Phase II Anti-PD1 Epigenetic Therapy Study in NSCLC

NCT01928576

4/14/2021

If appropriate for this study, a scanned copy of the signed consent form should be uploaded to the participant's Epic/EMR record.

Patient I.D. plate

RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY AUTHORIZATION FORM

Protocol Title: **A Phase II Study of Epigenetic Therapy with Azacitidine and Entinostat with Concurrent Nivolumab in Subjects with Metastatic Non-Small Cell Lung Cancer. (Protocol Version 13; September 17, 2020)**

Application No.: **NA_00084192**

Sponsor: **Stand Up To Cancer; Rising Tide Foundation; Jim Toth**

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1. What you should know about this study:

- You are being asked to join a research study. This consent form explains the research study and your part in it. Please read it carefully and take as much time as you need. Ask your study doctor or the study team to explain any words or information that you do not understand.
- You are a volunteer. If you join the study, you can change your mind later. There will be no penalty or loss of benefits if you decide to quit the study.
- During the study, we will tell you if we learn any new information that might affect whether you wish to continue to participate.
- If we think your participation in this study may affect your clinical care, information about your study participation will be included in your medical record, which is used throughout Johns Hopkins. Doctors outside of Johns Hopkins may not have access to this information. You can ask the research team to send this information to any of your doctors.
- When Johns Hopkins is used in this consent form, it includes The Johns Hopkins University, The Johns Hopkins Hospital, Johns Hopkins Bayview Medical Center, Howard County General Hospital, Johns Hopkins Community Physicians, Suburban Hospital, Sibley Memorial Hospital and All Children's Hospital.
- Biospecimens will be collected in this study. Biospecimens may include any of the following: blood, tissue, saliva, urine, bone marrow, cells, etc. Most biospecimens contain DNA, which is the genetic code for each person.

- A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.
- If you would like to review the information for this study, or a summary of the results, ask the study team doctor for the ClinicalTrials.gov study registration number.
- During this study, you will not have access to certain medical information and test results collected for study purposes. If an emergency occurs while you are in the study, medical information needed for your treatment can be made available to your study physician and other physicians who treat you. When the study is completed, all the information in your medical record will be available to you.

2. Why is this research being done?

This research is being done to see if the investigational two-drug combination when given at the same time as another investigational drug called nivolumab (also known as BMS-936558) improves the effectiveness of nivolumab in preventing cancer growth compared to nivolumab by itself.

You are being asked to join a study combining two drugs used before anti-cancer therapy with nivolumab (BMS-936558). These drugs are oral entinostat in combination with subcutaneous (under the skin) azacitidine.

Entinostat is not approved by the U. S. Food and Drug Administration (FDA) and is still being tested in research studies and is consider "Investigational". Azacitidine given subcutaneously is approved by the FDA for treatment of a blood cancer (myelodysplastic syndrome), but is not approved for the treatment of lung cancer. However, the FDA is allowing the combination use of Entinostat and subcutaneous azacitidine with the use of nivolumab (BMS-936558) in this study. The combination of entinostat with subcutaneous azacitidine with nivolumab is also investigational.

Nivolumab alone is approved for the treatment of:

- unresectable (can't be removed by surgery) or advanced melanoma, alone or in combination with ipilimumab
- previously treated metastatic non-small cell lung cancer
- previously treated advanced renal cell carcinoma
- previously treated progressive classical Hodgkin lymphoma
- previously treated recurrent or metastatic squamous cell carcinoma of the head and neck
- previously treated locally advanced or metastatic urothelial carcinoma (type of bladder cancer)

How do these drugs work?

Cancers can grow because they have mutations in genes, but they can also grow because the way a gene is controlled is abnormal even though gene has no mutations. Azacitidine and entinostat work trying to restore the way genes in a cancer are controlled to normal.

Epigenetic priming refers to the idea that using epigenetic therapy before chemotherapy might improve the way chemotherapy works. Certain genes, when turned off, allow the cancer to escape tumor shrinkage that might be caused by chemotherapy. Epigenetic priming may turn genes on that allow cancers to shrink more in response to chemotherapy.

Nivolumab is an antibody (a type of human protein) that is being tested to see if it will allow the body's immune system to work against tumor cells.

People with non-small cell lung cancer may join.

The goal of this study is to assess whether 6 cycles of concurrent (at the same time) epigenetic therapy consisting of azacitidine and entinostat with nivolumab can increase response compared to nivolumab alone in patients who are immunotherapy naïve (Arm D), or in patients whose disease has progressed on immunotherapy when compared to histological single agent docetaxel (Arms E & F).

Subjects will be assigned to one of three study arms according to previous cancer treatments.

How many people will be in this study?
About 120 people will take part in this multi-center study. About 75people will be enrolled at Johns Hopkins Hospital. The other participating sites are Norris Comprehensive Cancer Center at the University of Southern California, University of Pittsburgh.

3. What will happen if you join this study?

If you agree to be in this study, we will ask you to do the following things:

Screening Visit:
You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Medical history
- Past and current medication information will be collected
- A physical exam
- Your ability to do everyday activities will be determined
- Vital signs (blood pressure, heart rate, oxygenation and body temperature) will be collected
- Weight and height
- Routine blood tests (4 teaspoons) to assess your blood counts, liver, and kidney function
- A pregnancy test will also be done for women capable of becoming pregnant. The test will be done by collecting a urine sample or a blood sample (less than 1 teaspoon).
- MRI scan or CT scan of the brain

Study Procedures:
If the results of the "screening procedures" show that you are eligible for the study, the following procedures will be done before starting the study drugs:

- CT and/or MRI scans will be done to measure the extent of your tumor.

