The Ohio State University Combined Consent to Participate in Research and HIPAA Research Authorization

Study Title: **A Phase II Study of PD-1 Inhibition for the Prevention of Colon Adenomas in Patients with Lynch Syndrome and a History of Partial Colectomy**

Principal Investigator: **John Hays, MD, PhD**

Sponsor: **OSU**

- **This is a consent form for research participation.** It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate.
- **Your participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The Ohio State University. If you are a student or employee at Ohio State, your decision will not affect your grades or employment status.
- **You may or may not benefit as a result of participating in this study.** Also, as explained below, your participation may result in unintended or harmful effects for you that may be minor or may be serious depending on the nature of the research.
- **You will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.** If you decide to participate, you will be asked to sign this form and will receive a copy of the form. You are being asked to consider participating in this study for the reasons explained below.

1. Why is this study being done?

You are being invited to participate in this study because you have been diagnosed with Lynch syndrome and have already undergone partial colectomy due to a previous diagnosis of colon cancer.

This study is being done to assess the effect of treatment with the drug, nivolumab, on the incidence of colon adenomas in patients over the age of 18 with increased predisposition to colon cancer due to documented mutations in the genes MLH1 or MSH2 (Lynch Syndrome patients).

2. How many people will take part in this study?

There will be up to approximately 104 patients taking part in this study across all sites. There will be up to approximately 23 subjects enrolled in this study at The Ohio State University.

3. What will happen if I take part in this study?

Prior to taking part in this study you will be asked to review and sign this consent form.

After you have signed this consent form you will undergo a screening period to determine if you are eligible to participate in this study. If you are eligible to participate you will be enrolled in this study and begin taking the study treatment, nivolumab. You will continue your study treatment until the treatment is discontinued or the study has been completed.

Some of the tests completed during this study may be completed as part of your routine medical care. You should ask your study team if you have questions on what is part of your routine medical care and what are research procedures. You or your insurance are responsible for paying for costs of your routine medical care.

You will not be eligible to participate in this study if you are pregnant or if you are nursing. Men and Women who participate in this study should avoid pregnancy immediately before, during, and after you complete your study treatment. You must agree to use two methods of contraception, with one method being highly effective and the other being highly effective or less effective as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

a) Male condoms with spermicide
b) Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena®. Female patients who are of child bearing potential and female partners of male patients participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception.
c) Nonhormonal IUDs, such as ParaGard®
d) Tubal ligation
e) Vasectomy
f) Complete Abstinence*

**Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.*

LESS EFFECTIVE METHODS OF CONTRACEPTION

a) Diaphragm with spermicide
b) Cervical cap with spermicide
c) Vaginal sponge
d) Male Condom without spermicide*
e) Progestin only pills by WOCBP subject or male subject's WOCBP partner
f) Female Condom*

*A male and female condom must not be used together

If you are an Azoospermic (semen contains no sperm) male or a women of child bearing potential and are not heterosexually active you may not be required to use contraception as outline above; however, you will still be required to undergo pregnancy testing as described below.

If you become pregnant while you are participating in this study you will be immediately removed from the study but the health information related to you and your unborn child will continue to be monitored and collected for this study.

Screening:

At the time of screening your health information will be collected. This includes information regarding labs and biopsies. If this testing has not been completed recently it is possible some of this testing may need to be repeated.

Pre-screening (Visit 1):

- Your health information will be recorded
- Your current medications will be recorded
- You will complete a physical examination
- ECOG Performance Status (a measure of how well you are feeling)
- Vitals and Weight
- Blood will be collected for testing. Some of this blood will be collected as part of your standard medical care and some of this blood will be collected as part of this research study. In total approximately 11mL (~2.25 teaspoons) of blood will be collected at the time of screening.
- Urinalysis
- Colonoscopy
- Pregnancy Test (may be a blood or urine test)
- Your tissue will be collected for testing. This tissue may be obtained from tissue that has been previously collected from you (archival tissue) or collected by having you complete a biopsy (fresh tissue)

Nivolumab Treatment:

If you are found to be eligible for the study you will be enrolled and will begin the Nivolumab Treatment Period within approximately 3 days. Nivolumab will be given to

you on day 1 of each 3 month cycle (90 day) for 8 cycles. You will also be required to take an aspirin (at least 81 mg) by mouth once a day while you are on this study.

