TITLE: A phase I/II study of PI3Kinase inhibition (copanlisib) and anti-PD-1 antibody nivolumab in relapsed/refractory solid tumors with expansions in MSS colorectal cancer

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BAYER Protocol #:	IIR-US-2018-5354
ClinicalTrials.gov ID:	NCT03711058
Principal Investigator:	Nilofer Azad, MD [redacted]
BMS Supplied Agent:	Nivolumab (Opdivo®, BMS-936558)
Bayer Supplied Agent:	Copanlisib (BAY 80-6946)
IND Number:	139720
IND Sponsor:	Nilofer Azad, MD
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TRIAL SUMMARY

Abbreviated Title	Copanlisib and nivolumab in relapsed/refractory solid tumors with expansions in MSS colorectal cancer
Trial Phase	*I/II*
Clinical Indication	Phase I: Relapsed/refractory MSS solid tumors Phase II: MSS colorectal cancer
Trial Type	Dose Finding / Efficacy and safety
Type of control	Single arm (no control)
Route of administration	IV
Trial Blinding	Open Label
Treatment Groups	Copanlisib + Nivolumab
Number of trial participants	51-54
Estimated enrollment period	*18 months*
Estimated duration of trial	*24 months*

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LIST OF ABBREVIATIONS

Abbreviation	Definition
5-HT3	serotonin receptor
AE	adverse event
AKT	protein kinase B
ALT	alanine aminotransferase (also known as SGPT)
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase (also known as SGOT)
AUC	area under the concentration-time curve
BAY 80-6946	copanlisib
BMS	Bristol-Myers Squibb Company
BP	blood pressure
BRAF	v-RAD murine sarcoma viral homolog B1
BUN	blood urea nitrogen
C	cycle
CBC	complete blood count
CCL2	C-C motif chemokine ligand 2
CD	cluster of differentiation (e.g. CD28 = cluster of differentiation 28)
CEA	Carcinoembryonic Antigen
CFR	code of federal regulations
CLIA	Clinical Laboratory Improvement Amendments
Cmax	maximum serum concentration
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CRF	case report form
CRO	Clinical Research Office
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CV%	(% coefficient of variation
CXCL9	C-X-C motif chemokine ligand 9
CYP	cytochrome P450
D	day
DCR	disease control rate
DILI	drug induced liver injury
DLT	dose limiting toxicities
DoR	duration of response
DPP4	dipeptidyl peptidase 4
DSMP	data safety monitoring plan
e.g.	*exempli gratia*, for example
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviation	Definition
EGFR	epidermal growth factor receptor
EOT	end of treatment
ESR	expedited safety report
etc.	*et cetera*, and so forth
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FT4	free T4 (or free thyroxin)
g	gram(s)
GCP	good clinical practice
GFR	glomerular filtration rate
GVP&E	Global Pharmacovigilance and Epidemiology
h	hour(s)
H&E	hematoxylin and eosin
HbA1c	hemoglobin A1c
HBsAg	hepatitis B serum antigen
HDL	high-density lipoprotein
HepC	hepatitis C
HepCAb	hepatitis C antibody
HER	human epidermal growth factor receptor
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
i.e.	*id est,* that is
IB	Investigator's brochure
IC50	half maximal inhibitory concentration
IDO	indoleamine-pyrrole 2,3-dioxygenase
IF	immunofluorescence
IFNγ	interferon-gamma
IGF-1R	insulin-like growth factor 1 receptor
Ig	immunoglobulin
IgG4	immunoglobulin G4
IgV-type	Ig-variable–type
IHC	immunohistochemistry
IL	interleukin (IL-2 = Interleukin 2, IL-10 = interleukin 10, etc)
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IV	intravenous
JHU	Johns Hopkins University
kg	kilogram
KRAS	Kirsten ras oncogene homolog from the mammalian ras gene family
L	liter(s)
LAG3	lymphocyte-activation gene 3
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LFT	liver function test

Abbreviation	Definition
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
Med Hx	medical history
Met	mesenchymal epithelial transition factor
mg	milligram(s)
MHC	major histocompatibility complex
min	minute(s)
mL	milliliter(s)
mmHg	millimeter of mercury
mmol	millimoles(s)
MRI	magnetic resonance imaging
MSS	microsatellite stable
MTD	maximum tolerated dose
MUGA	Multi-gated acquisition scan
mTOR	mammalian target of rapamycin
N/A	not applicable
NCI	National Cancer Institute
NGS	next generation sequencing
nM	nanomole, nanomolar
NRAS	neuroblastoma RAS viral oncogene homolog
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
OI	opportunistic Infection
ORR	overall response rate
OS	overall survival
OTC	over the counter
OX-40	OX40 receptor, also known as CD134, or TNFRSF4
pAKT	phosphorylated AKT
PBMC	peripheral blood mononuclear cells
PBS	phosphate buffered saline
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PDGFR	platelet-derived growth factor receptor
PFS	progression-free survival
PI	Principal Investigator
PI3K	phosphatidylinositol 3-kinase
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase
PIP3	phosphatidylinositol-3,4,5-trisphosphate
PJP	Pneumocystis jiroveci pneumonia
PK	Pharmacokinetic(s)
PKCθ	protein kinase C-theta
PO	*per os*, orally