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- Routine blood work
- Periodic CT scans to assess cancer growth
- Tumor biopsy, if no tissue is available, is required to participate in this study
- Tumor biopsy prior to starting Nivolumab treatment and at the time of tumor progression is also required to participate in this study.

You will be enrolled on the study and assigned to one of three study arms according to previous cancer treatments.
When you are finished taking the drugs as part of the study, you will continue to be followed by the study team until your cancer has progressed, if this has not already occurred. Additionally, the study team may want to follow you for longer to observe how you respond to other therapies.

Arm D, E and F: Epigenetic and Nivolumab Combination Therapy

	Pre-study	Cycle 1-6				Nivolumab monotherapy				Follow up
		Week 1	Week 2	Week 3	Week 4	Week 1	Week 2	Week 3	Week 4	
Azacytidine [1]		d 1 - 5	d 8 - 10							
Entinostat [2]		d 3	d 10							
Nivolumab[11]		D1		D15		D1		D15		
Informed Consent	X									
History & Physical [3]	X	X				X				
Concurrent Meds	X	X	X			X	X			
CBC and Chemistry [4]	X	X	X	X		X		X		
Research Bloods [5]	X					X				
β-HCG	X									
AE assessment	X	X	X			X		X		
CT or MRI for Tumor Assessment[6]	X				X[7]				X[7]	
MRI or CT with contrast of Brain	X									
Tumor Biopsy	X[8]		X[8,9]	X[8]	X[9]				X[9]	
Review of medical records, telephone contact for recurrence-free and overall survival										Every 3 months for up to 5 years

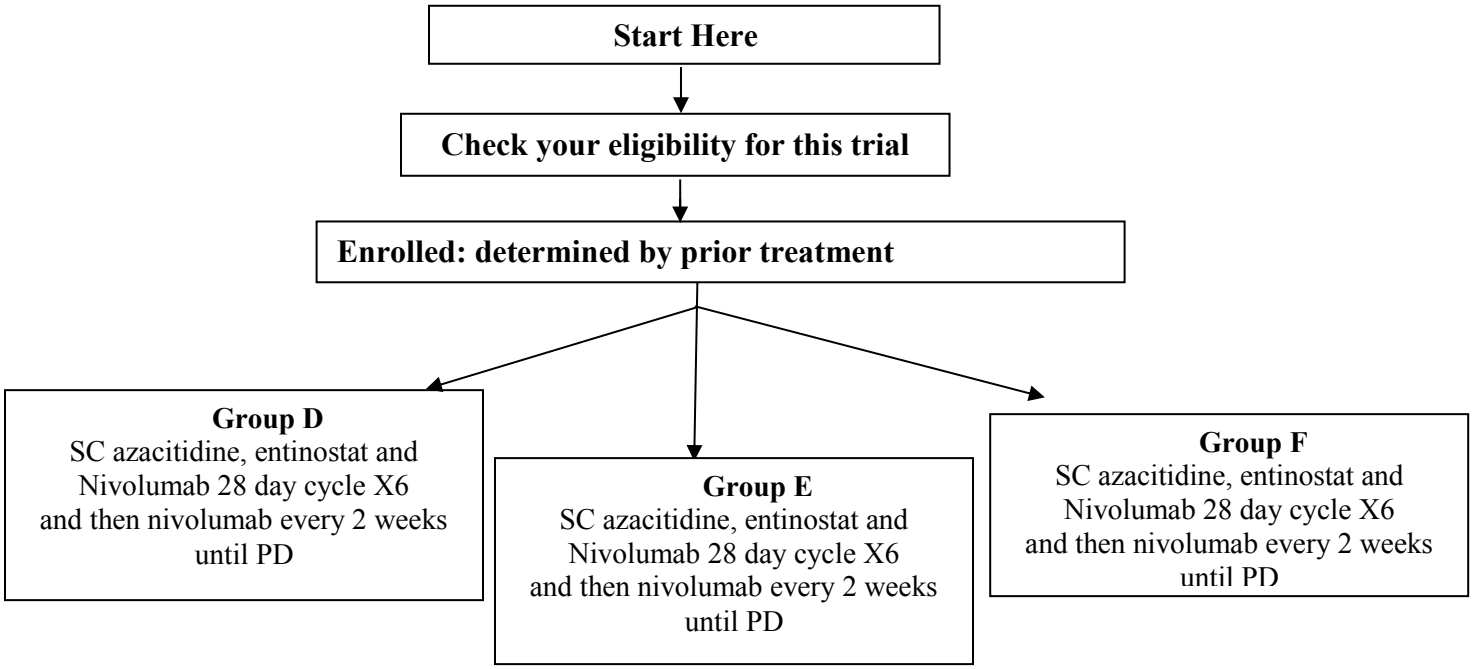
1. 40 mg/m2 s.c. days 1 – 5 and 8 – 10
2. 5 mg PO days 3 and 10
3. History and physical, includes interval history, oncologic driver mutation, smoking history, vital signs, height, weight, and performance status
4. Complete blood count and differential, comprehensive metabolic panel, serum magnesium and serum phosphate. Note-TSH, Free T4 once every 4 weeks.
5. Plasma for assessment of methylation, peripheral blood lymphocytes for assessment of gene expression WILL BE COLLECTED PRIOR TO TREATMENT ADMINISTRATION, at end of last cycle of combination therapy and then at the time of progression or study discontinuation

whichever occurs first. (see lab manual)

6. Tumor assessment at all later time points should include radiology scans to be performed every 8 weeks. The window is +/- 1 week.
7. Tumor biopsy required prior to treatment initiation
8. Required on treatment biopsy should be performed during Cycle 2 Week 2 or 3 FOLLOWING completion of epigenetics for that cycle; must be completed prior to Cycle 3 dosing.
9. Required biopsy at time of disease progression while on combination therapy or nivolumab monotherapy per patient course.
10. After a subject has completed 6 months of nivolumab, they can receive nivolumab 480 mg every 4 weeks instead of every 2 weeks. Day 15 lab assessments, history and physical and AE assessments are not required for patients receiving nivolumab every 4 weeks. These assessments will be captured on day 1 of every cycle for subjects on Nivolumab every 4 weeks.

