SPONSOR: The Ohio State University

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

IND NUMBER: 139418
ClinicalTrials.gov Identifier: NCT03631641

BMS# CA209-9EU
OSU IRB# 2018C0076
OSU Protocol# OSU-17198
IND# 139418
Protocol Version: 5/20/2020

Investigator:
John Hays, MD, PhD
Associate Professor
Division of Medical Oncology
Department of Internal Medicine
Comprehensive Cancer Center
2050 Kenny Rd
Columbus, OH 43221
Telephone: 614-293-6529
John.Hays@osumc.edu

Multi-Center Trial Program
Clinical Trials Office
The Ohio State University Comprehensive Cancer Center
Fax: 614-366-6652
E: OSUCCC-CTO-MCTP@osumc.edu

1.0 TRIAL SUMMARY

Abbreviated Title	
Trial Phase	II
Clinical Indication	Adult patients with Lynch syndrome (Hereditary Non-Polyposis Colorectal Cancer), proven by genetic testing, and a history of partial colectomy for colon cancer or advanced colon adenoma
Trial Type	Single arm
Type of control	Historical controls
Route of administration	IV (intravenous)
Trial Blinding	NA
Treatment Groups	One (nivolumab 240mg IV every three months for two years for a total of 8 doses)
Number of trial subjects	104 (for 94 evaluable)
Estimated enrollment period	1 year
Estimated duration of trial	4 years (1 year for enrollment and 3 years of follow-up)
Duration of Participation	5 years

2.0 STUDY SYNOPSIS

2.1 Trial Design

This study is a single-arm study to assess the efficacy of nivolumab infusion to prevent colon adenomas in a population of patients over the age of 18 with increased predisposition to colon cancer due to documented mutations in the mismatch repair proteins MLH1 or MSH2 (Lynch syndrome patients)who have already undergone partial colectomy. Individuals with Lynch syndrome who have previously had colon cancer are at higher risk than the rest of the Lynch population of developing a second colon cancer, subsequent adenomas, and subsequent high-risk adenomas. In addition, many of our Lynch patients are diagnosed at the time of their cancer diagnosis and have opted for surveillance rather than completion colectomy.

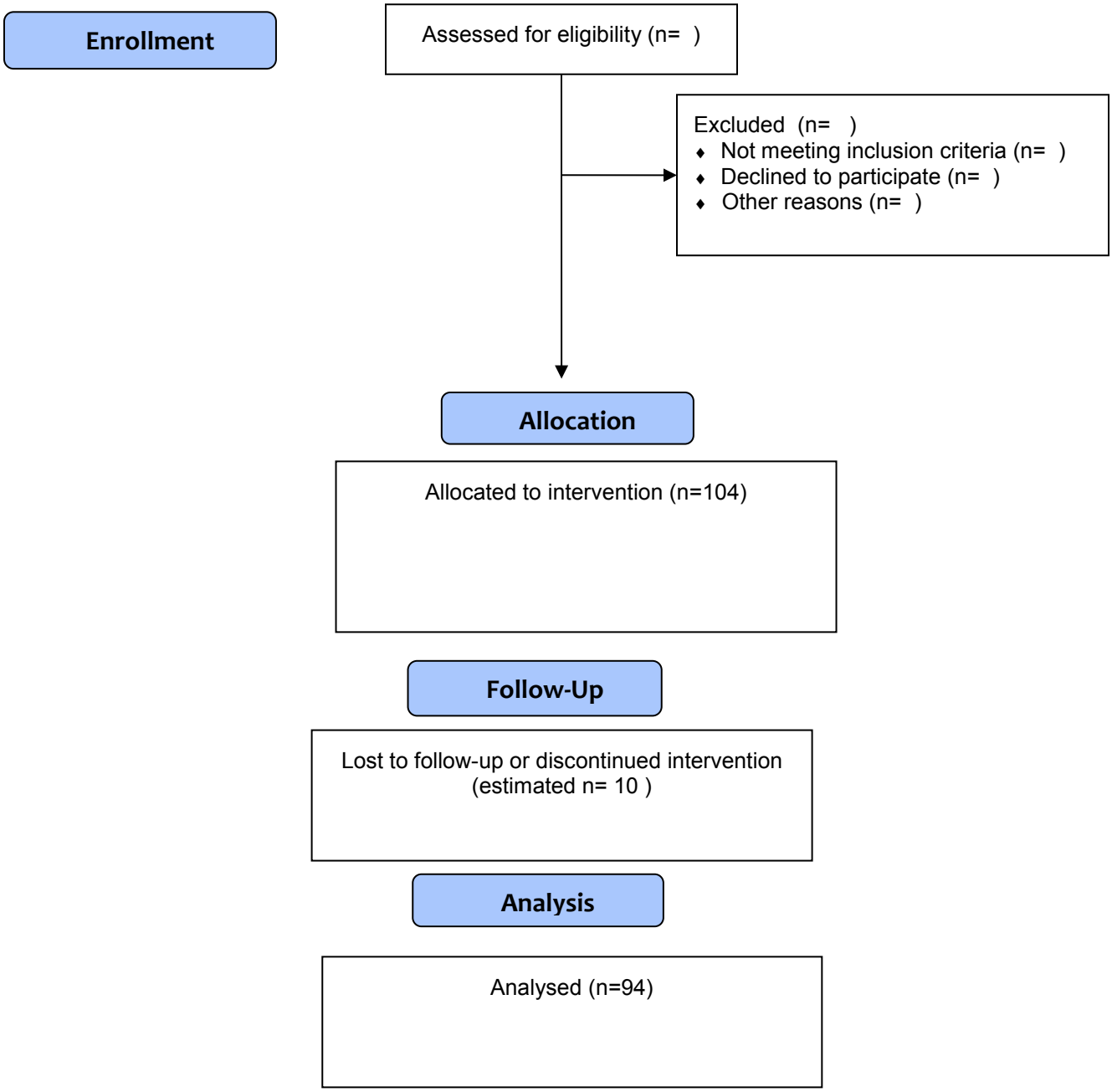
Subjects should have had their colon surgery at least one year prior to enrollment, and they should have completed any adjuvant chemotherapy at least 6 months prior to enrollment. In addition, all adverse effects of prior chemotherapy (with the possible exception of platinum-induced neuropathy) should be completely resolved at the time of enrollment. Within three months prior to enrollment, subjects will also have to have had a colonoscopy with adequate preparation in which either no lesions were detected or all detected lesions were removed and negative for cancer. Subjects with known autoimmune disease requiring frequent or continuous use of systemic corticosteroids exceeding 10mg prednisone or equivalent dosing of other

steroids per day will be excluded. Women of reproductive potential will be required to use appropriate birth control during study participation, including the year after treatment is completed. Women who are breastfeeding children will not be eligible for participation.

Subjects will be given nivolumab 240 mg IV every three months for two years (a total of 8 doses). Colonoscopies will be conducted after the fourth dose, after the eighth dose, and one year after the eighth dose.

This multi-site study will be coordinated through the Ohio State University Multi-Center Trial Program.

2.2 Trial Diagram



2.3 Treatment Schema

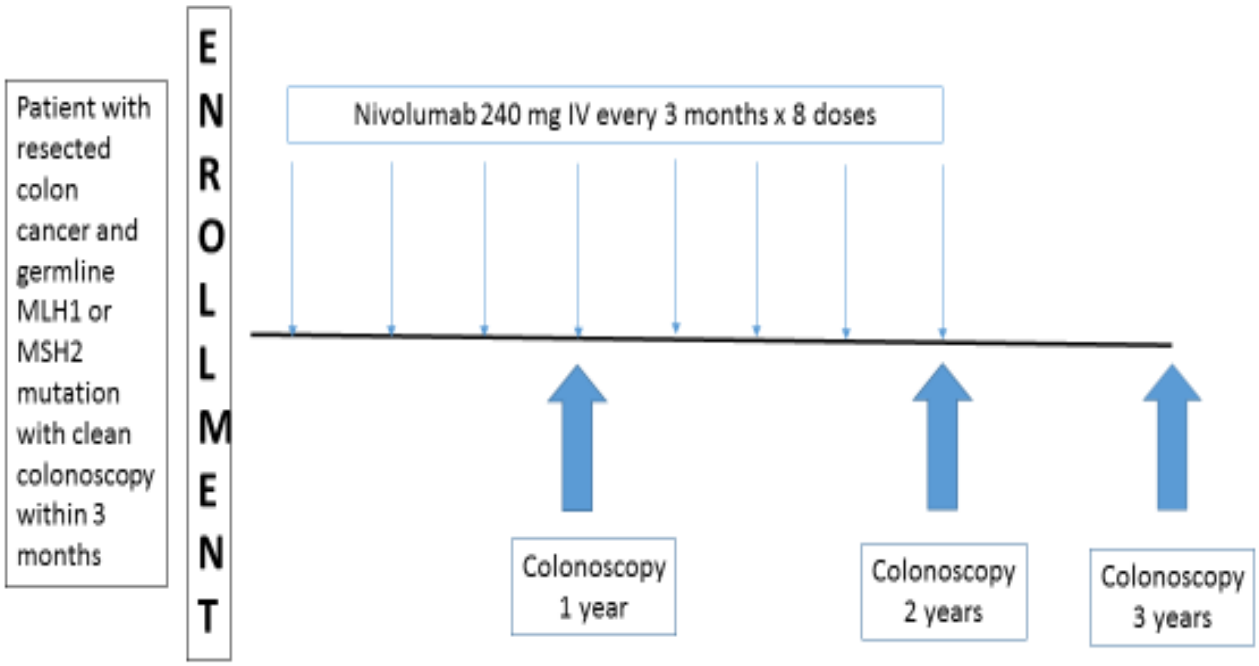


TABLE OF CONTENTS

TABLE OF CONTENTS

3.0 BACKGROUND & RATIONALE

3.1 Background

Lynch syndrome, also known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC), is an inherited disorder that is characterized by a markedly increased risk of colorectal cancers, with lifetime risks of this disease ranging up to 40-82%. (1, 2) Many individuals with this condition are diagnosed upon pathology review of their colon cancer after they have already had a partial colon resection. Because of the increased risk of a second, separate primary colon cancer in this population, some individuals opt for completion colectomy, but many choose a less-morbid approach to manage their risk, consisting of a segmental colectomy with close surveillance with annual colonoscopies of the remaining portions of their colons. These individuals have a high rate of colon adenomas (33%), high-risk colon adenomas (those with high-grade dysplasia or over 10 mm in size, 22%), and second primary colon cancers (15-25%) detected after partial colectomy. (3, 4) In this population, the median times to develop a high-risk adenoma or a colon cancer were 13 months and 69 months after surgery, respectively. (3) These results are consistent with the known reports of a short interval between "clean" colonoscopies and cancer diagnoses in Lynch patients, which range from 8-60 months in studies of patients without partial colectomy (median 23-42 months). (5, 6)