Abbreviation	Definition
PR	partial response
pRBC	packed red blood cell
PT	prothrombin time
PTEN	phosphate and tensin homolog
PTT	partial thromboplastin time
Q12W	every 12 weeks
QT	time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	corrected QT interval
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RNASeq	RNA sequencing
RP2D	recommended phase II dose
SAE	serious adverse event
SD	stable disease
SGLT2	sodium/glucose co-transporter 2
SGOT	serum glutamic-oxaloacetic transaminase (also known as AST)
SGPT	serum glutamic pyruvic transaminase (also known as ALT)
SKCCC	Sidney Kimmel Comprehensive Cancer Center
SOC	standard of care
SubQ	subcutaneously
T1/2	elimination half-life
T3	triiodothyronine
TCR	T-cell receptor
TME	tumor microenvironment
TNFα	tumor necrosis factor alpha
TSH	thyroid stimulating hormone
Tx	treatment
ULN	upper limit of normal
UPCR	urine protein:creatinine ratio
USP	United States Pharmacopeia
VEGF	vascular endothelial growth factor
VLDL	very low-density lipoprotein
VNS	vial, needle, and syringe
v-RAF	virus-induced rapidly accelerated fibrosarcoma
Vss	volume of distribution at steady state
WBC	white blood cell
WOCBP	women of childbearing potential
WT	wildtype

1. OBJECTIVES

1.1 Primary Objectives

1. Phase I: To determine the recommended phase II dose (RP2D) of copanlisib with fixed dose nivolumab

2. Phase II/Clinical: To determine 6-month objective response rate (ORR) of patients treated with copanlisib and nivolumab and compare the ORR of patients in Cohort A (MSS colorectal cancer patients with PIK3CA mutations) and Cohort B (MSS colorectal cancer patients with WT PIK3CA)

1.2 Secondary Objectives

1. To determine the 6-month disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), and overall survival (OS) and compare DCR, DoR, PFS, and OS of patients in cohort A and cohort B.

2. To assess safety and characterize toxicities of the combination of copanlisib and nivolumab

1.3 Exploratory Objective

1. To determine the effect of copanlisib + nivolumab on markers of immune exhaustion and pro-apoptotic factors in CD8+ effector T cells.

2. To determine the effect of copanlisib + nivolumab on immune cell subpopulations in the tumor microenvironment, including CD8+ T cells, PD-1/PD-L1 expression on tumor and tumor associated macrophages and monocytes, and MHC 1/2 expression.

3. To explore the effect of copanlisib and nivolumab on local and systemic immune activation pathways and immune suppressive pathways through expression profiling

4. To explore changes in immune cell subsets and cytokine profiles in the peripheral circulation

5. To evaluate potential molecular determinants of response, progression, and disease stability using next generation sequencing and other sequencing techniques

1.4 Hypotheses

1. PI3K inhibition with copanlisib in combination with nivolumab will be tolerable and result in tumor response in tumor types resistant to immune checkpoint therapy

2. Treatment with copanlisib in advanced solid tumors in combination with nivolumab will result in immunologic changes including:
   - increased numbers of CD8+ cytotoxic T cells
   - decreased T-cell exhaustion

- decreased CD4+ T regulatory T cells and myeloid derived suppressor cells
- changes in gene expression resulting in increased immune activation and decreased immune suppression pathways
- increased activated cytotoxic T-cells, TCR rearrangements, and decreased immune suppressive cells

1.5 Study Design

This is a multi-center, open-label, Phase I/II study. Phase 1 consists of a 3+3 dose de-escalation design to determine the dose of copanlisib for use in combination with nivolumab. Approximately 6-18 subjects with solid tumors will be treated in Phase I and will be monitored for dose limiting toxicities (DLTs) through their first cycle of treatment. Complete information on the definition of DLTs and dose de-escalation rules can be found in **Section 4.3**.

The Phase II portion of the study will evaluate the safety and clinical activity of copanlisib and nivolumab in two cohorts of patients with previously treated metastatic colon cancer. Cohort A will enroll patients with PI3K mutation and Cohort B will enroll patients with wildtype PI3K status. Twenty-one patients are targeted for enrollment in each cohort, for an approximate total of 42 patients in Phase II. Enrollment in Phase II will be initiated once the recommended phase II dose (RP2D) has been determined in Phase I.

For all patients, the study will consist of a screening period, a treatment period, and a follow-up period. Screening evaluations will be done within 28 days prior to the start of study treatment.

Each treatment cycle is 28 days. Patients in both Phase I and Phase II will receive nivolumab on Day 1 of each cycle (every 4 weeks) and copanlisib on either Day 1, Day 8, and Day 15 of each cycle (3 week on, one week off) or on Day 1 and 15 of each cycle (every 2 weeks), depending on the dose level and RP2D. Complete information on study drug administration, schedule, and dosing can be found in **Section 4.2.**

Phase II enrollment will be carried out in 2 stages so that the study can terminate early if the combination of copanlisib and nivolumab is not sufficiently effective. In the first stage, 12 subjects will be accrued to each cohort. If there are no responders among the first 12 patients, the study will be terminated for futility. Otherwise, 9 additional patients will be accrued for a total of 21 treated subjects. If ≥3 out of the 21 patients have a response, then the trial will be considered a success for that cohort.