Study Plan:

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.



As part of this study, we will study genes measured in blood samples taken before the start of the study regimen, after completion of the study regimen with entinostat and azacitidine, and when your cancer grows. These blood samples will be about 8 tablespoons each. We will also study genes from the tumor biopsies on this study. We will study all subjects' tumors biopsied before a study regimen begins (your original tumor sample used for diagnosis may be used for this test). Research tumor biopsies on study are required to be a part of this study, then these samples will also be used for genetic testing. The blood samples and initial tumor tissue and a second biopsy are ***required*** for the study. These blood samples and these biopsies are for research purposes only. The reason to study genes in these samples is to look for genes that may predict who benefits from this drug regimen and who does not.

The Genetic Information Nondiscrimination Act (GINA) may help protect you from health insurance or employment discrimination based on genetic information.

The law provides that health insurance companies and group health plans

- may not ask for genetic information from this research and
- may not use genetic information when making decision about eligibility or premiums

The law will not stop health insurance companies from using genetic information to decide whether to pay claims. The law also will not help you get other types of insurance (such as: life, disability, or long-term care).

How long will you be in the study?

You will be in the study until the lung cancer has progressed. After you are finished with the study regimen, the study doctor will ask you to visit the office for follow-up exams for at least 3 months, and to continue to monitor your health by office visits or by telephone every 12 weeks for 5 years. Keeping in touch with you and checking on your condition helps us look at the long-term effects of the study.

CONSENT/AUTHORIZATION TO OBTAIN MEDICAL RECORDS AFTER STUDY REGIMEN DISCONTINUATION:

(Mark choice with an "X")

☐ I agree to allow my medical records to be obtained for this study after study regimen discontinuation.

☐ I do not agree to allow my medical records to be obtained for this study after study regimen discontinuation.

Subject Initials: _____ Date of Initials: _____

CONSENT/AUTHORIZATION FOR USE OF YOUR TISSUE FOR FUTURE RESEARCH:

(Mark choice with an "X")

☐ I agree to allow my tissue (specimen) to be kept for use in research to learn about, prevent, or treat cancer.

☐ I do not agree to allow my tissue (specimen) to be kept for use in research to learn about, prevent, or treat cancer.

Subject Initials: _____ Date of Initials: _____

☐ I agree to allow my tissue (specimen) to be kept for use in research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

☐ I do not agree to allow my tissue (specimen) to be kept for use in research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Subject Initials: _____ Date of Initials: _____

Future Contact
We would like your permission to contact you about other studies that you may be eligible for in the future.

Please check box and sign to indicate your choice below:

YES ☐ _____
Signature of Participant

NO ☐ _____
Signature of Participant

4. What are the risks or discomforts of the study?

Risks to Azacitidine
You may have side effects while you are in the study, but you will be carefully checked by the study doctor for any problems. There may be risks or side effects of the study drug that are unknown at this time. You should tell the study doctor/staff about anything that is bothering you or any side-effects you may have, even if you do not think they are related to the study drug.

The most commonly reported side-effects with azacitidine treatment were the following:

- anemia (decrease in cells that carry oxygen)
- low number of white blood cells with or without fever
- Infection especially when white blood cell count is low
- Shortness of breath
- injection site reactions (inflammation in or damage to the tissue surrounding where an injection was given)

Low blood counts may result in significant anemia, infection, bleeding, and feeling tired and weak. The dosage and treatment schedule of azacitidine will be adjusted if certain levels of toxicity are found in your laboratory results. The following is a list of the most medically significant or most common side effects reported in completed and ongoing studies considered to be related to azacitidine. In some cases, side effects can be serious, long-lasting, may never go away, or can cause death. This is not a complete list of all side effects that may occur. Other side effects not listed here may occur. For more information about risks and side effects, please ask the study doctor. The study doctor may give you medicines to help lessen the side effects.

Very Common (≥10%)

- Anemia which may require blood transfusion
- Febrile neutropenia
- Neutropenia
- Low white bloods cell count (Leukopenia)
- Low platelets in the blood (Thrombocytopenia)
- Abdominal pain (including abdominal discomfort and upper abdominal pain)
- Constipation
- Diarrhea
- Nausea
- Vomiting

- Decreased muscle strength (Asthenia)
- Chest pain
- Fatigue
- Injection site erythema
- Injection site pain
- Injection site reaction
- Fever (Pyrexia)
- Common cold (Nasopharyngitis)
- Pneumonia (including bacterial, fungal and viral)
- Weight loss
- Decreased appetite
- Low potassium (Hypokalemia)
- Arthralgia
- Musculoskeletal pain (includes back pain, bone pain and pain in extremity)
- Muscle pain (Myalgia)
- Dizziness
- Headache
- Insomnia
- Shortness of breath (Dyspnea)
- Nosebleed (Epistaxis)
- Bruising (Ecchymosis)
- Tiny round brown-purple spots due to bleeding under the skin (Petechiae)
- Itching/Pruritus (includes pruritus generalized)
- Rash

Common (≥1%-≤10%)