Colon cancers that are associated with Lynch syndrome often display microsatellite instability; in fact, this characteristic is used for universal tumor screening to identify colorectal cancer patients who are more likely to have Lynch syndrome. Recent work by Le et al. demonstrated that colon cancers with microsatellite instability were markedly more sensitive to treatment with pembrolizumab (response rate of 40% compared to 0% in microsatellite-stable tumors). (7) Immune-related progression-free survival at 20 weeks was also markedly increased in the population with microsatellite-instable tumors (78% versus 11% in those with microsatellite-stable tumors). It is anticipated that this is a class effect that would be found for all PD-1 inhibitors.

The development of microsatellite instability is considered an early event in colon tumor development. Microsatellite instability testing is not performed routinely on colon polyps for individuals with Lynch syndrome, but research reports indicate that 41-86% of adenomas in this population are microsatellite-instable (average 70%). (8-15) Lynch patients have germline mutations in mismatch repair genes, which lead to a high number of somatic mutations in their tumors. (16-18). Studies have shown that tumors with high mutational burden are more likely to respond to PD-1 inhibitors, and the first tumor type that demonstrated success with this treatment was melanoma, which is known to have a large number of somatic mutations. (19, 20)

The population at high risk for cancer is an attractive one for further study for several reasons. The events are more frequent, leading to a shorter study requiring fewer subjects. The patients in this population are motivated to decrease their risk. Despite the high risk of colon cancer, the only available option for chemoprevention for Lynch patients at this time is aspirin, and

data are conflicting regarding its efficacy. A chemoprevention study done with Erlotinib in patients with Familial Adenomatous Polyposis (FAP) demonstrated the willingness of patients with an inherited colorectal cancer syndrome to take cancer therapeutic drugs for polyp reduction and prevention and the acceptability of this approach to Human Subjects Protection groups. (21)

Based on this evidence and rationale, we propose a study of nivolumab to reduce the incidence of colorectal adenomas in individuals with Lynch syndrome with germline mutations in MLH1 or MSH2.

3.1.1 Pharmaceutical and Therapeutic Background

3.1.1.1 Nivolumab

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on Nivolumab.

3.2 Rationale

3.2.1 Rationale for the Trial and Selected Subject Population

Lynch syndrome is characterized by a markedly increased risk of colorectal cancers, with lifetime risks of this disease ranging up to 40-82%. (1, 2) Many individuals with this condition are diagnosed upon pathology review of their colon cancer after they have already had a partial colon resection. Despite the increased risk of a second, separate primary colon cancer in this population, many choose a less-morbid approach to manage their risk, consisting of a segmental colectomy with close surveillance of the remaining portions of their colons with annual colonoscopies. These individuals have a high rate of colon adenomas (33%), high-risk colon adenomas (those with high-grade dysplasia or over 10 mm in size, 22%), and second primary colon cancers (15-25%) detected after partial colectomy. (3, 4) Colon cancers associated with Lynch syndrome often display microsatellite instability, and investigators have demonstrated that colon cancers with microsatellite instability were markedly more sensitive to treatment with PD-1 inhibition. Microsatellite instability testing shows that 41-86% of adenomas in this population are microsatellite-instable (average 70%). (8-15) Based on this evidence and rationale, we propose a study of nivolumab to reduce the incidence of colorectal adenomas in individuals with Lynch syndrome with MLH1 or MSH2 germline mutations.

The population at high risk for cancer is an attractive one for further study for several reasons. The events are more frequent, leading to a shorter study requiring fewer subjects. The patients in this population are motivated to decrease their risk. Despite the high risk of colon cancer, the only available option for chemoprevention for Lynch patients at this time is aspirin, and data are conflicting regarding its efficacy. A chemoprevention study done with Erlotinib in patients with Familial Adenomatous Polyposis (FAP) demonstrated the willingness of patients with an inherited colorectal cancer syndrome to take cancer therapeutic drugs for polyp

reduction and prevention and the acceptability of this approach to Human Subjects Protection groups. (21)

3.2.2 Rationale for Dose Selection/Regimen/Modification of Nivolumab

Pharmacokinetic studies have shown that the efficacy of Nivolumab as studied in other populations does not appear to be dose-dependent. The safety and efficacy of 240 mg Q2W flat dose of nivolumab is expected to be similar to 3 mg/kg Q2W dosing regimen. A flat dose of nivolumab 240 mg Q2W was selected since it is identical to a dose of 3 mg/kg for subjects weighing 80 kg, the observed median body weight in nivolumab treated cancer patients. Using a PPK model, the overall distributions of nivolumab exposures (Cavgss, Cminss, Cmaxss, and Cmin1) are comparable after treatment with either 3 mg/kg or 240 mg nivolumab. The predicted range of nivolumab exposures (median and 90% prediction intervals) resulting from a 240 mg flat dose across the 35 to 160 kg weight range is maintained well below the corresponding exposures observed with the well tolerated 10 mg/kg nivolumab Q2W dosage. Across the various tumor types in the clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy and safety has been found to be relatively flat. Given the similarity of nivolumab PK across tumor types and the similar exposures predicted following administration of 240 mg flat dose compared to 3 mg/kg Q2W regimen, it is expected that the safety and efficacy profile of 240 mg Q2W nivolumab will be similar to that of 3 mg/kg nivolumab. Recent changes to the prescribing information for Nivolumab have endorsed a flat dose of 240mg Nivolumab for adults with metastatic melanoma, non-small cell carcinoma of the lung, and renal cell carcinoma when given as a single agent.

Therefore, for ease of administration and cost considerations, we will plan on using 240 mg as our flat dose for patients in the study. Dose reductions for toxicity will be considered per the package insert and investigator's brochure.

Nivolumab has primarily been studied in a cancer treatment setting with a dose schedule of every two weeks. Given the lower-risk population in this cancer prevention study, a less frequent schedule would be preferable both for patient acceptability as well as toxicity concerns. The proposed dosing schedule for Nivolumab every three months was derived from the maintenance schedule of Ipilimumab, a CTLA-4 inhibitor with a similar mechanism of action, side effect profile, and reported half-life as Nivolumab. The mean terminal T-HALF of a single dose of nivolumab is reported as 17 to 25 days across the dose range of 0.3 mg/kg to 10 mg/kg. Therefore, a 90-day period would be approximately 3 half-lives.

3.2.3. Rationale for Endpoint

3.2.3.1 Efficacy Endpoints

Individuals with Lynch syndrome and a history of a first primary colon cancer have a high rate of colon adenomas (33%), high-risk colon adenomas (those with high-grade dysplasia or over 10 mm in size, 22%), and second primary colon cancers (15-25%) detected after partial colectomy. (3, 4) Adenomas in individuals with Lynch syndrome were more likely to be villous, to have high grade dysplasia, and were somewhat more likely to have increased size. (22) Polyp dwell time in Lynch syndrome patients has been calculated at approximately 33 months, which is approximately 1/3 of the time found in the general population. (23, 24) Annual metachronous rates of colorectal cancer were approximately 2% for individuals with MLH1 or MSH2 mutations. (25) Another study found a cumulative colon cancer risk after segmental colectomy of 16% (95% CI 10% to 25%) at 10 years, 41% (95% CI 30% to 52%) at 20 years and 62% (95% CI 50% to 77%) at 30 years. (26) Annual colonoscopy is considered the standard of care for individuals with a history of Lynch syndrome and remaining colon at risk.

4.0 OBJECTIVES & HYPOTHESES

4.1 Primary Objective & Hypothesis

Objective:

- To determine if maintenance therapy with nivolumab can decrease the incidence of colon adenomas at three years in a population of patients with genetic predisposition to colorectal cancer and a history of hemicolectomy due to colon cancer or advanced colon adenoma.

Hypothesis:

We hypothesize that the use of nivolumab 240 mg IV every three months for two years will result in a 40% reduction in the incidence of adenomas in a Lynch syndrome population with history of partial colectomy at three years.

4.2 Secondary Objectives & Hypotheses

Objectives:

- To assess the safety of nivolumab maintenance therapy in this population.

- To obtain preliminary data on the short-term incidence of advanced colon adenomas (measuring greater than 10mm or with high-grade dysplasia) and colon and non-colonic cancers in Lynch patients treated with maintenance nivolumab at three years.

Hypotheses:

We hypothesize that therapy with nivolumab 240 mg IV every three months for two years will be associated with a level of toxicity that is acceptable to this high-risk population.

We hypothesize that the use of nivolumab 240 mg IV every three months for two years will result in a 50% reduction in the incidence of high-risk adenomas (those with high-grade dysplasia or greater than or equal to 10mm) in this population at three years. As an exploratory aim, we also hypothesize that overall colon and non-colon cancer incidence will be decreased.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

A. Patient must have a diagnosis of Lynch syndrome confirmed by the identification of a germline mutation in MLH1 or MSH2.