Clinical and immune responses will be evaluated at baseline and during treatment through tumor assessments, biopsies, and PBMC and plasma collection. Tumor assessments will be made using RECIST 1.1.

All subjects may continue in the treatment period until discontinuation due to disease progression, unacceptable toxicity, subject withdrawal, or study closure. Complete criteria for removal from treatment are found in **Section 4.5**.

Subjects will undergo end-of-treatment (EOT) evaluations at the time it is determined they will

be discontinuing study treatment. All subjects will be followed for at least 30 days after their last dose of study drug for the development of AEs. SAEs that occur within 100 days of the last infusion of nivolumab or before initiation of a new antineoplastic treatment should also be followed and recorded. Complete information on safety reporting can be found in **Section 5**.

After completion of treatment and EOT assessments, all subjects will continue to be followed every 3 months by telephone, e-mail, or optional clinic visit until death, withdrawal of consent, or closure of study. Information on survival and new cancer therapies will be collected. Subjects that discontinue treatment for reason other than disease progression may also continue to be monitored by radiologic imaging every 10 weeks until start of a new anti-cancer therapy, disease progression, death, withdrawal of consent, or the close of the study, whichever occurs first.

2. BACKGROUND

2.1 Copanlisib (BAY 80-6946)

[redacted]

Copanlisib has been tested in approximately 772 patients with advanced cancers in either single-agent or combination studies. When given as a single agent, the most common drug-related adverse events (>20% of patients) included hyperglycemia, nausea, and hypertension. Other toxicities occurring with copanlisib administration included serious infections (19%), grade 4 neutropenia (12%), non-infectious pneumonitis (5%), and transient serious hypertension (1%) or hyperglycemia (1%).

For additional preclinical and clinical trial information, refer to the Investigator's Brochure.

2.2 Nivolumab

Nivolumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, nivolumab has high affinity and potent receptor blocking activity for PD-1. Nivolumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. OPDIVO™ (nivolumab) is approved for the treatment of several types of cancer because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator brochure.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2).[1, 2]

The structure of murine PD-1 has been resolved.[3] PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an

immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade.[2, 4-6] The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins.[7, 8]

The PK of single-agent nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses every 2 or 3 weeks. Nivolumab clearance decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of approximately 24.5% (47.6%) resulting in a geometric mean steady state clearance (CLss) (CV%) of 8.2 mL/h (53.9%); the decrease in CLss is not considered clinically relevant. The geometric mean volume of distribution at steady state (Vss) (CV%) is 6.8 L (27.3%), and geometric mean elimination half-life (t1/2) is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by approximately 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3.7-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks.

Refer to the Investigator's Brochure for Preclinical and Clinical data.

Recent trials of immune checkpoint blockade have shown striking clinical activity against a range of tumors. However, response to immune checkpoint blockade targeting CTLA4 and PD-1 is still limited, with only a subset of solid tumor patients showing clinical response[9-13].

[redacted]

Loss of PTEN promotes resistance to T cell–mediated immunotherapy

PTEN is a negative regulator of PI3K, therefore loss of PTEN phenocopies gain of function of PI3K. When PTEN is lost, the PI3 Kinase pathway is thought to rely on the β isoform of PI3K for signaling[14]. Melanoma patients with PTEN loss were enriched in nonresponders to anti-PD-1 and their tumors had fewer infiltrating CD8+ T cells. In a mouse *Braf-/- Pten-/-* mutant model of induced melanoma treated with adoptive transfer of antigen specific T cells and a tumor antigen vaccine, synergistic response was seen with GSK2636771, a PI3Kβ inhibitor, and anti-PD-1[15].

Loss of PTEN is associated with resistance to Anti-PD-1 checkpoint blockade therapy in metastatic uterine leiomyosarcoma

A single patient experience was described to address a mechanism of resistance to PD-1. A patient with metastatic uterine leiomyosarcoma had up front resection followed by enrollment

on a Phase II trial of pembrolizumab. The bulk of disease responded, however a single lesion progressed on therapy. This lesion was then resected and subject to whole genome and RNA sequencing, which was compared to sequencing performed at diagnosis. The only genomic difference was biallelic loss of *PTEN*, leading the authors to hypothesize that this genomic difference may underlie differential sensitivity to PD-1 blockade. Decreased inflammation was shown in the PTEN null progressive lesion by RNASeq of immune activation genes.[16]

PI3K inhibition reduces mammary tumor growth and facilitates anti-tumor immunity and anti-PD1 responses

Response to PI3K inhibition and PD-1 blockade was studied in orthotopic implants of mammary tumor cell lines 4T1 and PyMT. PI3K inhibition was achieved by pan-PI3K inhibitor BKM120. BKM120 increased sensitivity to anti-PD-1. The proposed mechanism in this study was recruitment of a myeloid population dependent on PI3Kγ.[17]