- Bone marrow failure
- Low counts for red blood cell, white blood cell and platelets (Pancytopenia)
- Red patch appearing in the white of the eye beneath the clear lining of the eye (Conjunctival hemorrhage)
- Eye hemorrhage
- Indigestion (Dyspepsia)
- Gastrointestinal hemorrhage (includes mouth hemorrhage)
- Bleeding gums/Gingival bleeding
- Hemorrhoidal bleeding
- Mouth sores (Stomatitis)
- Catheter site hemorrhage
- Chills
- Injection site bruising, discoloration, hematoma, hemorrhage, induration, inflammation, nodule, pruritus, and rash
- Malaise
- Bacterial skin infection (Cellulitis)
- Inflammation or infection of one or more small pouches in the digestive tract (Diverticulitis)
- Serious infection (Neutropenic sepsis)
- Oral fungal infection
- Pain or irritation in the throat (Pharyngitis)
- Respiratory tract infection (including bronchitis and upper respiratory tract infection)

- Stuffy nose (Rhinitis)
- Sepsis (including bacterial, fungal and viral)
- Sinus infection (Sinusitis)
- Skin infection
- Urinary tract infection
- Blood creatinine increased
- Dehydration
- Muscle spasms
- Stroke (Intracranial hemorrhage)
- Lack of energy (Lethargy)
- Excess sleepiness (Somnolence)
- Loss of consciousness, fainting (Syncope)
- Anxiety
- Blood in urine (Hematuria)
- Renal failure
- Shortness of breath on exertion (Dyspnea exertional)
- Laryngeal pain
- Fluid buildup between the lungs and chest (Pleural effusion)
- Hair loss (alopecia)
- Reddening of the skin (Erythema)
- Skin lesion
- Hives (Urticaria)
- Bruise (Hematoma)
- Hypertension
- Hypotension
- Orthostatic hypotension

Uncommon (≥0.1%- <1%)

- Hypersensitivity

Additional events not otherwise noted above include: Rapid death of cancer cells where the accumulating contents of dying cancer cells cause an imbalance in the chemistry of the body which can lead to kidney damage.

Risks of Entinostat

Common, Some May be Serious

In 100 people receiving MS-275 (SNDX-275, entinostat), more than 20 may have:

- Fatigue (tiredness)
- Nausea
- Decreased number of platelets in the blood that may cause you to bruise easily and for your blood to clot slowly after bleeding
- Decrease in the number of blood cells that carry oxygen which may cause you to feel tired or short of breath
- Vomiting
- Decreased number of a type of white blood cell called neutrophils in the blood which may increase your risk of infection
- Diarrhea
- Decreased number of a type of white blood cell called leukocytes in the blood

- Feeling not hungry (decreased appetite)
- Decreased level of phosphate in the blood which may cause muscle weakness or confusion
- Low level of salt in blood that may cause you to feel tired, confused, or have headache, muscle cramps or upset stomach
- Decreased level of a form of protein called albumin in the blood
- Headache
- anorexia

Occasional, Some May be Serious

In 100 people receiving MS-275 (SNDX-275, entinostat), from 10 to 20 may have:

- Shortness of breath or difficulty breathing
- Constipation
- Increased level of glucose in the blood
- Decreased level of calcium in the blood, which may cause you to feel, tired, or have muscle weakness or muscle cramps.
- Decreased level of potassium in the blood, which may cause you to feel tired, weak, have constipation, or muscle cramps.
- Swelling in the legs, feet and/or ankles
- Increase in the level of alkaline phosphatase in your blood
- Decreased number of lymphocytes in the blood, which may cause enlarged lymph nodes, cold like symptoms, painful joints or rash.
- Pain in your abdomen
- Fever
- Cough
- Muscle pain
- Salty, metallic taste sensation
- Indigestion
- Dehydration

Rare, and Serious

In 100 people receiving MS-275 (SNDX-275, entinostat), 3 or fewer may have:

- Fatigue (tiredness)
- Shortness of breath or difficulty breathing
- Feeling not hungry (decreased appetite)
- Decreased number of a type of white blood cell called neutrophils in the blood which may increase your risk of infection
- Dehydration
- Decrease in the number of blood cells that carry oxygen which may cause you to feel tired or short of breath
- Fever
- Nausea
- Pain in your abdomen
- Diarrhea
- Infection
- Decreased number of platelets in the blood that may cause you to bruise easily and for your blood to clot slowly after bleeding

Risks of Nivolumab:
Cancer regimens often have side effects, including some that are life-threatening. There is the possibility of death occurring as a result of this study regimen and its side effects. There may be additional unknown risks.

If you experience side effects associated with the study drug, please contact your study doctor right away. Your doctor may prescribe medications to treat the side effect(s), future dosing of the study drug may be delayed, or may be stopped permanently. Any significant new findings that develop during the course of the research and may relate to your willingness to continue participation will be provided to you.

Nivolumab may cause the side effects listed below. This information is based on data from subjects in other clinical trials with nivolumab. In addition, there may be side effects that are not yet known that may occur. You should tell your doctor or nurse about any side effects you experience.

Most common side effects (≥ 10%) of nivolumab are:

- Diarrhea
- Fatigue
- Itching
- Rash

Common side effects of Nivolumab may include (> 1% - < 10%):

- Abdominal pain
- Alkaline phosphatase increased: lab test result associated with liver or bone abnormalities
- Allergic reaction/hypersensitivity
- ALT increased: lab test result associated with abnormal liver function
- Amylase increased: lab test result associated with pancreas inflammation
- AST increased: lab test result associated with abnormal liver function
- Bilirubin (liver function blood test) increased
- Chills
- Constipation
- Cough
- Creatinine increased: lab test result associated with decreased kidney function
- Decreased appetite
- Dizziness or vertigo (feeling off balance which can lead to dizziness)
- Dry mouth
- Dry skin
- Fever
- Headache
- Increased blood sugar
- Inflammation of the colon
- Inflammation of the mouth
- Infusion related reaction
- Lipase increased: lab test result associated with pancreas inflammation
- Loss of color (pigment) from areas of skin
- Lung inflammation (pneumonitis - see details below)
- Musculoskeletal pain
- Nausea

- Redness (of the skin)
- Shortness of breath
- Sodium levels in the blood low
- Swelling, including face, arms, and legs
- Thyroid gland function decreased
- Thyroid gland function increased
- Thyroid stimulating hormone increased (lab test associated with abnormal thyroid function
- Tingling, burning, numbness or weakness, possibly in arms, legs, hands and feet
- Vomiting

When additional side effects are noted, we will contact your study doctor to make sure these are being followed carefully.