B. Patient must have a history of colon cancer or advanced colon adenoma requiring hemicolectomy with at least 60 cm of colon remaining without evidence of disease (as determined by prior colonoscopy or assessment by the surgeon performing the hemicolectomy).

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent/assent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Have a performance status of 0 or 1 on the ECOG Performance Scale.
4. Demonstrate adequate organ function as defined in Table 1.

All screening labs must be performed within 28 days of treatment initiation.

Table 1. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	

Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

5. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug. Pregnancy tests will be conducted in WOCBP every 6 weeks.
6. Women must not be breastfeeding
7. WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus 5 half-lives of nivolumab (19 weeks) plus 30 days (duration of ovulatory cycle) for a total of 5 months post-treatment completion.
8. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus 5 half-lives of the study drug (19 weeks) plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion.
9. Hemicolectomy and adjuvant chemotherapy (if given) must be completed at least one year prior to study entry.
10. All subjects must take at least 81 mg of aspirin per day. Daily doses up to 650 mg of aspirin per day will be accepted.
11. Within three months prior to enrollment, subjects must have had a colonoscopy in which either no lesions were detected or all detected lesions were removed and negative for cancer. If their last colonoscopy falls outside of this time frame, it will need to be repeated prior to study enrollment.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.

2. Has a diagnosis of immunodeficiency or is receiving immunosuppressive therapy within 7 days prior to the first dose of trial treatment. Individuals who are receiving systemic steroid therapy at a stable dose less than or equal to 10mg of prednisone per day or its equivalent will be permitted to participate.

3. Has a known history of active TB (Bacillus Tuberculosis)

4. Hypersensitivity to nivolumab or any of its excipients.

5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

6. Has had hemicolectomy, prior chemotherapy, targeted small molecule therapy, or radiation therapy within one year prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

    - Note: Subjects with ≤ Grade 2 neuropathy and/or alopecia are an exception to this criterion and may qualify for the study.

7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or *in situ* cervical cancer.

8. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids exceeding 10 mg prednisone per day or its equivalent, or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

9. Has known history of, or any evidence of, active, non-infectious pneumonitis.

10. Has an active infection requiring systemic therapy.

11. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

12. Have a known history of a bleeding disorder or gastrointestinal ulceration that would preclude the use of a daily 81 mg aspirin.

13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

14. Is pregnant or breastfeeding, or is expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

15. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

16. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

17. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

18. Has received a live vaccine within 30 days of planned start of study therapy.

    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

19. Subjects with germline MSH6, PMS2, or EPCAM mutations will be excluded from participation.

20. Prisoners or individuals who are compulsorily detained will be excluded from participation.

5.2 Subject Registration Procedures

Patients will be registered after meeting all entry requirements and signing of the informed consent.

OSU patients will be registered by the OSU research coordinator, as per their standard practice.

Subsite patients will have eligibility verified and will be entered on study centrally at The Ohio State University by the Multi-Center Trial Program. All subsites must email the Multi-Center Trial Program Coordinator to verify slot availabilities prior to consenting patients. Once a patient signs consent, the signed consent document and documentation of the consenting process must be faxed or securely emailed to the Multi-Center Trial Program. The required forms, including Eligibility Criteria Checklist and Registration Form, can be found in the Supplemental Forms Document.

To register a subsite patient, the following documents must be completed by the subsite research team and faxed or securely e-mailed to the Multi-Center Trial Program Coordinator:

- Copy of all baseline tests required per the protocol calendar. Tests must be within the specified window.
- Signed Patient Consent Form
- Signed Patient HIPAA Authorization Form (if separate)
- Consent Documentation Note
- Completed & Signed Eligibility Checklist (refer to Supplemental Forms Document)
- Registration Form (refer to Supplemental Forms Document)
- Source documents verifying every inclusion & exclusion criteria
    - Note: every inclusion and exclusion criteria must be documented in the patient's medical record (emails or other notes outside the medical record will not be considered source documentation)

Upon receipt of registration documents, the Multi-Center Trial Program will send an email confirmation of receipt. If confirmation of receipt is not received within 1 hour of submission, please call or page the Multi-Center Trial Program Coordinator to confirm receipt.

Upon receipt of all required registration documents and upon verification the subsite patient meets all eligibility criteria, the Multi-Center Trial Program Coordinator will:

- Assign the patient a study sequence ID
- Register the patient on the study
- Fax and/or e-mail to the subsite the completed Registration Form with the assigned study sequence ID as confirmation of patient registration

Following registration, patients should begin protocol treatment within 5 business days. Issues that would cause treatment delays should be discussed with the Principal Investigator and Multi-Center Trial Program Coordinator as soon as possible. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled, after discussion with the PI and Multi-Center Trial Program Coordinator.

Each participating institution will order study agents directly. Agents may be ordered by a participating site only after the required regulatory documents, including the initial IRB approval for the site, have been forwarded to the Multi-Center Trial Program.

Patient sequence IDs will be assigned in the following fashion:

- [Site ID]-XXX
    - Site ID = NCI issued institutional ID
    - XXX = sequential numbers by order of enrollment

5.3 Trial Treatments

The treatment to be used in this trial is outlined below in **Table 2**.

Table 2. Trial Treatments

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Nivolumab	240 mg	Q90 days	IV infusion	Day 1 of each 3 month cycle for 8 cycles	Experimental

5.3.1 Dose Selection/Modification

5.3.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

Details on preparation and administration of nivolumab are available in the approved drug package inserts. Refer to manufacturer's approved labeling for preparation and administration.

.

5.3.1.2 Dose Modification

5.3.1.2.1 Nivolumab

Nivolumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exception:
  - Grade 2 drug-related fatigue does not require a treatment delay.

- Grade 2 drug-related creatinine, AST, ALT or Total Bilirubin abnormalities
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality (excluding AST, ALT or Total Bilirubin) with the following exceptions for lymphopenia, and asymptomatic amylase or lipase:
  - Grade 3 lymphopenia does not require dose delay
  - Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met.

Nivolumab treatment should be permanently discontinued for the following:

Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment

Any Grade 3 non-skin, drug-related adverse event lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:

- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
- Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
- Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
  - ♦ Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
  - ♦ Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
  - ♦ Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN

* In most cases of Grade 3 AST or ALT elevation, study drug(s) will be permanently discontinued.

- Consideration will be made for permanent discontinuation of treatment for grade 2 colitis or grade 2 pneumonitis.

5.3.2 Please see section 5.7 for specific management algorithms for adverse effects. Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

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. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 60 minutes: -5 min/+10 min).

5.3.3 Trial Blinding/Masking

This is an open-label, single-arm trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

5.4 Randomization or Treatment Allocation

This is a single arm trial; therefore, randomization or treatment allocation is not applicable.

5.5 Stratification

No stratification is applicable in this trial.

5.6 Concomitant Medications/Vaccinations (allowed & prohibited)

The inclusion and exclusion criteria provide details for medications allowed and prohibited in this study. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited that arises during the course of trial participation, discontinuation from trial therapy may be required. The investigator should discuss any questions regarding this with the BMS Clinical team and the principal investigator. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.6.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject’s welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care and the inclusion and exclusion criteria. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

All subjects will take 81mg of aspirin per day. Subjects who were taking greater than 81 mg of aspirin at the time of enrollment will be permitted to take their pre-study dose of aspirin during the course of the study, up to 650 mg per day.

5.6.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than nivolumab
- Radiation therapy
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids up to 10 mg of prednisone per day or its equivalent may be approved after consultation with the Sponsor.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.7. Management Algorithms

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

5.7.1. Management of Infusion Reactions: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Error! Reference source not found. below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of nivolumab.

Table 3. Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of nivolumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