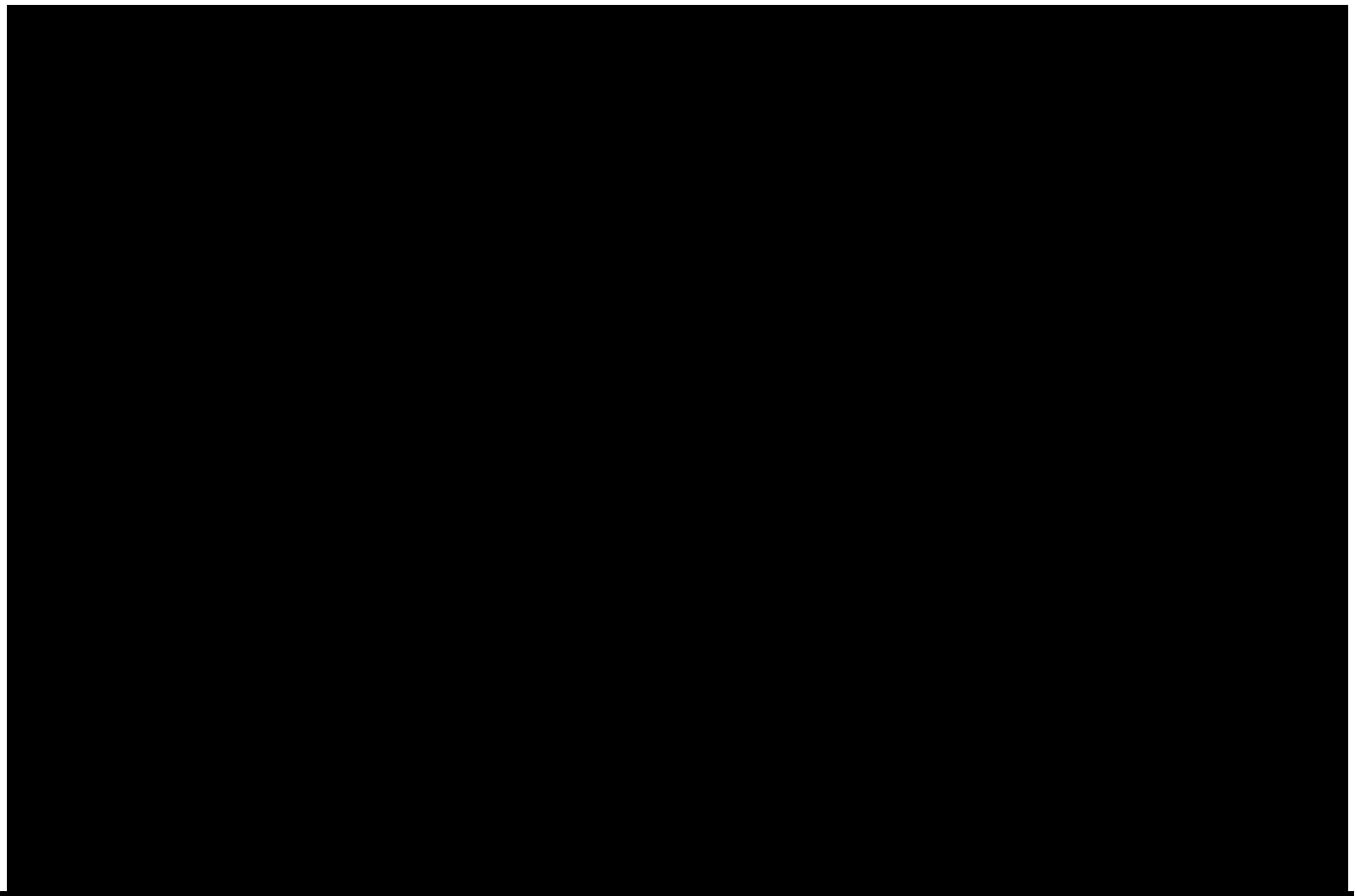
PIK3CA H1047R confers resistance to checkpoint blockade

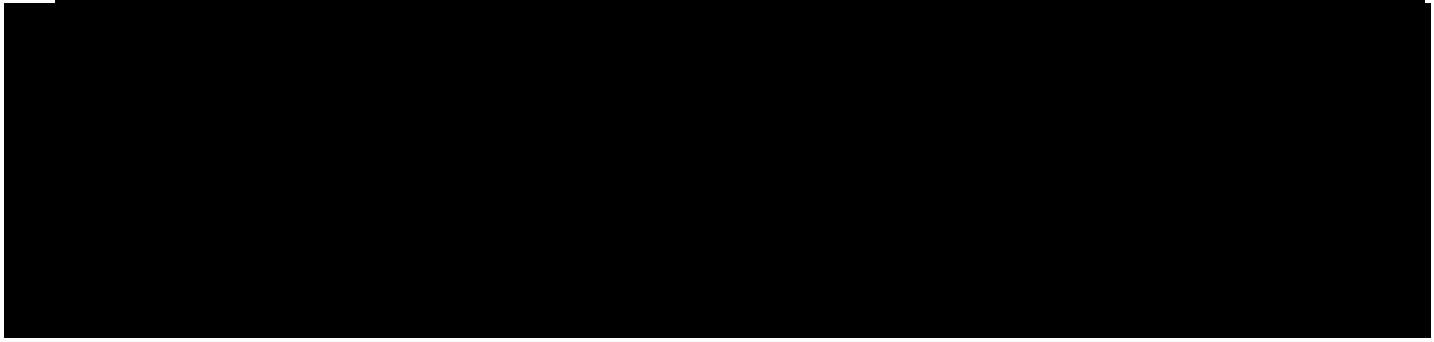
An experimental system was developed to identify genes used by cancer cells to evade immune attack using pooled, gain-of-function genetic screens in mouse transplantable models of cancer[18]. Murine tumor cells (MC38 colon carcinoma or B16 melanoma) were transduced with a pool of vectors encoding mutant alleles as open reading frames (ORFs) corresponding to a