Uncommon side effects of nivolumab include (> 0.1% to < 1%):

- Adrenal gland function decreased
- Bronchitis
- Dehydration
- Diabetes
- Double Vision
- Dry eye
- Erythema multiforme
- Hair loss
- Heart rate increased
- Heart rhythm abnormal
- High blood pressure
- Hives
- Inflammation of the eye
- Inflammation of the kidney
- Inflammation of the pancreas
- Inflammation of the pituitary gland
- Inflammation of the stomach
- Inflammation of the thyroid gland
- Joint pain or stiffness
- Liver inflammation
- Low blood pressure
- Muscle inflammation
- Pemphigoid: blistering of the skin or mouth caused by the immune system attacking healthy tissue
- Pituitary gland function decreased
- Psoriasis: characterized by patches of abnormal, scaly skin
- Renal (kidney) failure or kidney injury
- Respiratory failure
- Upper respiratory tract infection
- Vision blurred

Rare side effects of nivolumab include: [≥ 1/10,000 to < 1/1,000 or > 0.01% to < 0.1%]

- Anaphylactic reaction (severe allergic reaction)

- Cranial nerve disorder
- Damage to the protective covering of the nerves in the brain and spinal cord
- Diabetes complications resulting in excess blood acids
- Disease caused by the body's immune system attacking healthy organs
- Drug induced liver injury
- Guillain-Barre syndrome, an autoimmune disorder associated with progressive muscle weakness or paralysis
- Inflammation of blood vessels
- Inflammation of the brain, potentially life-threatening or fatal
- Inflammation of the lining of the brain and spinal cord
- Inflammation of the heart
- Lung infiltrates, associated with infection or inflammation
- Myasthenic syndrome (neurologic syndrome characterized by muscle weakness) including myasthenia gravis, a nerve disease that may cause weakness of eye, face, breathing, and swallowing muscles.
- Polymyalgia rheumatica
- Rhabdomyolysis: muscle fiber released into the blood stream which could damage your kidneys
- Rosacea: acne-like skin condition resulting in redness of face
- Rupture of the intestine/hole in the intestine
- Sarcoidosis, a disease involving abnormal collections of inflammatory cells (granulomas) in organs such as lungs, skin, and lymph nodes
- Stevens Johnson syndrome: inflammatory disorder of skin and mucous membranes, resulting in blistering and shedding of skin
- Syndrome associated with fever, white blood cell activation and abnormal function (including destruction of other blood cells by certain white blood cells), low blood cell counts, rash, and enlargement of the spleen
- Toxic epidermal necrolysis: a potentially fatal disease characterized by blistering and peeling of the top layer of skin resembling a severe burn
- Histiocytic necrotizing lymphadenitis or Kikuchi lymphadenitis: disorder of the lymph nodes which causes the lymph nodes to become enlarged, inflamed and painful, commonly affecting lymph nodes of the neck and possibly associated with fever or muscle and joint pains.
- Vogt Koyangi Harada syndrome: a disease that affects the pigmented tissue; this may affect the eye leading to swelling, pain and/or blurred vision, the ear leading to hearing loss, ringing in the ears and/or the skin leading to loss of skin color
- Fulminant type 1 diabetes mellitus
- Hepatic enzyme increased
- Immune-mediated nephritis
- Immune-mediated pneumonitis

Lung Inflammation (pneumonitis): It is possible that nivolumab may cause inflammation of the tissues of the lung. This adverse effect has been reported in about 3% of people given nivolumab. While many people with x-ray or CT abnormalities have not developed any symptoms some people have developed mild to severe symptoms and 2 people have died as a result of their lung inflammation. Symptoms of lung inflammation may include difficulty breathing, pain or discomfort while breathing, chest pain, cough, shortness of breath, increased rate of breathing, fever, or fatigue.

Your study doctor and nurse will watch you closely for changes in your ability to breathe and for other signs or symptoms that might show you are developing this type of lung inflammation and will perform regular tests including physical exams, measurement of oxygen levels through non-invasive testing (i.e., pulse oximeter), blood tests, chest x-rays and/or CT scans.

Please inform your study doctor or nurse AT ONCE if you experience any of the following:

- Any new or increased shortness of breath;
- Any new or increased chest pain;
- Any new or increased pain/difficulty while breathing;
- Any new or increased cough or any significant change in your type of cough; for example, any new or increased mucous or blood in your cough;
- Any change in the amount of oxygen you require
- Any fever, fatigue, or other symptoms that occur at the same time as any changes to your breathing or other lung symptoms.
- Any new-onset rash

If you start to develop symptoms, your study doctor will ask you to return to the clinic for additional tests, which could include a physical exam, measurement of oxygen levels, blood tests, chest x-rays, and/or CT scans. You will be monitored very closely for changes to your overall lung symptoms, monitoring may require hospitalization. You may also be seen by a doctor called a pulmonologist, who is an expert in how your lungs work.

Kidney failure: It is possible that nivolumab can cause kidney damage due to inflammation to the structures within the kidney called nephrons. This adverse event is very rare. You should let your study doctor know if you notice any decreased amount of urine, difficulty urinating, sudden weight gain, increased tiredness, increased thirst or inability to tolerate liquids. This may require treatment with steroids and holding the nivolumab.

