Drug Diary Accountability		X				X		X		X		X		X		X	X			
Survival Follow up																				X[k]
Record adverse events[m]		← X →																		

A: For Cycle 1 only, patient will begin treatment with Ascorbic Acid 3 days prior to initial treatment of Azacitidine
B: Azacitidine administration has a +/- 3 day window to account for breaks in treatment for weekends, and holidays
C: Day 7 has a +/- 3 day window to account for breaks in treatment for weekends, holidays, and institutional standards
D: See Appendix VI for required tests
E: See Appendix I for performance status grading
F: See Section for 12.0 for MDS/AML response assessment criteria
G: If patient is eligible for the extended treatment period, and moving forward on the next cycle without a dosing delay, the C6D28 visit can serve as the visit of C7D1. If the patient is not eligible for the extended treatment period the patient's C6D28 visit can serve as the EOT visit.
H: The cycle 6 bone marrow biopsy can occur up to 14 days (C6D14) prior to the C6D28 visit.
I: EOT bone marrow biopsy is optional per discretion of the treating physician
J: These tests in follow up are optional pending discretion of the treating physician
K: Survival Follow Up will occur bimonthly (60 days +/- 7 days) for a duration of 1 year from patient's EOT visit.
L: 10 ML of whole blood or bone marrow aspirate whichever available will be collected in extra lab tube for these tests.
M: If these procedures require a physician visit, these can occur 3 calendar days prior to the day 1 of that cycle (window of – 3 days).
N: Cycle 1 Day 14 has a +/- 1 day window to account if the day falls on a holiday or weekend.

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

If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss
- The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.
- There is also a risk that you could have side effects from the study drugs approach.
- There is a risk someone could get access to the personal information in your medical records or other information researchers have kept about you. Someone might be able to trace this information back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job. There are laws against misuse of genetic information, but they may not give full protection. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible side effects of Azacitidine,

COMMON, SOME MAY BE SERIOUS In 100 people receiving Azacitidine more than 20 and up to 100 may have:
▪ Fever ▪ Fatigue ▪ Headache ▪ Nausea ▪ Vomiting ▪ Diarrhea ▪ Constipation ▪ Loss of appetite ▪ Bruising ▪ Low blood cell counts ▪ Weakness ▪ Joint pain ▪ Shivering ▪ Cough ▪ Difficulty Breathing

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Azacitidine from 4 to 20 may have:
▪ Chest pain ▪ Pale skin ▪ Swelling (such as in arms and legs) ▪ Abnormal heart sound ▪ Fast heart beat ▪ Low blood pressure ▪ High blood pressure ▪ Fainting ▪ Dizziness ▪ Anxiety ▪ Depression ▪ Difficulty sleeping ▪ Lack of energy ▪ Numbness ▪ Pain ▪ Skin hives and /or rash ▪ Dry skin and /or itching ▪ Sweating ▪ Low blood levels of potassium, which can lead to muscle and bone pain and increased fatigue ▪ Weight loss ▪ Abdominal pain, tenderness, and/or swelling ▪ Mouth blisters

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Azacitidine from 4 to 20 may have:
▪ Upset stomach ▪ Hemorrhoid bleeding ▪ Difficulty swallowing ▪ Sore or painful throat ▪ Difficult and/or painful urination ▪ Blood in urine ▪ Pain ▪ Stuffy and/or runny nose ▪ Wheezing ▪ Lymph node swelling ▪ Infection ▪ Hair loss

RARE, AND SERIOUS In 100 people receiving Azacitidine 3 or fewer may have:
▪ Irregular heartbeat ▪ Heart failure ▪ Stoppage of heart and lung function ▪ Bleeding in and/or around the brain ▪ Seizure ▪ Skin condition with fever and skin lesions ▪ Abnormal Blood acid/base balance (possible organ damage) ▪ Dehydration ▪ Inflammation of the gallbladder ▪ Tarry or coffee ground-like blood in the stool ▪ Enlarged spleen ▪ Liver failure ▪ Kidney failure, even requiring dialysis ▪ Build-up of bodily waste products in the blood ▪ Coughing up blood ▪ Lung inflammation (possible difficulty breathing) ▪ Allergic reaction, which may be life-threatening ▪ Body-wide inflammation ▪ Breakdown products of the cancer cells entering the blood stream