[redacted]

[redacted]

PI3K Inhibition with copanlisib is synergistic with anti-PD-1 in the A20 mouse lymphoma model





[redacted]

3. PATIENT SELECTION

3.1 Eligibility Criteria

In order to be eligible for participation in this study, all of the following criteria must apply:

1. Be willing and able to provide written informed consent for the trial

2. Be at least 18 years of age on the day of signing informed consent

3. Have histologically confirmed metastatic or unresectable:
    a. Mismatch-repair proficient (MSS) solid tumor (for phase I dose de-escalation) OR
    b. Mismatch-repair proficient (MSS) colorectal cancer with known PI3K-mutation status (for expansion cohorts). NGS and PCR based testing by a CLIA certified lab will be used to determine PI3K status per **Section 7.5.1**.

4. In terms of prior therapies:
    a. For phase I dose de-escalation: have received all curative treatment options AND at least 2 lines of systemic therapy in the metastatic setting
    b. For MSS colorectal cancer cohorts in phase II expansion: have received at least 2 prior lines of standard therapy including a fluoropyrimidine, oxaliplatin, and irinotecan-containing regimen. KRAS/NRAS/BRAF wild type patients must have received or refused anti-EGFR therapy.

5. Have measurable disease based on RECIST 1.1. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

6. Have biopsiable disease. If biopsy is attempted and unsuccessful (the patient undergoes an invasive procedure), the patient may still be treated.

7. Have a performance status of 0 or 1 on the ECOG Performance Scale at study entry (See Appendix A).

8. Have a life expectancy of 3 months

9. Demonstrate adequate baseline laboratory values as defined below; all screening labs should be performed within 21 days of treatment initiation.

System – Lab	**Laboratory Value**
Hematological	
Absolute neutrophil count (ANC)	≥ 1500/µL
Platelets	≥ 75 000/µL
Hemoglobin	≥ 8.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Serum Creatinine	≤ 1.5 × ULN **or** Glomerular filtration rate (GFR) ≥40 mL/min/1.73
Urine protein:creatinine ration (UPCR)	< 3.5 on a random urine sample
Hepatic/pancreatic	
Total bilirubin	≤ 1.5 ×ULN (< 2 x ULN for patients with Gilbert's syndrome)
AST (SGOT) and ALT (SGPT)	≤ 3 × ULN
Lipase	< 1.5X ULN
Endocrine	
HbA1c	≤ 7%
Glucose	< 160 mg/dL (fasting) or < 200 mg/dL (non-fasting)
Coagulation	
International normalized ratio (INR) **and** partial thromboplastin time (PTT)	≤ 1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
Cardiac	
Left ventricular ejection fraction (LVEF)	≥ 50%
[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 1 week. [b] Creatinine clearance (CrCl) should be calculated per institutional standard.	

10. Male subjects must agree to use a contraception as detailed in **Appendix B** of this protocol during the treatment period and for at least 6 months after the last dose of study drug and refrain from donating sperm during this period.

11. Female subjects must not be pregnant (negative urine or serum test within 72 hours of first dose of study drug) or breastfeeding, and at least one of the following conditions must apply:
    a. Not a woman of childbearing potential (WOCBP) as defined in **Appendix B or**
    b. A WOCBP who agrees to follow the contraceptive guidance in **Appendix B** during the treatment period and for at least 6 months after the last dose of study drug.

3.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

1. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX-40, CD137).

2. Prior therapy with a PI3K inhibitor

3. Has received prior chemotherapy, targeted small molecule therapy, or surgery within 4 weeks of the first dose of treatment. Participants must have recovered from all AEs due to previous interventions to ≤Grade 1 or baseline. Participants with ≤ grade 2 neuropathy, anemia, and/or alopecia may be eligible.

4. Has received prior radiotherapy within 2 weeks of start of study treatment. Participants must have recovered from all radiation-related toxicities to ≤Grade 1 or baseline, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease. Participants with ≤ grade 2 neuropathy, anemia, and/or alopecia may be eligible.

5. Is currently participating in or has participated in a study of an investigational agent or investigational device within 4 weeks prior to the first dose of study treatment. (i.e. must be 4 weeks after the last dose of the previous investigational agent).

6. Has received a live vaccine within 30 days prior to the first dose of study drug. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy.

8. Has known CNS metastases and/or carcinomatous meningitis.

9. Has symptomatic ascites or has required a paracentesis in the last 12 weeks

10. Has known hypersensitivity to nivolumab, copanlisib, or any ingredients in the formulation of these study drugs.

11. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.

12. Has active autoimmune disease that has required systemic treatment in the past 12 months, or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy are exceptions. Intermittent use of bronchodilators or local steroid injections are not excluded. Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Autoimmune diagnoses not listed must be approved by the protocol chair.

13. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

14. Has an active infection requiring systemic therapy.

15. Has a known history of Human Immunodeficiency Virus (HIV) infection.

16. Has a known history of Hepatitis B (HBsAg reactive) or active Hepatitis C virus infection (HepCAb followed by HepC RNA if Ab test is positive).

17. CMV PCR positive

18. Has a history or concurrent condition of interstitial lung disease or severely impaired lung function (as judged by the investigator)

19. Has Type I diabetes or Type II diabetes requiring treatment with a sulfonylurea, meglitinide, or insulin.

20. Uncontrolled cardiovascular disease
    a. Congestive heart failure > New York Heart Association (NYHA) class 2
    b. Unstable angina (symptoms at rest), new-onset angina (within the last 3 months).
    c. Myocardial infarction less than 6 months before start of test drug
    d. Uncontrolled arterial hypertension despite optimal medical management

21. Use of anti-arrhythmic therapy (beta blockers or digoxin are permitted)

22. Use of CYP3A4 inhibitors and inducers within 2 weeks of starting study drug and throughout treatment. Examples of inhibitors of CYP3A4: ketoconazole, itraconazole, clarithromycin, ritonavir, indinavir, nelfinavir and saquinavir. Examples of inducers of CYP3A: rifampin, phenytoin, carbamazepine, phenobarbital, St. John's Wort. See **Table 7** for complete list.

23. Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism within 3 months before the start of study medication

24. Non-healing wound, ulcer, or fracture

25. Patients with evidence or history of bleeding diathesis. Any hemorrhage or bleeding event ≥ CTCAE Grade 3 within 4 weeks prior to the start of study medication

26. Had a blood or platelet transfusion within 7 days of Cycle 1 Day 1 treatment

27. Seizure disorder requiring anti-seizure medication

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

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

30. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 6 months after the last dose of trial treatment

31. Is a prisoner or is compulsorily detained

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. TREATMENT PLAN

4.1 Registration and Enrollment

Eligible patients will be entered on study centrally at the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins University by the Lead Study Coordinator. All sites should contact the Lead Study Coordinator to verify ongoing study enrollment. The Registration Form and Eligibility Checklist will be supplied to each participating site.
If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

[redacted] de-identified documents should be completed and sent to [redacted]

- Registration Form
- Signed patient consent form with printed patient name and DOB redacted
- Eligibility Checklist
- Participating Sites: copy of required screening tests, scans, and notes used to verify eligibility
- Coordinating Center (Johns Hopkins University): required screening tests, scans, and notes will be verified for eligibility through internal electronic clinic system.

The Research Nurse or Lead Study Coordinator at the participating site will then e-mail the Protocol Chair to verify eligibility. To complete the registration process, the Lead Study Coordinator will:

- Assign a patient study number
- Register the patient on the study
- Fax or e-mail the patient study number to the participating site
- Call or e-mail the research nurse or data manager at the participating site and verbally confirm registration.

4.2 Agent Administration

There will be two phases in this study: A Phase I dose-finding stage followed by a Phase II expansion.

Copanlisib will be administered as a 60 minute IV infusion (-5min/+10min) at the doses and days shown in **Table 1** and **Table 2** below. Subjects should be observed for a minimum of 30 minutes after administration of Copanlisib prior to administration of nivolumab.

Nivolumab 480 mg will be administered as a 30 minute IV infusion (-5min/+10min) on Day 1 of each 28 day cycle.

The Pharmacy Manual contains specific instructions for the preparation and administration of these study drugs.

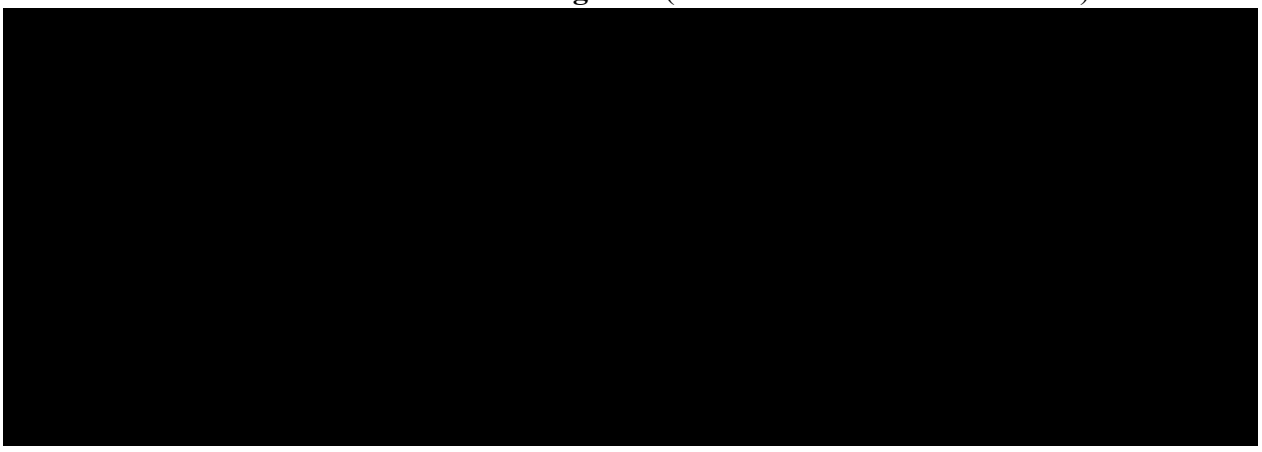
Study treatment should be administered after all procedures/assessments have been completed for that visit as detailed on the Study Calendar (**Section 8**). Study treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle, up to 1 day after the scheduled Day 8, or up to 3 days after Day 15 of each cycle due to administrative reasons as long as there is a minimum of 7 days between copanlisib infusions.