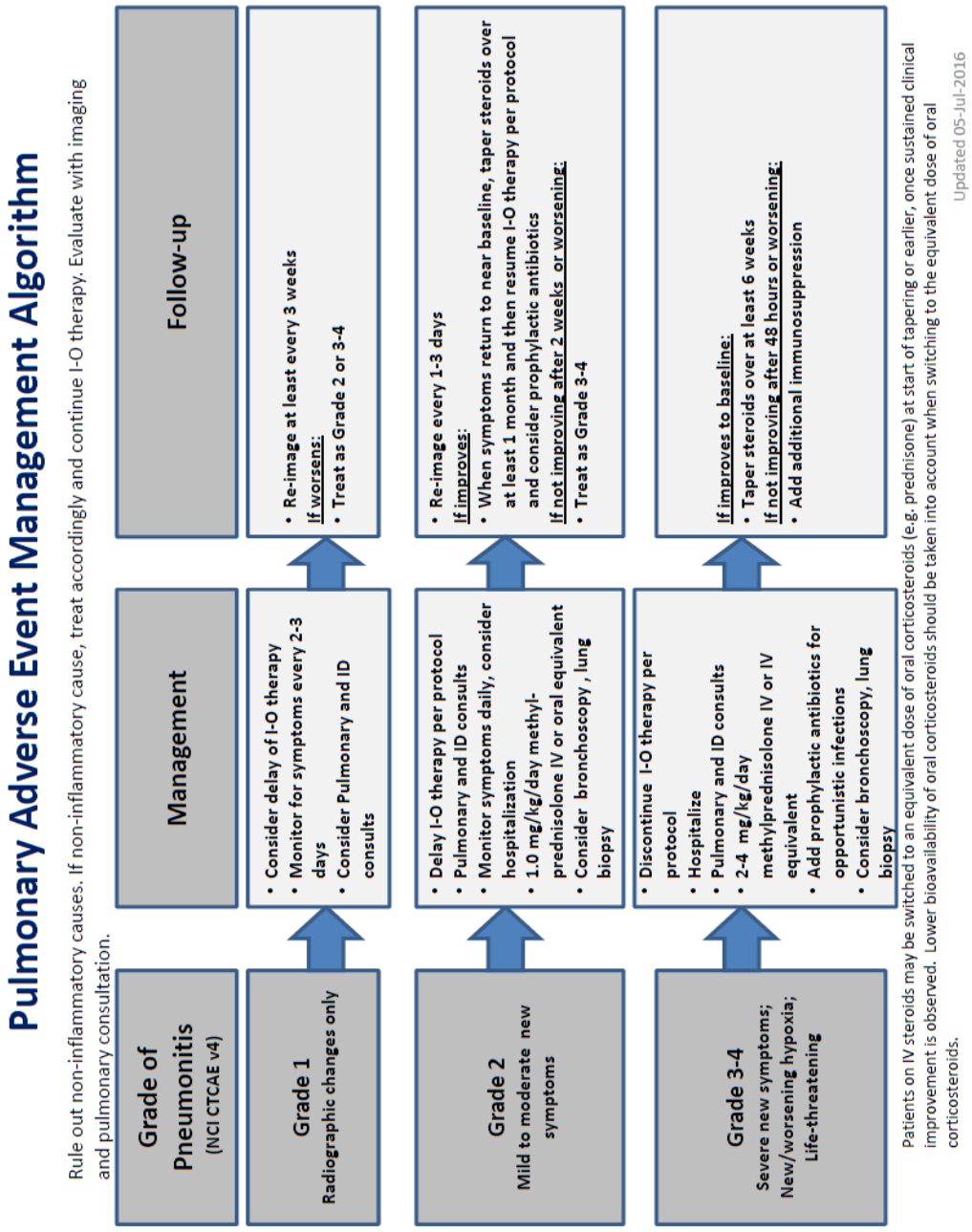
GI Adverse Event Management Algorithm

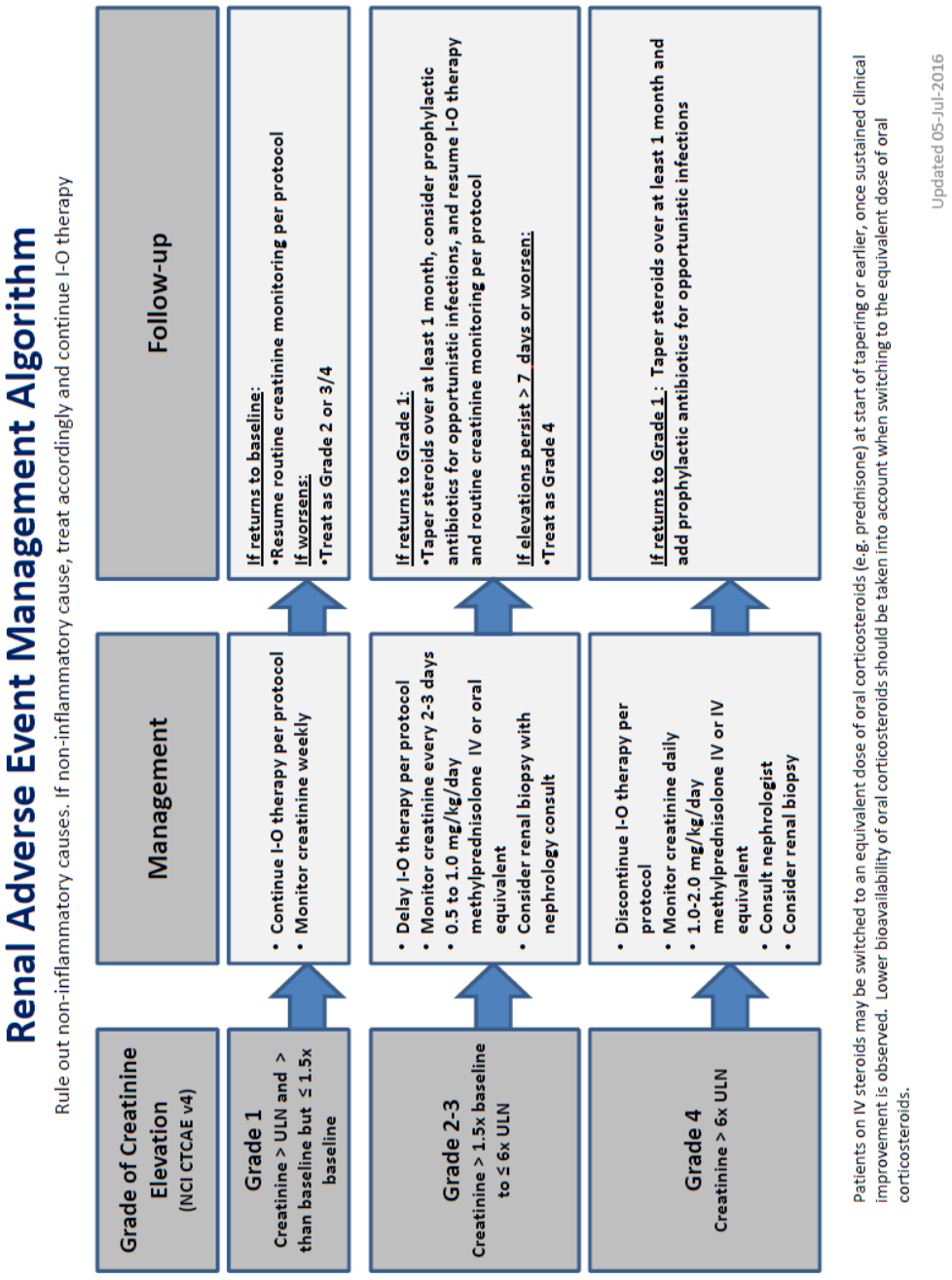
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

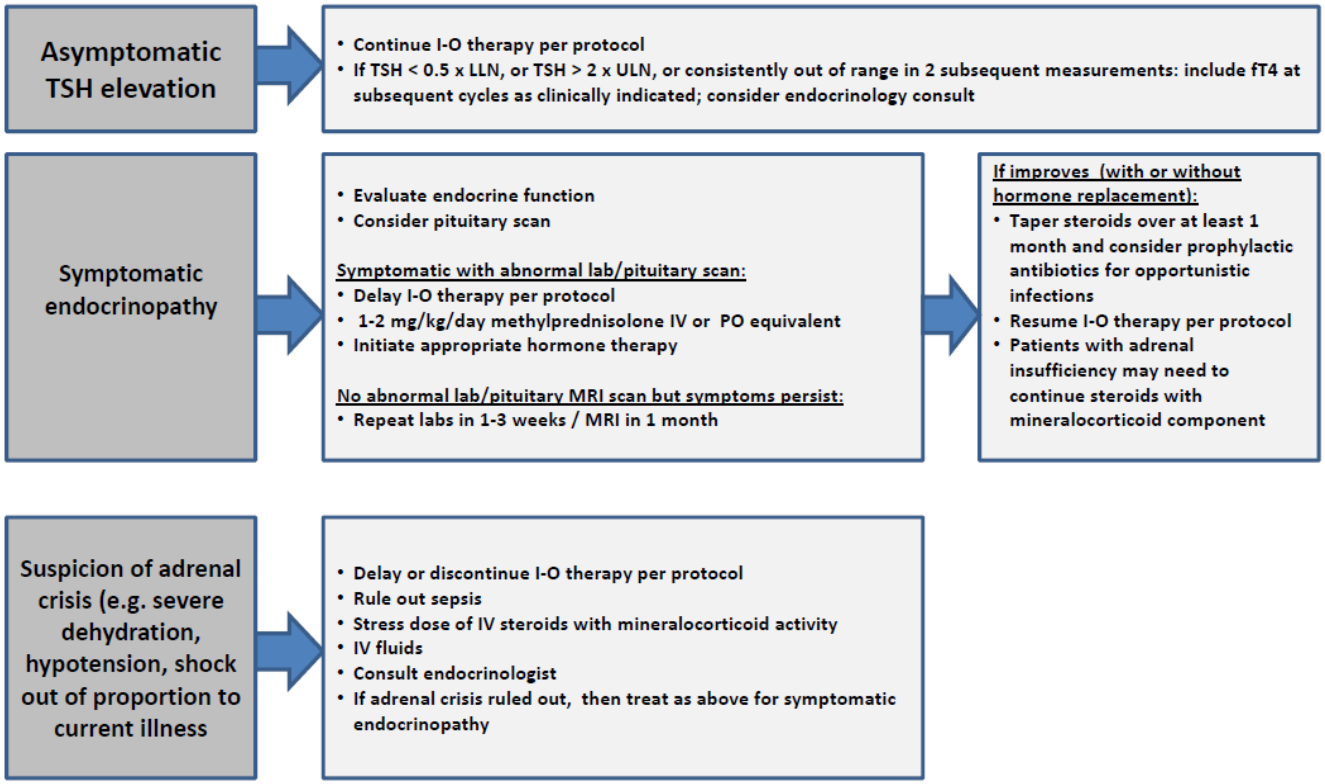
Updated 05-Jul-2016


Pulmonary Adverse Event Management Algorithm
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.
Grade of Pneumonitis (NCI CTCAE v4)
Management
Follow-up
Grade 1
Radiographic changes only
• Consider delay of I-O therapy
• Monitor for symptoms every 2-3 days
• Consider Pulmonary and ID consults
• Re-image at least every 3 weeks
If worsens:
• Treat as Grade 2 or 3-4
Grade 2
Mild to moderate new symptoms
• Delay I-O therapy per protocol
• Pulmonary and ID consults
• Monitor symptoms daily, consider hospitalization
• 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent
• Consider bronchoscopy , lung biopsy
• Re-image every 1-3 days
If improves:
• When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics
If not improving after 2 weeks or worsening:
• Treat as Grade 3-4
Grade 3-4
Severe new symptoms; New/worsening hypoxia; Life-threatening
• Discontinue I-O therapy per protocol
• Hospitalize
• Pulmonary and ID consults
• 2-4 mg/kg/day methylprednisolone IV or IV equivalent
• Add prophylactic antibiotics for opportunistic infections
• Consider bronchoscopy, lung biopsy
If improves to baseline:
• Taper steroids over at least 6 weeks
If not improving after 48 hours or worsening:
• Add additional immunosuppression
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
Updated 05-Jul-2016