Nivolumab 240 mg will be administered as a 60 minute IV infusion every 3 months. Sites should make every effort to target infusion timing to be as close to 60 minutes as possible.

On Day 1 of each cycle the following will occur:

- Prior and current medical review
- You will complete a physical examination
- Vitals and Weight
- ECOG Performance Status
- Pregnancy Test (may be a blood or urine test)
- Blood will be collected for testing. Some of this blood will be collected as part of your standard medical care and some of this blood will be collected as part of this research study. In total approximately 6mL (~1.2 teaspoons) of blood will be collected on day 1 of each cycle.

On Day 1 cycle 5:

- In addition to all procedures in Day 1 Cycle 1 you will complete a Urinalysis

You will be monitored for side effects continuously while participating in this study.

End of Treatment

3 months after your last dose of Nivolumab you will undergo the following:

- Prior and current medical review
- You will complete a physical examination
- Vitals and Weight
- ECOG Performance Status
- Pregnancy Test (may be a blood or urine test)
- Blood will be collected for testing Some of this blood will be collected as part of your standard medical care and some of this blood will be collected as part of this research study. In total approximately 11mL (~2.25 teaspoons) of blood will be collected at the end of treatment.
- Urinalysis

Long-Term Follow-Up

After completion of the study you will be followed approximately every 6 months for 1 year. After this year no additional follow up will be completed unless you were removed for a side effect then you will be followed until 1 year or resolution or stabilization of the side effect whichever is later.

6 month Long-Term Follow-Up visit you will undergo the following:

- You will complete a physical examination
- Vitals and Weight

- ECOG Performance Status
- Blood will be collected for testing

4. How long will I be in the study?

You may take your study treatment for up to two years. After you have stopped taking the study treatment you will be followed up 3 months, 6 months and 1 year after the last dose.

Treatment may be discontinued if:

- You have disease recurrence (your treatment may continue at the discretion of the doctor)
- You experience intolerable side effects
- You experience unacceptable side effects
- You have an another illness that prevents further administration of treatment
- You wish to participate in an another clinical trial or start a new anticancer therapy
- You no longer take the study treatment as directed
- The drug sponsor terminates the study

5. Can I stop being in the study?

You may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. Your decision will not affect your future relationship with The Ohio State University.

6. What risks, side effects or discomforts can I expect from being in the study?

Risks of Nivolumab

Nivolumab may cause one or more of the side effects listed below. This information is based on data from cancer 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 right away about any possible side effects you experience.

Very common side effects of nivolumab are: [≥ 1/10 or ≥10%]

- Diarrhea
- Fatigue
- Itching
- Rash

Common side effects of nivolumab include: [≥ 1/100 to < 1/10 or ≥1% to <10%]

- Abdominal pain
- Alkaline phosphatase increased: lab test result associated with liver or bone

abnormalities
- ALT increased(abnormal blood test which could indicate possible liver damage)
- Amylase increased(abnormal blood test which could indicate possible pancreas damage)
- AST increased(abnormal blood test which could indicate possible liver damage)
- Chills
- Constipation
- Cough
- Creatinine increased (increased blood level of creatinine, a substance normally eliminated by the kidneys into the urine. This may mean that your kidneys are not functioning properly)
- Decreased appetite
- Dizziness
- Dry mouth
- Dry skin
- Fever
- Headache
- Increased blood sugar
- Inflammation of the colon
- Inflammation of the mouth
- Infusion related reaction
- Joint pain or stiffness
- Lipase increased (abnormal blood test which could indicate possible pancreas damage)
- Loss of color (pigment) from areas of skin
- Lung inflammation (pneumonitis - see details below)
- Musculoskeletal pain
- Nausea
- Redness (erythema)
- 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 result associated with abnormal thyroid function
- Tingling, burning, numbness or weakness, possibly in arms, legs, hands and feet
- Vomiting