Azacitidine may cause you to develop another type of cancer such as leukemia, a type of blood cancer

Possible side effects of ascorbic acid

COMMON, SOME MAY BE SERIOUS In 100 people receiving ascorbic acid more than 20 and up to 100 may have:
• Fatigue ▪ Headache ▪ Nausea ▪ Vomiting ▪ Diarrhea ▪ Constipation ▪ Loss of appetite ▪ Bruising ▪ Low blood cell counts ▪ Weakness ▪ Joint pain ▪ Shivering ▪ Cough ▪ Difficulty Breathing

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving ascorbic acid from 4 to 20 may have:
▪ Pale skin ▪ Swelling (such as in arms and legs) ▪ Abnormal heart sound ▪ Fast heart beat ▪ Low blood pressure ▪ High blood pressure ▪ Fainting ▪ Dizziness ▪ Anxiety ▪ Depression ▪ Lack of energy ▪ Numbness ▪ Pain ▪ Skin hives and /or rash ▪ Dry skin and /or itching ▪ Sweating

RARE, AND SERIOUS
In 100 people receiving ascorbic acid 3 or fewer may have:
▪ Kidney stones ▪ Kidney failure ▪ Bleeding that could be life threatening ▪ Loss of blood due to hemolysis (a process where red cell gets destroyed)

Potential Risk or Discomfort from Research Procedures

Blood Draws
The insertion of the needle to draw blood is painful; however, the discomfort is usually brief. For most people, needle punctures to get blood samples do not cause any serious problems; however, they may cause bleeding, bruising, discomfort, infections, dizziness, or fainting.

Bone Marrow Biopsy
There are also risks associated with taking samples of your bone marrow. Your study doctor or his/her designee will insert a needle into your hip or breastbone to withdraw a sample of fluid containing bone marrow cells. The risks of bone marrow sampling commonly include discomfort, pain, redness, swelling, and/or bruising where the sample is taken from your hip or chest. Sometimes bleeding can occur at the place where the sample is drawn. Fainting and infection can happen, but rarely. Many patients also experience soreness or stiffness in the hips for several days after the procedure.

Reproductive risks
You should not get pregnant, breastfeed, or father a baby while in this study. The drugs used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

Genetic Risks
A Federal law, called the Genetic Information Nondiscrimination Act (GINA), effective May 21, 2010, generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

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

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

We cannot know if you will have any benefit as a result of your participation in the study; it is possible the study treatment may improve your blood disorder, which may give you relief from some symptoms, improve your quality of life or prolong your survival. However, it is possible that your condition could worsen. Your participation in this study will help to obtain information about treating subjects with same disease that you have in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the Cleveland Clinic, the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study requirements
- If the study is stopped by the sponsor, Institutional Review Board (IRB) or FDA.
- If you become pregnant.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

What are the costs of taking part in this study?

Your involvement in this research study is voluntary and you will not be paid for your participation.

The study agent, Azacitidine will be billed to your insurance company as this is an FDA approved drug in your disease. Ascorbic acid will be provided free of charge. You will receive a 30 day (monthly) supply of 1000mg ascorbic acid oral tablets at each study visit upon the return of your prior ascorbic acid prescription. Although ascorbic acid is an over the counter medication for the purpose of this study, you will be supplied your ascorbic acid tablets from the Investigationl Pharmacy. Neither you nor your insurance provider will be responsible for the costs of any research-only tests or procedures specifically the mutational analysis and methylation proficle. The blood work for research purposes will not be charged to you. It will

be paid for by the research study.

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your blood disorder in this study (i.e., medical history, review of medications, physical exams, performance status, routine blood tests, pregnancy test, hospitalizations, x-rays and/or scans for tumor measurement). Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular blood disorder treatment.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://www.cancer.gov/clinicaltrials/learningabout.

What happens if I am injured or hurt because I took part in this study?

If you believe that you are injured as a result of the research procedures being performed, please immediately contact the study doctor.