Renal Adverse Event Management Algorithm
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy
Grade of Creatinine Elevation (NCI CTCAE v4)
Management
Follow-up
Grade 1
Creatinine > ULN and > than baseline but ≤ 1.5x baseline
• Continue I-O therapy per protocol
• Monitor creatinine weekly
If returns to baseline:
•Resume routine creatinine monitoring per protocol
If worsens:
•Treat as Grade 2 or 3/4
Grade 2-3
Creatinine > 1.5x baseline to ≤ 6x ULN
• Delay I-O therapy per protocol
• Monitor creatinine every 2-3 days
• 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent
• Consider renal biopsy with nephrology consult
If returns to Grade 1:
•Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol
If elevations persist > 7 days or worsen:
•Treat as Grade 4
Grade 4
Creatinine > 6x ULN
• Discontinue I-O therapy per protocol
• Monitor creatinine daily
• 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent
• Consult nephrologist
• Consider renal biopsy
If returns to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
Updated 05-Jul-2016

Endocrinopathy Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

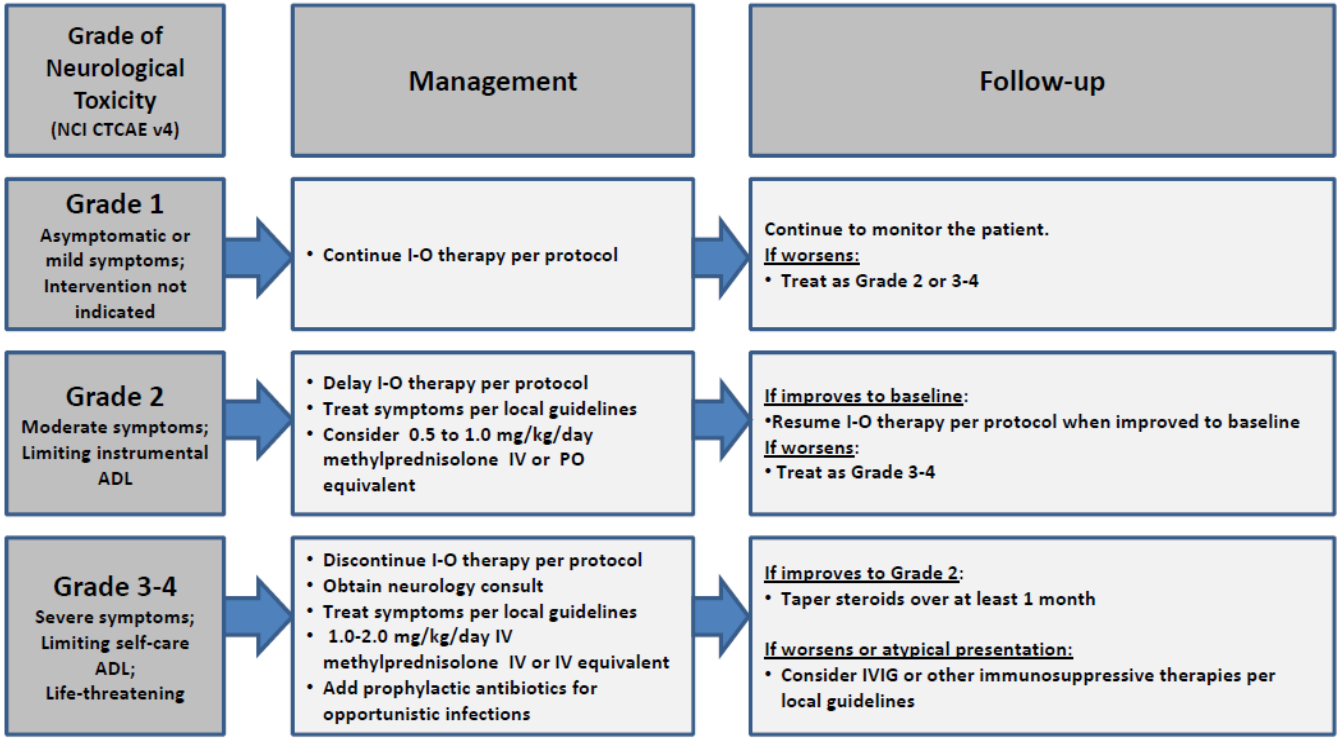


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

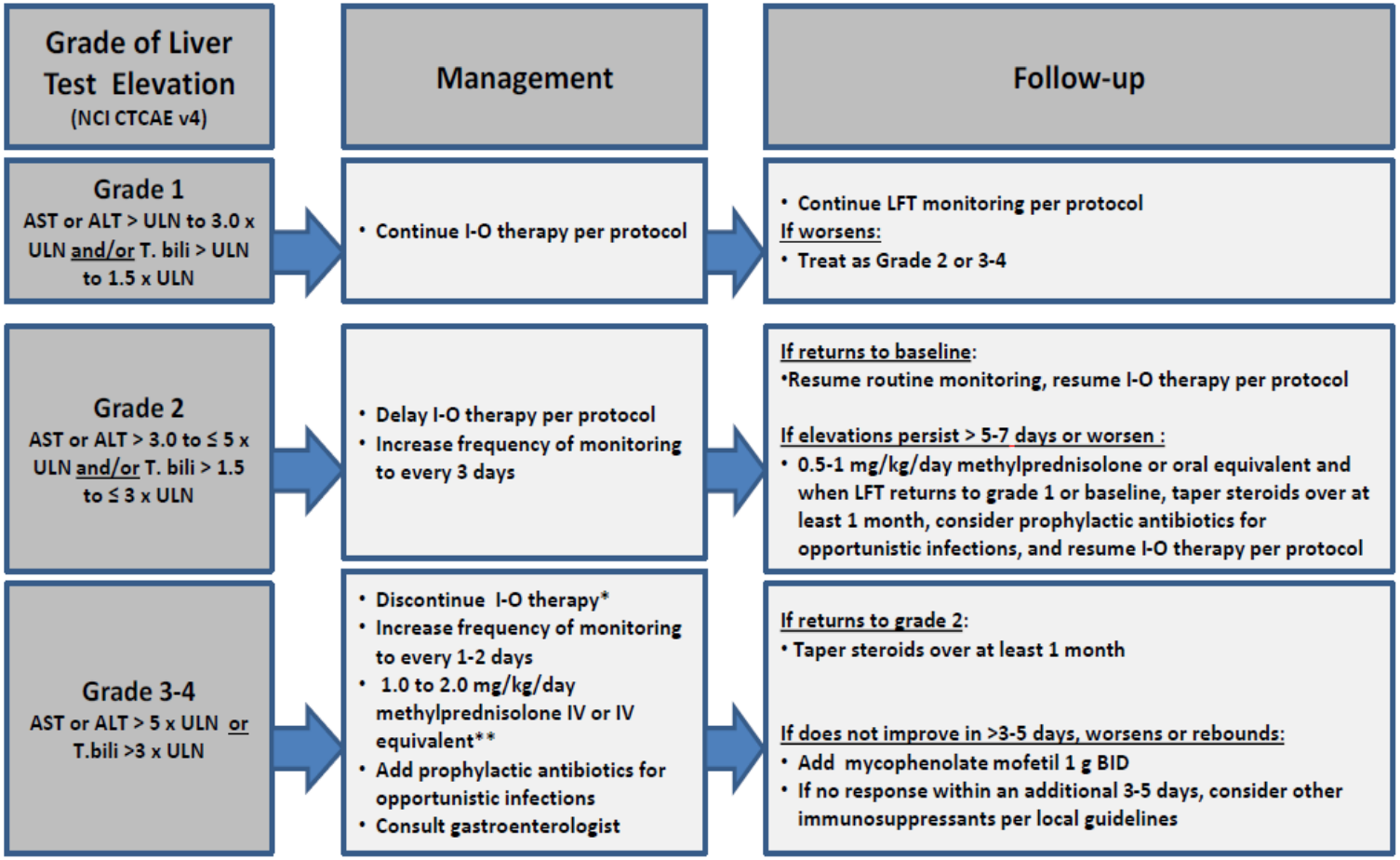


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



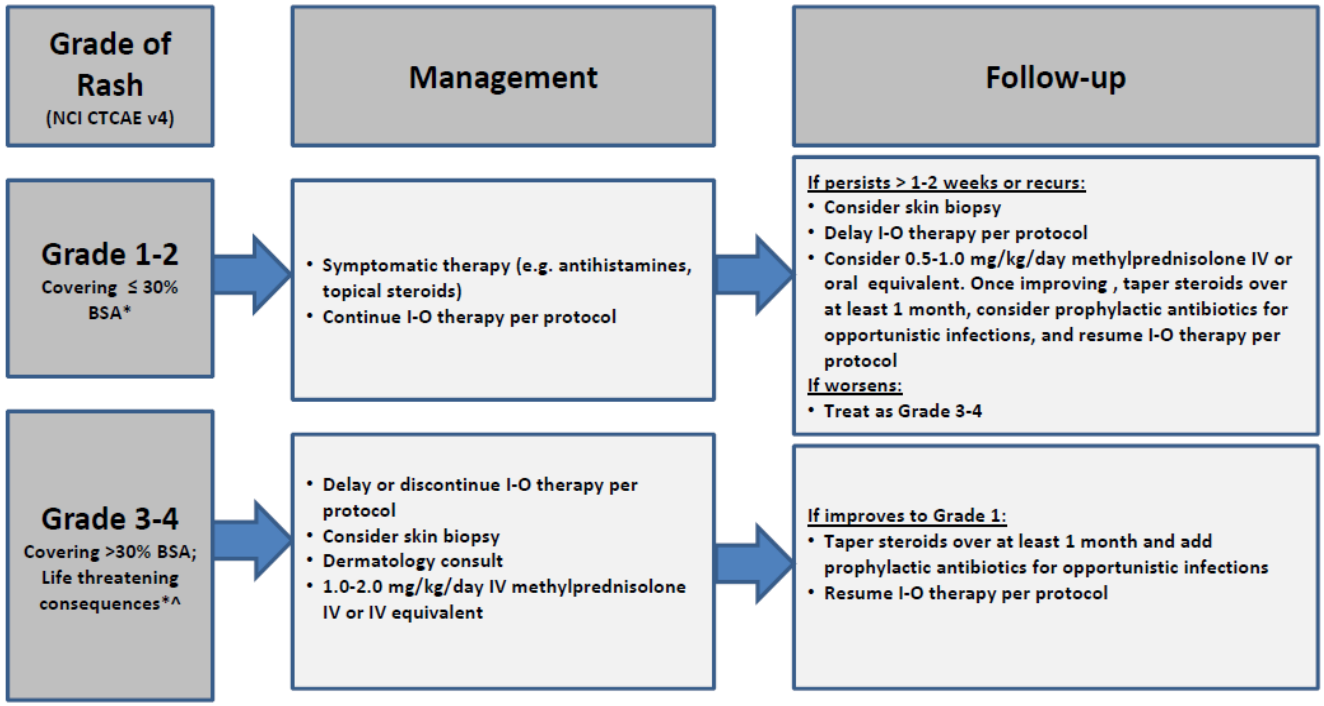
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Updated 05-Jul-2016

5.8 Diet/Activity/Other Considerations

5.8.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.8.2 Contraception

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% per year when used consistently and correctly.

At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Male condoms with spermicide

a) Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug.
b) Nonhormonal IUDs, such as ParaGard®
c) Tubal ligation
d) Vasectomy.
e) 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

(f) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section.

5.8.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with nivolumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Bristol Myers Squibb without delay and within 24 hours to the Sponsor and within 2 working days to Bristol Myers Squibb if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Bristol Myers Squibb and followed as described above and in Section 8.0.

5.8.4 Use in Nursing Women

It is unknown whether nivolumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.9 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease recurrence or a new primary cancer
- Unacceptable adverse experiences

- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with nivolumab or 8 administrations of study medication, whichever is later.

  Note: 24 months of study medication is calculated from the date of first dose.

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment). Subjects who discontinue for reasons other than recurrent disease will have post-treatment follow-up for disease status until disease recurrence, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease recurrence each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.10 Subject Replacement Strategy

No subject replacement is anticipated; however, if patients discontinue therapy due to toxicity, replacement may be considered to allow the primary objective of reduction in adenoma incidence to be addressed.

5.11 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug

In the event of a Bristol Myers Squibb decision to discontinue supply of the study drug, ample notification will be provided so that appropriate adjustments can be made.

6.0 TRIAL FLOW CHART

Trial Period	Screening Phase	Treatment Cycles[1]											
Treatment Cycle	Main Study Screening	1	Interim Visit 1[12,13]	2	Interim Visit 2[12,13]	3	4		5	6	7	8	
Scheduling Window (days)[2]	-28 to -1	+/- 7	6 weeks	+/- 7	6 weeks	+/- 7	+/- 7		+/- 7	+/- 7	+/-7	+/- 7	
Informed Consent[3]	X												
Consent for future biomedical research	X												
Inclusion/Exclusion Criteria	X												
Demographics/ Medical History[4]	X												
Prior/Concomitant Medications[4]	X	X	X	X	X	X	X		X	X	X	X	
Trial Treatment Administration		X		X		X	X		X	X	X	X	
Review Adverse Events[5]			X	X	X	X	X		X	X	X	X	
Full Physical Examination	X	X	X	X	X	X	X		X	X	X	X	
Vital Signs/Weight[6]	X	X	X	X	X	X	X		X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	X		X	X	X	X	
Pregnancy Test (Urine or Serum beta-HCG)[7]	X	X	X	X	X	X	X		X	X	X	X	
CBC w/ Differential[8]	X	X	X	X	X	X	X		X	X	X	X	
Comprehensive Serum Chemistry Panel[8]	X	X	X	X	X	X	X		X	X	X	X	
Urinalysis[8]	X								X				
T3, FT4, and TSH[8]	X		X	X	X	X	X		X	X	X	X	
PT, INR, aPTT[8]	X								X				
Colonoscopy								X					X
Tissue Collection[9]								X					X

1. In general, assessments/procedures should be performed on Day 1 and prior to the first dose of study medication for each cycle unless otherwise specified. Treatment cycles for nivolumab = 3-month (90-day) cycles.
2. In general, the window for each visit is ± 7 days unless otherwise specified.
3. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g. within 28 days prior to the first dose of study drug). Assign Baseline number when the study informed consent is signed.
4. Date of last prior cancer treatment must be documented if applicable. Report complete medication history for 30 days prior to the screening visit (Visit 1).
5. AEs and laboratory safety measurements will be graded per NCI CTCAE version 5.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness. AEs occurring within 30 days after the last dose of study drug should be recorded. After this time, record only AEs that are considered related to study drug.
6. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at the screening visit (Visit 1) only.
7. For women of reproductive potential, a urine pregnancy test will be performed within 24 hours prior to first dose of study medication. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required.