Opportunistic Infections due to Immunosuppression: Some subjects may require prolonged treatment with high dose corticosteroids or alternative immunosuppressants for the treatment of nivolumab related adverse events. If you start to develop symptoms, your study doctor will ask you to return to the clinic for additional tests, which could include a physical exam, measurement of oxygen levels, blood tests, chest x-rays, and/or CT scans. You will be monitored very closely for changes in your overall lung symptoms, monitoring may require hospitalization. You may require specific treatment in order to control infections. You may also be seen by a special doctor called a pulmonologist, who has special training to be an expert in how your lungs work.

Solid Organ and Tissue Transplant

Solid organ and tissue transplant rejection has been reported in patients who have previously undergone transplantation. Treatment with Nivolumab may increase the risk of rejection in solid organ or tissue transplant recipients.

Rapid-onset and serve Graft Versus Host Disease (GVHD), some with fatal outcome, has been reported in patients who had undergone prior allogeneic hematopoietic stem cell transplantation (HSCT).

Complications of allogeneic HSCT after treatment administered before allogeneic HSCT may be associated with an increased risk of transplant-related complications, including GVHD. Fatal cases have been reported in clinical studies.

Potential Risks - Study Procedures

Blood Drawing
Taking blood may cause discomfort, bleeding or bruising where the needle enters the body; in rare cases, it may result in fainting. There is a small risk of infection. If you feel dizzy, you should lie down for a few minutes to avoid hurting yourself if you fall.

Confidentiality Loss
There is the risk that information about you may become known to people outside this study. To protect against this, all study records will be identified with code numbers instead of your name.

Despite the GINA protections and the best efforts of the research team, there may still be a risk if information about you were to become known to people outside of this study.

CT Scans When you receive a CT scan, you will be exposed to radiation and you may be allergic to the contrast dye used during the study. The radiation exposure you will receive from participating in this study is equivalent to an exposure of 1.5 rems to your whole body (for each CT scan). The scans may also need to be repeated every 8 weeks. Naturally occurring radiation (cosmic radiation, radon, etc.) produces whole body radiation exposures of about 0.3 rem per year. Occupationally exposed individuals are permitted to receive whole body exposures of 5 rems per year.

Other risks of the study:
If you agree to have a biopsy as part of this study, there are risks associated with any biopsy. The risks of the biopsy will depend on the site of the biopsy. All biopsies will be done by physicians who specialize in collecting biopsies. The risks of biopsy can include soreness and discomfort. You may feel a stinging sensation each time the biopsy needle pierces the tumor. Serious bleeding and infection are very rare, but minor bleeding is common. Tell you study doctor immediately if the bleeding is heavy or lasts a long time. Signs of infection include pain, swelling, redness, or fever. Infection is the bloodstream (sepsis), causing high fever, is rare but serious. If your lung is biopsied, there is a risk of collapsed lung.

There may be side effects and discomforts that are not yet known.

5. Are there risks related to pregnancy?

Females: Azacitidine can cause harm to an embryo or fetus if given to a pregnant woman. You cannot take part in this study if you are pregnant or breast-feeding. Because of the possible risks to an embryo or fetus, if you are a female who can become pregnant, you will be asked to take a pregnancy test within 2 weeks prior to starting the study drug regimen and prior to each study drug cycle.

If you decide to take part in this study, you must agree to use medical doctor-approved contraception (such as, oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) throughout the study, and for 3 months after your last dose of study drug. If you become pregnant during the study you must tell the study doctor right away. If this happens, your participation in this study will be discontinued. If you become pregnant within 3 months after taking your last dose of study drug you must tell the study doctor right away. The study sponsor will follow you and your pregnancy to birth and then for some time after birth.

Males: If you have a partner who is able to become pregnant, you must agree to use a medical doctor-approved form of contraception throughout the study, and should avoid fathering a child for 3 months

after your last dose of study drug. If your partner becomes pregnant during the study or within 3 months after you took your last dose of study drug, you must tell the study doctor right away.

Reproductive Risks to nivolumab (BMS-936558) General Statement:
You must not be pregnant or breastfeeding, and you should not become pregnant or breastfeed while you are taking the study drug. You must use an adequate method to avoid pregnancy for the duration of this study and for up to 23 weeks after the last dose of nivolumab (BMS-936558). Male subjects who are sexually active with a woman who is able to become pregnant should also use an adequate method of birth control to avoid pregnancy of their partner for up to 31 weeks after the last dose of study drug. You should immediately contact your study doctor if there is a change in your method to avoid pregnancy or if you start any prescription drug or other medication (including over-the-counter drugs and herbal supplements) not prescribed by the study doctor.

Unforeseeable Risks
There may be unknown risks to you, your embryo or fetus, or nursing infant if you are or become pregnant during this study or are breastfeeding during this study.

MRI imaging is not known to cause risk to the developing fetus though there may be risks that are not known at this time. MRI contrast is known to cross the placenta and subsequent risks to the developing fetus are not known.

Laboratory and Animal Reproductive Toxicology Findings
While laboratory and animal studies have been conducted to determine possible risks, the results do not necessarily show what will happen when the drug is used in humans.

No studies have been conducted to determine if nivolumab (BMS-936558) causes damage to genetic material (DNA). Because nivolumab (BMS-936558) is an antibody, the risk of damage to DNA is believed to be low.

Laboratory and animal studies have not been conducted using nivolumab (BMS-936558) to determine if nivolumab (BMS-936558) may cause cancer, or to determine possible risks to reproduction or to an embryo or fetus.

Human Pregnancy Outcomes
No pregnancy outcomes have been documented in women or partners of subjects during administration of nivolumab (BMS-936558).

Findings with Similar Drugs in the Class
There is no data/information for similar drugs in this class that may be under evaluation in other clinical trials.