Uncommon side effects of nivolumab include: [≥ 1/1,000 to < 1/100 or ≥ 0.1% to <1%]

- Adrenal gland function decreased
- Allergic reaction/hypersensitivity
- Bilirubin (liver function blood test) increased
- Bronchitis
- Cranial nerve disorder

- Diabetes
- Dry eye
- 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
- Liver inflammation
- Low blood pressure
- Lung infiltrates (inflammation of the lungs which can cause shortness of breath and difficulty breathing. If severe this can be life threatening)
- Pituitary gland function decreased
- Psoriasis: characterized by patches of abnormal, scaly skin
- Renal (kidney) failure or damage to your kidneys
- Respiratory failure
- Upper respiratory tract infection
- Vertigo feeling off balance which can lead to dizziness
- 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)
- Damage to the protective covering of the nerves in the brain and spinal cord
- Diabetes complications resulting in excess blood acids and diabetic coma
- Erythema multiforme: skin inflammatory reaction
- 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 heart
- Muscle inflammation
- Death of the cells within your muscle
- 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, an inflammatory disorder causing muscle pain and stiffness
- Rhabdomyolysis: muscle fiber released into the blood stream which could damage your kidneys
- Rosacea: acne-like skin condition resulting in redness of face

- 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
- 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 Koyanagi 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.

Lung Inflammation (pneumonitis): It is possible that nivolumab may cause inflammation of the tissues of the lung. This side effect has been reported in patients treated with nivolumab. While many patients with x-ray or CT abnormalities have not developed any symptoms, some patients have developed mild to severe symptoms and in rare cases, death has occurred as a result of their lung inflammation. Signs and symptoms of lung inflammation may include difficulty breathing, pain or discomfort while breathing, chest pain, cough, shortness of breath, increased rate of breathing, fever, low blood oxygen levels, 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 <u>AT ONCE</u> 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.

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 pneumonitis. 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.

Prolonged treatment with medicines that suppress inflammation, sometimes needed to manage the side effects of nivolumab treatment, may lower your body's ability to fight off certain infections (i.e., opportunistic infections). These infections may require treatment with antibiotic or antifungal medications and may be fatal.

Complications, including fatal events, have occurred in patients who received allogeneic hematopoietic stem cell transplantation (HSCT) after nivolumab. HSCT is a process in which a person receives cells that can form blood from a donor who is genetically similar but not identical (typically a brother or sister but could also be an unrelated donor).

Complications, including rejection, have also been reported in patients who have received an organ or tissue transplant. Treatment with nivolumab may increase the risk of rejection of the organ or tissue transplant.

7. What benefits can I expect from being in the study?

You may not receive any direct benefit from participating in this study. It is possible you may benefit from the investigational treatment Nivolumab but this benefit is not yet known. The information collected in this study may help treat future patients with solid tumor cancers

8. What other choices do I have if I do not take part in the study?

You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled.

You may receive the standard medical care for your type of cancer, participate in another clinical trial for your type of cancer, or go without treatment.

9. What are the costs of taking part in this study?

The investigational drug used in this study, Nivolumab, will be provided to you and will not be billed to you or your insurance company while you are on the study. You and/or your insurance company will not be charged for the cost of any tests or procedures that are required as part of the research and are outside the standard of care services (what is normally done) for your condition.

You and/or your insurance company will be responsible for the cost of routine medications, tests and procedures that you would receive even if you were not in this research study. You and/or your insurance company will be billed for the costs for these routine tests and procedures in the usual manner.

Participating in this research study may lead to additional costs to you. In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research study.

You are responsible for any co-payments, co-insurance, and deductibles as required by your insurance company or charges your insurance company does not pay. To find out more about costs, you can ask the study doctor or study staff. If you have any questions about study expenses like medical bills and hospital bills, please speak with the study doctor. You may also need to speak to your insurance company about medical insurance coverage.

10. Will I be paid for taking part in this study?

You will not be paid to participate in this study.

11. What happens if I am injured because I took part in this study?

If you suffer an injury from participating in this study, you should notify the researcher or study doctor immediately, who will determine if you should obtain medical treatment at The Ohio State University Wexner Medical Center.