8. Routine laboratory tests (serum chemistry; hematology; urinalysis; PT/INR and aPTT; and T3, FT4, and TSH) for screening should be performed within 28 days prior to the first dose of study drug. Starting with the first interim visit, laboratory samples may be collected up to 48 hours prior to the scheduled time point. Lab results must be known and acceptable prior to dosing. See Appendix regarding laboratory tests.
9. Optional biopsy samples: Biopsies may be obtained at the time of each colonoscopy. Collection of these samples for purpose of biomarker analysis is strongly encouraged, but must be discussed with the sponsor prior to the procedure. The optional biopsy consent must be signed before collecting the samples. If the subject signs the Future Biomedical Research (FBR) consent, an aliquot of the tissue biopsies will be designated for FBR and the tissue sample should have proper size to enable multiple planned biomarker analyses, but not artificially decrease the longest diameter of the lesion. In addition, any leftover tissue biopsies that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.
10. The mandatory Safety Follow----Up visit should be conducted approximately 100 days after the last dose of study drug or before the initiation of a new antineoplastic treatment, whichever comes first. Patients with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0---1 or until beginning of a new antineoplastic therapy, whichever occurs first.
11. The first follow-up visit (FUV 1) should be scheduled 3 months (90 days) after the last dose of study drug. Subsequent follow-up visits should occur every 6 months (180 days) for the first year.
12. Interim monitoring visits with labs, physical examination, and toxicity checks, will be performed six weeks after the first and six weeks after the second administration of study drug. Additional monitoring visits will be added if dictated by symptoms.
13. Followup toxicity checks by phone will be made every 2 weeks during the first 6 weeks of treatment and every 4 weeks thereafter while the subject is receiving study drug or more frequently as symptoms dictate.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Bristol Myers Squibb for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.1.1.6 Assignment of Screening Number

All patients who are screened will be assigned a unique screening number.

7.1.1.7 Assignment of Randomization Number

Subjects on this study will not be randomized.

7.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)

Duration of exposure to study drug during the treatment phase and compliance will be summarized. Summary data listings will be provided for concomitant therapy both prior to and after start of study drug administration.

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug will be summarized by Anatomical Therapeutic Chemical (ATC) class, preferred term and age group. The clinical pharmacist or assigned personnel will review potential drug interactions with other concomitant medications as stated in Section 5.6.1

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0 (see Section 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with nivolumab, all AEs of unknown etiology associated with nivolumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see section 7.2.3.2.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

7.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Diagnostic Testing for Lynch Syndrome

A genetic test positive for a germline mutation in MLH1 or MSH2 is required to enter this trial. The diagnosis of Lynch syndrome needs to be determine by commercially available germline testing in a CLIA-approved laboratory. Preferred laboratories for this testing include Invitae, Ambry, GeneDx, or Myriad; however, results from other facilities that are CLIA-approved for this test will also be considered. Individuals with a history of a microsatellite-instable colon cancer without an identified germline mismatch repair gene mutation will not be eligible.

7.1.2.7 Colonoscopy Requirements

Colonoscopies will require a good to excellent bowel prep in order to be appropriate for assessment. If an inadequate bowel prep is done, the colonoscopy must be repeated within two months for appropriate assessment for study purposes. At the time of each colonoscopy, in addition to any biopsies of concerning lesions, five biopsies of normal-appearing colon mucosa will be taken. These biopsies of normal-appearing tissue will not be submitted as clinical specimens for pathologic review but will be retained for research purposes.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5.

Table 5. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total triiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free thyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or bicarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		
	Creatinine		
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
‡ If considered standard of care in your region.

After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.3.1 Pharmacokinetic/Pharmacodynamic Evaluations

No blood collection for pharmacokinetic/pharmacodynamic evaluations is planned in this study.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4.2 Blinding/Unblinding

Not applicable to this single arm open label trial.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening Period

Patients will be assigned a unique screening number after signing informed consent. During screening, patients will undergo history and physical, baseline labs and other investigations as outlined in the flow sheet in Section 6.0.

7.1.5.2 Treatment Period

After screening, patients meeting all requirements of the inclusion and exclusion criteria will be assigned a unique allocation number. Patients not meeting criteria after screening will not be assigned an allocation number. All screened and enrolled patients will be accounted by the center. A patient participation log is to be completed with the patient's baseline number, allocation number (if patient is enrolled), date of consent, and date of the initial administration of study drug. If a patient is not enrolled, the reason for exclusion from the study will be documented on this log. Beginning of treatment within 3 days after enrollment is preferable.