6. Are there benefits to being in the study?
You may or may not benefit from being in this study. We do not know whether you will benefit from being in the study. Taking part in this study may help others in the future.

7. What are your options if you do not want to be in the study?
You do not have to join this study. If you do not join, your care at Johns Hopkins will not be affected. Alternative options may include other chemotherapy, radiation therapy, other investigational research studies, no treatment, or comfort care (palliative care, which is designed to reduce suffering).

Please ask any questions you may have and take as much time as you need to make your decision.

8. Will it cost you anything to be in this study?

The Study Drugs (azacitidine, entinostat, and nivolumab) will be provided at no charge to the Study subjects.

You will receive a separate Insurance and Research Participant Financial Responsibility Information Sheet (Sheet). This Sheet will give you the following information:

- The procedures, tests, drugs or devices that are part of this research and that will be paid for by the study (no cost to you).
- The procedures, tests, drugs or devices that will be billed to you and/or your health insurer. If you have health insurance, you will be responsible for any co-pays or deductibles not covered by your insurance.

9. Will you be paid if you join this study?

No.

10. Can you leave the study early?

- You can agree to be in the study now and change your mind later.
- If you wish to stop the study at any time, please notify us right away.
- Leaving this study early will not stop you from getting regular medical care.
- If you leave the study early, Johns Hopkins may use or give out your health information that it already has if the information is needed for this study or any follow-up activities**.**

11. Why might we take you out of the study early?

You may be taken out of the study if:

- Staying in the study would be harmful.
- You need treatment not allowed in the study.
- You fail to follow instructions.
- You become pregnant.
- The study is cancelled.
- There may be other reasons to take you out of the study that we do not know at this time.

If you are taken out of the study early, Johns Hopkins may use or give out your health information that it already has if the information is needed for this study or any follow-up activities**.**

12. How will your privacy be protected?

We have rules to protect information about you. Federal and state laws and the federal medical Privacy Rule also protect your privacy. By signing this form you provide your permission, called your "authorization," for the use and disclosure of information protected by the Privacy Rule.

The research team working on the study will collect information about you. This includes things learned from the procedures described in this consent form. They may also collect other information including your name, address, date of birth, and information from your medical records (which may include information about HIV status, drug, alcohol, or STD treatment, genetic test results, or mental health treatment).

The research team who may be a part of Johns Hopkins Health System, Johns Hopkins University or the Johns Hopkins Applied Physics Laboratory will know your identity and that you are in the research study. Other people at Johns Hopkins, including your doctors, may also see or give out your information. We make this information available to your doctors for your safety.

People outside of Johns Hopkins may need to see or receive your information for this study. Examples include government agencies (such as the Food and Drug Administration), safety monitors, other sites in the study and companies that sponsor the study.

If you are in a cancer study that receives federal funding, the National Cancer Institute (NCI) now requires that we report identifiable information (such as, zip code) about your participation. You may contact the NCI if you have questions about how this information is used.

We cannot do this study without your authorization to use and give out your information. You do not have to give us this authorization. If you do not, then you may not join this study.

We will use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside Johns Hopkins who receive your information may not be covered by this promise or by the federal Privacy Rule. We try to make sure that everyone who needs to see your information keeps it confidential – but we cannot guarantee that your information will not be re-disclosed.

The use and disclosure of your information has no time limit. You may revoke (cancel) your permission to use and disclose your information at any time by notifying the Principal Investigator of this study by phone or in writing. If you contact the Principal Investigator by phone, you must follow-up with a written request that includes the study number and your contact information. The Principal Investigator's name, address, phone and fax information are on page one of this consent form.

If you do cancel your authorization to use and disclose your information, your part in this study will end and no further information about you will be collected. Your revocation (cancellation) would not affect information already collected in the study, or information we disclosed before you wrote to the Principal Investigator to cancel your authorization.

13. What is a Certificate of Confidentiality?

Your study information is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out your information even if requested using legal means.

It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

14. What does a conflict of interest mean to you as a participant in this study?

A researcher has a financial or other interest in this study, which may affect the researcher's judgment when conducting the study.

In some situations, the results of the study may lead to a financial gain for the researcher(s) and/or Johns Hopkins. This interest has been reviewed in accordance with Johns Hopkins' policies and approved with certain conditions

If you have any questions about this financial interest, please talk to Dr. Julie Brahmer at 410-502-7159. This person is a member of the study team, but does not have a financial interest related to the study. You may also call the Office of Policy Coordination (410-361-8667) for more information. The Office of Policy Coordination reviews financial interests of investigators and/or Johns Hopkins.

15. What treatment costs will be paid if you are injured in this study?

Johns Hopkins does not have a program to pay you if you are hurt or have other bad results from being in the study. However, medical care at Johns Hopkins is open to you as it is to all sick or injured people.

- If you have health insurance: The costs for any treatment or hospital care you receive as the result of a study-related injury will be billed to your health insurer. Any costs that are not paid for by your health insurer will be billed to you.

- If you do not have health insurance: You will be billed for the costs of any treatment or hospital care you receive as the result of a study-related injury.

By signing this form you will not give up any rights you have to seek compensation for injury.

16. What other things should you know about this research study?

a. What is the Institutional Review Board (IRB) and how does it protect you?

The Johns Hopkins Medicine IRB is made up of:

- Doctors
- Nurses
- Ethicists
- Non-scientists
- and people from the local community.

The IRB reviews human research studies. It protects the rights and welfare of the people taking part in those studies. You may contact the IRB if you have questions about your rights as a participant or if you think you have not been treated fairly. The IRB office number is 410-955-3008. You may also call this number for other questions, concerns or complaints about the research.