If injury occurs as a result of your involvement in this research, medical treatment is available from, Cleveland Clinic or another medical facility but you/your medical insurance will be responsible for the cost of this treatment. A research injury is an injury that happens as a result of taking part in this research study. If you are injured by a medical treatment or procedure that you would have received even if you weren't in the study, that is not considered a "research injury". There are no plans for payment of medical expenses or other payments, including lost wages, for any research related injury. To help avoid injury, it is very important to follow all study directions.

Further information about research-related injuries is available by contacting the) Cleveland Clinic Institutional Review Board at (216) 444-2924.

HIPAA AUTHORIZATION
Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you volunteer to participate in this research, your protected health information (PHI) that identifies you will be used or disclosed to Dr. Aziz Nazha, MD, Dr. Benjamin Tomlinson, MD, Dr. Mikkael Sekeres, MD, Dr. Jaroslaw Maciejewski, MD, the research study staff at Cleveland Clinic for the purposes of this research and to Case Western Reserve University for administration.

The PHI that we may use or disclose (release) for this research may include your name, address, phone number, date of birth, Social Security number, information from your medical record, lab tests, or certain information relating to your health or condition..

Some of the tests and procedures done solely for this research study may also be placed in your medical record so other doctors know you are in this study. Upon completion of the study, you may have access to the research information that is contained in your medical record.

In addition to the investigators and research staff listed above, your PHI may be looked at by other groups involved with the study such as the Cleveland Clinic Institutional Review Board and the Case Comprehensive Cancer Center Protocol Review and Monitoring Committee. Your PHI may also be used by and/or disclosed (released) to:

- Case Comprehensive Cancer Center members and collaborators
- The Food and Drug Administration;
- The Department of Health and Human Services;
- The National Cancer Institute (NCI);
- Other Institutional Review Boards;
- Data Safety and Monitoring Boards;

Once your personal health information is released it may be re-disclosed and no longer protected by privacy laws.

Your research information may be used and disclosed indefinitely, but you may stop these uses and disclosures at any time by writing to:

Aziz Nazha, MD
Case Comprehensive Cancer Center
Cleveland Clinic
9500 Euclid Ave.
Cleveland, OH 44195

Your participation in the research will stop, but any information previously recorded about you cannot be removed from the records and will continue to be used as part of this research. Also, information already disclosed outside the Cleveland Clinic cannot be retrieved. This will not affect your rights to treatment or benefits outside the research study.

The Cleveland Clinic will not use your information collected in this study for another research purpose without your written permission; unless the Cleveland Clinic Institutional Review Board (IRB) assures your privacy and confidentiality is protected. The IRB is a committee whose job it is to protect the safety and welfare of research subjects.

By signing this informed consent form, you are authorizing such access to your research and medical record information. If you choose not to sign this consent form, you will not be able to participate in this research study. This Authorization does not have an expiration date.

Voluntary Participation

Your participation in this research study is voluntary. Choosing not to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise

entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed.

In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating.

Questions about the Research

If you have any questions, you can ask the Principal Investigator and/or research staff at (216) 445-7009

Emergency or after-hours contact information

If you are a Cleveland Clinic patient, you should contact the page operator at (216) 444-2200 or toll free at (800) 223-2273, and ask for the oncologist (cancer doctor) that is on call.

Where Can I Get More Information?

If the researchers cannot be reached, or if you would like to talk to someone other than the researcher(s) about: concerns regarding the study, research participant's rights; research-related injury; or other human subjects issues, you may contact the Institutional Review Board (IRB) at Cleveland Clinic IRB 216-444-2924.

You may call the National Cancer Institute's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

US National Institutes of Health (NIH) Clinical Trial Database:
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, if applicable, 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.

Signature
Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your participation in the study. By signing this consent form, you do not waive

any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

Signature of Participant	Date	Printed Name of Participant

I have discussed the information contained in this document with the participant and it is my opinion that the participant understands the risks, benefits, alternatives and procedures involved with this research study.

Signature of Person Obtaining Consent	Date	Printed Name of Person Obtaining Consent