7.1.5.3 Post-Treatment Visits

7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 100 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

7.1.5.3.2 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease recurrence or new primary cancer will move into the Follow-Up Phase and should be assessed every 6 months (± 14 days). Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

7.1.5.3.1 Survival Follow-up

Once a subject experiences confirmed recurrence, a new primary cancer, or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

8.0 ADVERSE EVENT REPORTING FOR INTERVENTIONAL PROTOCOLS

All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety (Worldwide.Safety@BMS.com; SAE Facsimile Number: 609-818-3804). If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The BMS SAE form should be used to report SAEs. If the BMS form cannot be used, another acceptable form (ie, CIOMS or Medwatch) must be reviewed and approved by BMS. The BMS protocol ID number must be included on whatever form is submitted by the Sponsor/Investigator. The CIOMS form is available at: http://www.cioms.ch/index.php/cioms-form-i.

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure. The duration of SAE collection should be extended to100 days for nivolumab

In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously

described in the IB). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).

Other important findings which may be reported by BMS as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on BMS or an approved form; pregnancies must be reported on a Pregnancy Surveillance Form.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

For studies conducted under an Investigator IND in the US, any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible and no later than 7 days (for a death or life-threatening event) or 15 days (for all other SAEs) after the investigator's or institution's initial receipt of the information. BMS will be provided with a simultaneous copy of all adverse events filed with the FDA.

SAEs should be reported on MedWatch Form 3500, which can be accessed at http://www.accessdata.fda.gov/scripts/medwatch/.

MedWatch SAE forms should be sent to the FDA at:
MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/

An SAE report should be completed for any event where doubt exists regarding its seriousness.

For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection in the protocol.

- The Sponsor will reconcile the clinical database SAE cases (case level only) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com). Frequency of reconciliation should be every 3 months and prior to the database lock or final data summary. BMS GPV&E will email, upon request from the Investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization. All SAEs should be followed to resolution or stabilization.

8.1.1 Subsite Serious Adverse Event Reporting

NOTE: External participating sites are not permitted to report directly to the OSU IRB. In addition to BMS Worldwide Safety, all external site SAEs are to be reported to the OSU Principal Investigator and Multi-Center Trial Program (MCTP). The Multi-Center Trial Program will facilitate submission of external site SAEs to the OSU IRB. Reporting of SAEs to BMS will be done by the subsite study team. Reporting information for BMS is listed in section 8.0.

All SAEs must be reported to the OSU Principal Investigator, Multi-Center Trial Program (MCTP) and BMS within 24 hours of knowledge of the event using the BMS SAE form and the "SAE Submission Form" cover sheet (refer to the Supplemental Forms Document).

Copies of de-identified source documentation pertaining to the SAE must be submitted to OSU. If a patient is permanently withdrawn from the study because of a SAE, this information must be included in the initial or follow-up SAE report form.

All SAEs must be submitted to the local IRB per local IRB and institutional policy. Upon request of additional data or information that is deemed necessary must be reported to OSU as soon as possible but no later than 5 calendar days.

DEFINITIONS

The protocol must include a definition for Serious Adverse Events (SAE)**.**

SERIOUS ADVERSE EVENTS

A **S*erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, potential drug-induced liver injury (DILI) and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

NOTE: (PI determines if this information regarding hospitalizations are considered SAEs and should be included in the protocol. This is supplemental information that is included in BMS-sponsored trials)

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

ADVERSE EVENTS

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

NONSERIOUS ADVERSE EVENT

- Nonserious Adverse Events are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [e.g. IND US trial] as part of an annual reporting requirement.
- Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

A ***nonserious adverse event*** is an AE not classified as serious.

Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported as such.

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the participant to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

Potential Drug Induced Liver Injury (DILI)

Specific criteria for identifying potential DILI have not been identified for this protocol. Standard medical practice in identifying and monitoring hepatic issues should be followed.

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as: add your criteria

Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant).

The investigator must immediately notify Worldwide.Safety@bms.com of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form [provided upon request from BMS]

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

8.1.2 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 6. Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events as to:

V5.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Bristol Myers Squibb product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Bristol Myers Squibb product to be discontinued?	
Relationship to test drug	Did the Bristol Myers Squibb product cause the adverse event? The determination of the likelihood that the Bristol Myers Squibb product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Bristol Myers Squibb product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Bristol Myers Squibb product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Bristol Myers Squibb product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Bristol Myers Squibb product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Bristol Myers Squibb product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Bristol Myers Squibb product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Bristol Myers Squibb product; or (3) the trial is a single-dose drug trial); or (4) Bristol Myers Squibb product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Bristol Myers Squibb product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Bristol Myers Squibb product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE BRISTOL MYERS SQUIBB PRODUCT, OR IF REEXPOSURE TO THE BRISTOL MYERS SQUIBB PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Bristol Myers Squibb product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Bristol Myers Squibb product relationship).**
Yes, there is a reasonable possibility of Bristol Myers Squibb product relationship.		There is evidence of exposure to the Bristol Myers Squibb product. The temporal sequence of the AE onset relative to the administration of the Bristol Myers Squibb product is reasonable. The AE is more likely explained by the Bristol Myers Squibb product than by another cause.
No, there is not a reasonable possibility of Bristol Myers Squibb product relationship		Subject did not receive the Bristol Myers Squibb product OR temporal sequence of the AE onset relative to administration of the Bristol Myers Squibb product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

8.1.3 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

8.2 Data Safety Monitoring Plan

The data and safety monitoring plan will involve the continuous evaluation of safety, data quality and data timeliness. Investigators will conduct continuous review of data and patient safety at their regular Disease Group meetings (at least monthly) and the discussion will be documented in minutes. The Principal Investigator, study coordinator, and statistician, in consultation with treating physicians as appropriate, will review all toxicities to inform the model for dose level adjustments. The Principal Investigator of the trial will review toxicities and responses of the trial where applicable at these disease center meetings and determine if the risk/benefit ratio of the trial changes. Frequency and severity of adverse events will be reviewed by the Principal Investigator and compared to what is known about the agent/device from other sources; including published literature, scientific meetings and discussions with sponsors, to determine if the trial should be terminated before completion. Serious adverse events will be reviewed by the OSUCCC Data and Safety Monitoring Committee (DSMC). The Principal Investigator will also submit progress reports that will be reviewed by the committee per the DSMC plan. All reportable SAEs will be reported to the IRB of record as per the policies of the IRB.

Monthly safety and trial review teleconferences will be scheduled and moderated by the Multi-Center Trial Program. All sites involved in the study are expected to have a representative present every month to review and discuss patients on study and other applicable agenda items. Meeting minutes will be used to document each monthly teleconference. The minutes will be stored in the Multi-Institution Program protocol files.

8.3 Data Submission

The study will be managed per the Multi-Center Trial Program policies. Data must be submitted to the Multi-Center Trial Program Data within 2 weeks of completion of each cycle. Data will be submitted using case report forms and the Data Submission Form (refer to Supplemental Forms Document) supplied by the Multi-Center Trial Program. All data submitted must be accompanied by supporting source documents. Access to the OSU OnCore database may be provided to external participating for direct electronic data entry.

9.0 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

The statistical analysis will estimate the incidence rates of both adenomas and high-risk adenomas at 3 years. The associated confidence intervals will be reported and used to determine if the incidence rates are significantly different from those reported among Lynch patients not receiving nivolumab, 0.33 and 0.22 for adenomas and high-risk adenomas, respectively. (3,4) Further, the incidence rates of colon and non-colonic cancers in Lynch patients treated with nivolumab will be estimated

9.2 Statistical Analysis Plan

The sample size was calculated based on testing if the incidence of colon adenomas among the study population receiving nivolumab significantly differs from 0.33, the reported incidence race of colon adenomas among Lynch syndrome patients not receiving nivolumab. A minimum sample size of 94 is needed to detect a 40% reduction in the incidence of adenomas with 80% power and a two-tailed significance level of 0.05. If we account for a 10% loss to follow-up, the sample size recruited should be increased to 104.

The primary statistical analysis will estimate the incidence rate of adenomas at 3 years. The associated confidence intervals will be reported and used to determine if the incidence rate is significantly different from that reported among Lynch patients not receiving nivolumab, 0.33.

A secondary statistical analysis will estimate the incidence rate of high-risk adenomas at 3 years. Similar to the primary analysis, the associated confidence interval will be reported and used to determine if the incidence rate is significantly different from 0.22, the reported incidence of high-risk adenomas among Lynch syndrome patients not receiving nivolumab. Based on the available power from the sample size of 96, we would be able to detect a 50% reduction in high-risk adenomas as the secondary objective with a power of 80% and two-sided significance level of 0.05. Further, the incidence rates of colon and non-colonic cancers in Lynch patients treated with nivolumab will be estimated with corresponding confidence intervals.

9.3. TIMELINE

Expected first patient first visit: 2nd quarter 2018

Expected last patient first visit: 4th quarter 2019

Expected first patient last visit: 2nd quarter 2021

Expected last patient last visit: 4th quarter 2022

Accrual by month is anticipated to be approximately 5 patients per month.

Duration of study is anticipated to be 6 years.

10.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

10.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by Bristol Myers Squibb as summarized in Table 7.

Table 7. Product Descriptions

Product Name & Potency	Dosage Form
Nivolumab 100 mg/ 10mL vial	Clear to opalescent, colorless to pale yellow liquid.
Nivolumab 40 mg/ 4mL vial	Clear to opalescent, colorless to pale yellow liquid

10.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

10.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

10.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

10.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Bristol Myers Squibb or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

11.0 ADMINISTRATIVE AND REGULATORY DETAILS

11.1 Confidentiality

The MCTP will work with the appropriate parties to obtain an executed Confidentiality Disclosure Agreement (CDA) with each external participating site prior to protocol document sharing. OSUCCC PIs MUST NOT share protocol documents prior to CDA execution.