When the Johns Hopkins School of Medicine Institutional Review Board (IRB) reviews a study at another site, that site (institution) is solely responsible for the safe conduct of the study and for following the protocol approved by the Johns Hopkins IRB.

b. What do you do if you have questions about the study?

Call the principal investigator, Dr. Brahmer at 410-502-7159. If you wish, you may contact the principal investigator by letter or by fax. The address and fax number are on page one of this consent form. If you cannot reach the principal investigator or wish to talk to someone else, call the IRB office at 410-955-3008.

If you are taking part at Sibley Memorial Hospital call Dr. Benjamin Levy at 202-660-6500.

c. What should you do if you are injured or ill as a result of being in this study?
If you have an urgent medical problem related to your participation in this study, call either Dr. Brahmer at 410-502-7159 or the medical oncologist on call at 410-955-4331.

If you think you are injured or ill as a result of being in this study, call the principal investigator, Dr. Brahmer at 410-502-7159.

If you are taking part at the Bayview Medical Center and you have an urgent medical problem related to your taking part in this study, call Dr. Julie Brahmer at 410-502-7159. You can also call the Doctor "On Call" from Bayview at 410-550-1711 if you have an urgent medical problem related to you taking part in this study.

If you are taking part at Sibley Memorial Hospital and you have a medical problem related to your taking part in this study, call Dr. Benjamin Levy at 202-660-6500. If this doctor is not available, the operator will page the "on call physician."

d. What happens to Data and Biospecimens that are collected in the study?
Johns Hopkins and our research partners work to understand and cure diseases. The biospecimens and/or data you provide are important to this effort.

If you join this study, you should understand that you will not own your biospecimens or data, and should researchers use them to create a new product or idea, you will not benefit financially.

With appropriate protections for privacy, Johns Hopkins may share your biospecimens and information with our research sponsors and partners.

17. What is Genomic Data Sharing?

Genomic studies, including genome-wide association studies (GWAS), examine genetic differences in the entire human genome (the complete set of human genes) and the association between these genetic differences and health conditions.

As part of this study, we will collect information about your health and your individual genes. This information may be sent to a National Institutes of Health (NIH) designated data repository or other controlled access repositories (such as the European Genome Phenome Archive). These repositories collect all kinds of genomic data from studies funded by the NIH or other funding mechanisms. .

The aim of collecting this information is to look for genetic connections that:

- May increase the likelihood of getting a certain disease (such as asthma, cancer, diabetes, heart disease or mental illness) or a condition (such as high blood pressure or obesity)
- May affect the progress of a certain disease or condition
- May affect treatments (medicines, etc.) that work for certain diseases in some people, but not in others.

We will remove direct identifiers (such as your name) and instead code your information before sending it to the repository**.** NIH or other controlled access repositories will never get this code or the identifiers we have removed.

The repository is a controlled-access repository. Controlled-access data is only available to researchers and companies who apply to the repository. The NIH or other controlled access repositories will review

data requests for scientific merit and for methods to protect data and methods to ensure data will be used for the approved purpose. We will not know what types of health-related research will be done with the data that are sent to the repository.

18. Continuing Treatment beyond Disease Progression

Accumulating evidence indicates a small number of subjects treated with the study drug, nivolumab, may derive clinical benefit despite initial growth of their tumor(s).

You will be permitted to continue treatment with nivolumab beyond your initial tumor growth as long as:

- You continue to meet all other study protocol eligibility criteria.
- Your doctor has assessed the potential clinical benefit of continuing treatment.
- You do not have rapid tumor growth or clinical deterioration.
- The symptoms you are having from your disease are stable.
- You can tolerate nivolumab.
- Your treatment will not delay an immediate intervention of side effects due to tumor growth (e.g. Brain Metastases).

If you continue treatment with nivolumab, all foreseeable risks or discomforts and other alternative treatment options as described in the main informed consent form are applicable.

19. What does your signature on this consent form mean?

Your signature on this form means that: You understand the information given to you in this form, you accept the provisions in the form and you agree to join the study. You will not give up any legal rights by signing this consent form.

WE WILL GIVE YOU A COPY OF THIS SIGNED AND DATED CONSENT FORM

Signature of Participant	(Print Name)	Date/Time
Signature of Person Obtaining Consent	(Print Name)	Date/Time
Signature of Witness to Consent Procedures (optional unless IRB or Sponsor required)	(Print Name)	Date/Time

I have received the separate Insurance and Research Participant Financial Responsibility Information Sheet.

Signature of Participant, LAR or Parent/Guardian	(Print Name)	Date/Time

NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR AND A COPY MUST BE GIVEN TO THE PARTICIPANT. IF APPROPRIATE FOR THIS STUDY, A SCANNED COPY OF THE SIGNED CONSENT FORM SHOULD BE UPLOADED TO THE PARTICIPANT'S EPIC/EMR RECORD (UNLESS NO MEDICAL RECORD EXISTS OR WILL BE CREATED).

DOCUMENTATION OF PHYSICIAN/MID-LEVEL PROVIDER CONSENT PROCESS

My signature below indicates that I have discussed the risks, benefits, and alternatives, answered any questions, and believe the participant is able to make an informed choice to join the study.

Signature of Physician/Mid-Level Provider	(Print Name)	Date/Time
Signature of Participant	(Print Name)	Date/Time
Signature of Witness to Consent Procedures (optional unless IRB or Sponsor required)	(Print Name)	Date/Time

NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR AND A COPY MUST BE GIVEN TO THE PARTICIPANT. IF APPROPRIATE FOR THIS STUDY, A SCANNED COPY OF THE SIGNED CONSENT FORM SHOULD BE UPLOADED TO THE PARTICIPANT'S EPIC/EMR RECORD (UNLESS NO MEDICAL RECORD EXISTS OR WILL BE CREATED).