All trial treatments will be administered on an outpatient basis.

Phase I – Dose De-Escalation

Phase I will use a standard 3+3 design. The initial dose being tested is the recommended phase 2 dose of both study drugs as single agents, so the doses of copanlisib and nivolumab will not escalate higher than dose level 1. However, if the recommended phase II dose (RP2D) is exceeded in dose level 1, the dose of copanlisib will de-escalate as indicated below in Table 1. A maximum of 18 eligible subjects will be enrolled into this phase. All patients enrolled at each dose level will be evaluated for dose limiting toxicities (DLTs) during the first 28 day cycle for the purpose of determining the RP2D when given concurrently with nivolumab. DLTs and dose de-escalation rules are defined in **Section 4.3** and **Table 3**, respectively.

Table 1 – Phase I Dose Levels and Regimen (listed in order of administration)



Phase II – Expansion Cohorts

Phase II will enroll patients with mismatch-repair proficient colorectal cancer with known PI3K-mutation status. 21 patients will be enrolled into Cohort A (PIK3CA mutation) and 21 patients will be enrolled into Cohort B (PIK3CA WT). Both cohorts will receive the same treatment regimen. The dose of copanlisib given in Phase II will be the RP2D determined during Phase I of this study.

Table 2 - Phase II Regimen (listed in order of administration)

[redacted]

4.3 Dose Limiting Toxicities

Dose limiting toxicities (DLTs) are defined as any AE occurring within the first cycle of treatment that is temporally related to study drug administration, which is not due to the subject's underlying malignancy, for which there is no clear evidence for an alternative etiology, and that meets one of the following NCI CTCAE criteria:

Hematologic Toxicities

- Grade 4 anemia
- Grade ≥ 3 neutropenia lasting ≥ 14 days
- Grade ≥ 3 febrile neutropenia
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with clinically significant bleeding

Other Toxicities

- Treatment-related ≥ grade 4 AEs, except transient hyperglycemia
- Grade ≥ 3 Pneumonitis or recurrent Grade 2 pneumonitis
- Grade ≥ 3 Nephritis
- Grade ≥ 3 elevated AST, ALT
- Grade ≥ 2 eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to ≤ grade 1 severity within 2 weeks of starting therapy, or requires systemic therapy
- Any other Grade ≥ 3 toxicities except
    - Grade 3 nausea, vomiting, or diarrhea that resolves to Grade ≤ 1 within 7 days, with or without appropriate supportive therapy
    - Grade 3 rash that resolves to Grade ≤ 2 within 7 days
    - Grade 3 fatigue that resolves to ≤ Grade 2 within 14 days

- Grade 3 transient hypertension and transient hyperglycemia
- Grade ≥ 3 laboratory abnormalities that, in the judgment of the investigator, are not clinically significant
- Asymptomatic amylase/lipase elevation

Unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours if clinically indicated and monitored as necessary to determine if event meets toxicity criteria.

Table 3 – Dose De-Escalation Rules

Number of Patients with DLT at a Given Dose Level	**Dose De-Escalation Decision Rule** (dose levels found in Table 1)
0-1 out of 3	Enter 3 more patients at this dose level • If ≤ 1 of 6 subjects in this cohort experience a DLT, this is the recommended phase II dose (RP2D) • If ≥ 2 of 6 patients in this cohort experience a DLT, this dose level exceeded the RP2D. 3 patients will be entered at the next lower dose level.
≥ 2 out of 3	This dose level exceeded the RP2D. 3 additional patients will be entered at the next lower dose level.

4.4 Dose Modification and Toxicity Management

4.4.1 Dosing Delays and Modifications

Study treatments are scheduled on a 3 weeks on, 1 week off schedule.

- Start of a treatment cycle (Day 1) will be delayed for toxicity until retreatment criteria are met. The Principal Investigator must approve retreatment if delays last longer than 1 week. If delays are required due to toxicity related to one study drug but not the other, all study treatment will be delayed.

- If the day 8 or day 15 dose of copanlisib needs to be delayed longer than 2 days due to toxicity, the dose(s) should be skipped and the remainder of the cycle continued once retreatment criteria are met. The intention here is to keep the length of each cycle to 4 weeks, when possible. Skipped doses will be documented in the study database.

There will be no dose reductions to nivolumab. Dose reductions to copanlisib will use the dose levels outlined in **Table 1** and dose reduction criteria outlined in **Table 4**. If a patient is already receiving the lowest dose level of copanlisib and meets criteria for further decrease, study treatment will be discontinued permanently. There will be no dose re-escalation for DLTs. Dose re-escalation may be allowed for non-DLTs at the PI's discretion after patient has fully recovered from the toxicity and in the absence of any other

adverse events that require dose-reduction, with the exception of non-infectious pneumonitis.