Only the protocol specific subject ID number and/or subject initials must appear on all CRFs to ensure subject confidentiality.

11.2 Compliance with Financial Disclosure Requirements

Signed and dated Financial Disclosure Forms will be required for each Investigator listed on the 1572 form. This form is available through the OSU Multi-Site Clinical Trials Program.

11.3 Compliance with Law, Audit and Debarment

As the study sponsor, The Ohio State University Comprehensive Cancer Center (OSUCCC) will audit each site as per OSU policies. Audits will be performed by the OSUCCC Clinical Research Audit Team. For sites with an auditing mechanism in place that are able to share documentation of their auditing standards and processes followed, an agreement may be requested for the site to perform local auditing and provide formal audit reports to the OSUCCC Multi-Center Trial Program (MCTP) and the Quality Assurance Oversight Committee.

11.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

11.5 Data Management

Information regarding Data Management procedures for this protocol will be provided by the Clinical Research Organization (to be determined).

11.6 Publication Strategy

We will anticipate publication in a journal such as the Journal of Clinical Oncology or another journal with a similar or higher impact factor. Anticipated date of submission is 3rd quarter 2023.

12.0 APPENDICES

12.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

12.2 Screening laboratory tests

The laboratory tests listed below will be performed only by the local study site lab. Patient treatment and overall management decisions will be based on local lab data.

Hematology
White Blood Cell Count (total and differential)
Absolute Neutrophil Count
Absolute Lymphocyte Count
Red Blood Cell Count
Hemoglobin
Hematocrit
Platelets

Coagulation
PT (INR)
aPTT

Comprehensive Chemistry Panel
Sodium
Potassium

Chloride
Calcium
Phosphorus
Magnesium
Carbon Dioxide (CO_2 or bicarbonate)
Urea Nitrogen (BUN)
Creatinine
Uric acid
Protein, total
Albumin
Bilirubin, total
Alkaline Phosphatase
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Lactate dehydrogenase (LDH)
Bilirubin, direct and indirect
Glucose

Other
Urine and serum beta-HCG (for women of child bearing potential only).
Urinalysis to include dipstick and microscopic examinations (pH, protein, glucose, leukocyte esterase, ketones, nitrites, WBCs, RBCs, epithelial cells, and casts).

Thyroid function tests (Thyroid stimulating hormone, T3, free T4)

12.3 Common Terminology Criteria for Adverse Events V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

References:

1. Kohlmann W, Gruber SB. (updated May 22, 2014). Lynch Syndrome. In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle, 1993-2016. Available at http://www.genetests.org. Accessed May 9, 2016.

2. Bonadona V, Bonaiti B, Olschwang S, et al. French Cancer Genetics Network. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA 2011; 305:2304-2310.

3. Kalady MF, McGannon E, Vogel JD, Manilich E, Fazio VW, Church JM. Risk of colorectal adenoma and carcinoma after colectomy for colon cancer in patients meeting Amsterdam Criteria. Ann Surg 2010;252:507-513.

4. Cappel WH, Nagengast FM, Griffioen G, Menko FH, Taal BG, Kleibeuker JH, Vasen HF. Surveillance for hereditary nonpolyposis colorectal cancer: A long-term study in 114 families. Dis Colon Rectum 2002;45:1588-1594.

5. Jarvinen HJ, Aarnio M, Mustonen H, Aktan-Collan K, Aaltonen LA, Peltomaki P, de la Chappelle A, Mecklin J-P. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology 2000; 118:829-834.

6. Vasen HFA, Abdirahman M, Brohet R, Langers AMJ, Kleibeuker JH, van Kouwen M, Koornstra JJ, Boot H, Cats A, Dekker E, Sanduleanu S, Poley J-W, Hardwick JCH, et al. Gastroenterology 2010;138:2300-2306.

7. Le DT, Uram JM, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, Luber BS, Azad NS, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Duffy SM, Goldberg RM, de la Chapelle A, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509-20.

8. Bacher JW, Sievers CK, Albrecht DM, Grimes IC, Weiss JM, Matkowskyj KA, Agni RM, Vyazumona I, Clipson L, Storts DR, Thliveris AT, Halberg RB. Improved detection of microsatellite instability in early colorectal lesions. PLOS One 2015;10(8): e0132727.

9. Iino H, Simms L, Young J, Arnold J, Winship IM, Webb SK, Furlong KL, Leggett B, Jass JR. DNA microsatellite instability and mismatch repair protein loss in adenomas presenting in hereditary non-polyposis colorectal cancer. Gut 2000;47:37-42.

10. Shia J, Klimstra DC, Nafa K, Offit K, Guillem JG, Markowitz AJ, Gerald WL, Ellis NA. Value of immunohistochemical detection of DNA mismatch repair proteins in predicting germline mutation in hereditary colorectal neoplasms. Am J Surg Pathol 2005;29(1):96-104.

11. Giuffre G, Muller A, Brodegger T, Bocker-Edmonston T, Gebert J, Kloor M, Dietmaier W, Kullmann F, Buttner R, Tuccari G, Ruschoff J, German HNPCC Consortium. Microsatellite analysis of hereditary nonpolyposis colorectal cancer-associated colorectal

adenomas by laser-assisted microdissection: correlation with mismatch repair protein expression provides new insights in early steps of tumorigenesis. J Mol Diagn 2005;7(2)160-70.

12. Muller A, Beckmann C, Westphal G, Edmonston TB, Friedrichs N, Dietmaier W, Brasch FE, Kloor M, Poremba C, Keller G, Aust DE, Fas J, Buttner R, Becker H, Ruschoff J, German HNPCC Consortium. Prevalence of the mismatch-repair-deficient phenotype in colonic adenomas arising in HNPCC patients: results of a 5-year follow-up study. Int J Colorectal Dis 2006;21:632-41.

13. Ferreira AM, Westers H, Sousa S, Wu Y, Niessen RC, Olderode-Berends M, van der Sluis T, Reuvekamp PTW, Seruca R, Kleibeuker JS, Hollema H, Sijmons RH, Hofstra RMW. Mononucleotide precedes dinucleotide repeat ins5tability during colorectal tumour development in Lynch syndrome patients. J Pathol 2009;219:96-102.

14. Walsh MD, Buchanan DD, Pearson S-A, Clendenning M, Jenkins MA, Win AK, Walters RJ, Spring KJ, Nagler B, Pavluk E, Arnold ST, Goldblatt J, George J, Suthers GK, et al. Immunohistochemical testing of conventional adenomas for loss of expression of mismatch repair proteins in Lynch syndrome mutation carriers: a case series from the Australasian site of the colon cancer family registry. Modern Pathology 2012;25:722-30.

15. Yurgelun MB, Goel A, Hornick JL, Sen A, Turgeon DK, Ruffin MT 4th, Marcon NE, Baron JA, Bresalier RS, Syngal S, Brenner DE, Boland CR, Stoffel EM. Microsatellite instability and DNA mismatch repair protein deficiency in Lynch syndrome colorectal polyps. Cancer Prev Res (Phila) 2012; 5(4)574-82.

16. Timmermann B, Kerick M, Roehr C, et al. Somatic mutation profiles of MSI and MSS colorectal cancer identified by whole exome next generation sequencing and bioinformatics analysis. PLoS One 2010; 5(12): e15661.

17. Eshleman JR, Lang EZ, Bowerfind GK, et al. Increased mutation rate at the hprt locus accompanies microsatellite instability in colon cancer. Oncogene 1995; 10: 33-7.

18. Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. Nature 2012; 487: 330-7.

19. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. N Engl J Med 2012; 366: 2443-54.

20. Berger MF, Hodis E, Heffernan TP, et al. Melanoma genome sequencing reveals frequent PREX2 mutations. Nature 2012;485: 502-6.

21. Samadder NJ, Neklason DW, Boucher KM, Byrne KR, Kanth P, Samowitz W, Jones D, Tavtigian SV, Done MW, Berry T, Jasperson K, Pappas K, Smith L, Sample D, Davis R, Topham MK, Lynch P, Strait E, McKinnon W, Burt RW, Kuwada SK. Effect of Sulindac and Erlotinib vs. placebo on duodenal neoplasia in Familial Adenomatous Polyposis: A randomized clinical trial. JAMA 2016; 316(5):544-545.

22. Jass JR1, Stewart SM, Stewart J, Lane MR. Hereditary non-polyposis colorectal cancer--morphologies, genes and mutations. Mutat Res. 1994 Oct 1;310(1):125-33.

23. Edelstein DL1, Axilbund J, Baxter M, Hylind LM, Romans K, Griffin CA, Cruz-Correa M, Giardiello FM. Rapid development of colorectal neoplasia in patients with Lynch syndrome. Clin Gastroenterol Hepatol. 2011 Apr;9(4):340-3. doi:10.1016/j.cgh.2010.10.033. Epub 2010 Nov 9.

24. Winawer SJ, Fletcher RH, Miller L, et al. Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology 1997; 112:594 – 642.

25. Lin KM, Shashidharan M, Ternent CA, Thorson AG, Blatchford GJ, Christensen MA, Lanspa SJ, Lemon SJ, Watson P, Lynch HT. Colorectal and extracolonic cancer variations in MLH1/MSH2 hereditary nonpolyposis colorectal cancer kindreds and the general population. Dis Colon Rectum. 1998;41(4):428.

26. Parry S, Win AK, Parry B, Macrae FA, Gurrin LC, Church JM, Baron JA, Giles GG, Leggett BA, Winship I, Lipton L, Young GP, Young JP, Lodge CJ, Southey MC, Newcomb PA, Le Marchand L, Haile RW, Lindor NM, Gallinger S, Hopper JL, Jenkins MA. Metachronous colorectal cancer risk for mismatch repair gene mutation carriers: the advantage of more extensive colon surgery. Gut. 2011;60(7):950.