The cost for this treatment will be billed to you or your medical or hospital insurance. The Ohio State University has no funds set aside for the payment of health care expenses for this study.

12. What are my rights if I take part in this study?

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a participant in this study.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

An Institutional Review Board responsible for human subjects research at The Ohio State University reviewed this research project and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of participants in research.

13. Will my study-related information be kept confidential?

Efforts will be made to keep your study-related information confidential. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

Also, your records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- The sponsor supporting the study, their agents or study monitors; and
- Your insurance company (if charges are billed to insurance).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search the website at any time.

14. HIPAA AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

I. What information may be used and given to others?

- Past and present medical records;
- Research records;
- Records about phone calls made as part of this research;
- Records about your study visits;
- Information that includes personal identifiers, such as your name, or a number associated with you as an individual;
- Information gathered for this research about:
  - HIV / AIDS
  - Hepatitis infection
  - Sexually transmitted diseases
  - Other reportable infectious diseases
  - Physical exams
  - Laboratory, x-ray, and other test results
  - Diaries and questionnaires
  - The diagnosis and treatment of a mental health condition
- Records about any study drug you received;

II. Who may use and give out information about you?

Researchers and study staff.

III. Who might get this information?

- The sponsor of this research. "Sponsor" means any persons or companies that are:
  - working for or with the sponsor; or
  - owned by the sponsor.
- Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information;
- If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic or physician's office record;
- Bristol Myers Squibb

IV. Your information <u>may</u> be given to:

- The U.S. Food and Drug Administration (FDA), Department of Health and Human Services (DHHS) agencies, and other federal and state entities;
- Governmental agencies in other countries;
- Governmental agencies to whom certain diseases (reportable diseases) must be reported; and
- The Ohio State University units involved in managing and approving the research study including the Office of Research and the Office of Responsible Research Practices.

V. Why will this information be used and/or given to others?

- To do the research;
- To study the results; and
- To make sure that the research was done right.

VI. When will my permission end?

There is no date at which your permission ends. Your information will be used indefinitely. This is because the information used and created during the study may be analyzed for many years, and it is not possible to know when this will be complete.

VII. May I withdraw or revoke (cancel) my permission?

Yes. Your authorization will be good for the time period indicated above unless you change your mind and revoke it in writing. 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 researchers. If you withdraw your permission, you will not be able to stay in this study. When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

VIII. What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study and receive research-related treatment. However, if you are being treated as a patient here, you will still be able to receive care.

IX. Is my health information protected after it has been given to others?

There is a risk that your information will be given to others without your permission. Any information that is shared may no longer be protected by federal privacy rules.

X. May I review or copy my information?

Signing this authorization also means that you may not be able to see or copy your study-related information until the study is completed.

15. Who can answer my questions about the study?

For questions, concerns, or complaints about the study, or if you feel you have been harmed as a result of study participation, you may contact ***Dr. John Hays at 614-293-6529***.

For questions related to your privacy rights under HIPAA or related to this research authorization, please contact ***HIPAA Privacy Manager, The Ohio State University Medical Center, Suite E2140, 600 Ackerman Road, Columbus, OH 43202 or at 614-293-4477.***

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact **Ms. Sandra Meadows in the Office of Responsible Research Practices at 1-800-678-6251.**

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact ***Dr. John Hays at 614-293-6529.***

Signing the consent form

I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this combined consent and HIPAA research authorization form**.**

Printed name of subject	**Signature of subject**
	AM/PM
	Date and time
Printed name of person authorized to consent for subject (when applicable)	**Signature of person authorized to consent for subject (when applicable)**
Relationship to the subject	**AM/PM**
	Date and time

Investigator/Research Staff

I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

Printed name of person obtaining consent	**Signature of person obtaining consent**
	AM/PM
	Date and time

Witness(es) - *May be left blank if not required by the IRB*

Printed name of witness	**Signature of witness**
	AM/PM
	Date and time
Printed name of witness	**Signature of witness**
	AM/PM
	Date and time