Dosing of study therapy will be delayed for the following criteria (or **Table 4** criteria):

- AST/ALT >3 × ULN
- Total bilirubin > 1.5 x ULN (> 2.0 × ULN for subjects with Gilbert's syndrome)
- Creatinine > 1.5 × ULN or GFR < 40 mL/min/1.73 m^2
- Hemoglobin < 8 g/dL
- ANC < 1250/uL (day 1) and < 1000 (days 8 and 15) – hold both study drugs
- Platelets < 75 × 10^3/uL
- Fasting Glucose (Cycle 1 Day 1) >125 mg/dL (non-diabetic patients) or ≥160 mg/dL (diabetic patients)
- Fasting glucose (all other days) > 160 mg/dL
- CMV PCR > 500 IU/mL (tested each cycle for cycles 1-6, and every 3 months thereafter)
- Any Grade ≥ 2 non-skin, nivolumab-related adverse event, with the following exceptions:
  - Grade 2 fatigue
  - Grade 2 lab abnormalities
  - Grade 2 hypothyroidism or thyroiditis
- Any Grade ≥ 3 skin nivolumab-related AE
- Any Grade ≥ 3 nivolumab-related laboratory abnormality with the following exceptions:
  - Grade 3 lymphopenia
  - Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis
  - Isolated grade 3 or 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management
- Any AE, laboratory abnormality, or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Table 4 - Dose modification and toxicity management guidelines for AEs associated with copanlisib					
Drug-related AEs	**Grade (CTCAE v5.0) or measurement**	**Action taken to study drugs**	**Retreatment Dose Level**	**AE management**	**Monitor and follow-up**
Hyperglycemia	Grade 1: Asymptomatic glucose above baseline with no medical intervention	Withhold until pre-infusion glucose is <160 mg/dL (fasting)	No change in dose	• Hydration as appropriate • May follow without glucose-lowering tx if repeated glucose value is decreasing and hydration status is normal	• Repeat glucose testing • Endocrinologist consult recommended • Consider prophylaxis with oral glucose lowering tx for next dose: • **Recommended (preferred order):** SGLT2 inhibitor, DPP4 inhibitor, metformin, and/or thiazolidinedione • **Not recommended:** Use of sulphonylurea/ metaglinides, insulin secretagogues to manage increased glucose levels post drug infusions
	Symptomatic or persisting glucose >250mg/dL [1]	Withhold until pre-infusion glucose is <160 mg/dL (fasting)	No change in dose	• Hydration as clinically appropriate • Glucose-lowering medication should be given: • **Recommended (preferred order):** SGLT2 inhibitor, DPP4 inhibitor, metformin, and/or thiazolidinedione • **Not recommended:** Use of sulphonylurea/ metaglinides, insulin secretagogues to manage increased glucose levels post drug infusions	• Assess hydration status • Repeat glucose testing • Consult with endocrinologist • Consider prophylaxis with oral glucose lowering tx for next dose: • **Recommended (preferred order):** SGLT2 inhibitor, DPP4 inhibitor, metformin, and/or thiazolidinedione • **Not recommended:** Use of sulphonylurea/ metaglinides, insulin secretagogues to manage increased glucose levels post drug infusions
	Persistent glucose >500 mg/dL[1]	Withhold until pre-infusion glucose is <160 mg/dL (fasting)	Decrease by one dose level if repeated after 2 infusions. Discontinue if persistent at lowest dose level after at least one cycle, despite optimal tx and consult with diabetes specialist.		
	Max glucose >200mg/dL on subsequent days after infusion	N/A	N/A	• Treatment with glucose-lowering medication per local standards • **Recommended (preferred order):** SGLT2 inhibitor, DPP4 inhibitor, metformin, and/or thiazolidinedione • **Not recommended:** Use of sulphonylurea/ metaglinides, insulin secretagogues to manage increased glucose levels post drug infusions	• Endocrinologist consult recommended

Table 4 - Dose modification and toxicity management guidelines for AEs associated with copanlisib					
Drug-related AEs	**Grade (CTCAE v5.0) or measurement**	**Action taken to study drugs**	**Retreatment Dose Level**	**AE management**	**Monitor and follow-up**
Arterial Hypertension	Pre-dose BP >150/90 mmHg	Withhold[2]	No change in dose	• Consider BP-lowering medication	• Measure BP every 5-10 minutes (no more than 4 measurements) until acceptable for treatment.
	BP during infusion >160/100 mmHg	Interrupt if having symptoms attributable to hypertension[2]	Next dose reduced by one dose level at PI's discretion	• Initiate BP lowering medication according to standard of care	• Monitor BP as clinically indicated until <150/90.
	Post-dose BP >160/100 mmHg[3]	N/A			• Monitor BP as clinically indicated.
	Grade 4	Permanently discontinue	N/A		
Non-infectious Pneumonitis	Grade 2	Withhold	Decrease by one dose level		
	Grade 3 or 4 or recurrent Grade 2	Permanently discontinue	N/A		
Infections	Grade 3 or higher	Withhold	N/A		
	Suspected PJP infection of any grade	Withhold. Resume once infection resolves	N/A	If confirmed PJP, treat infection until resolution	Treat with concomitant PJP prophylaxis after resolution/ restarting of copanlisib
Dermatologic / Cutaneous AEs	Grade 2[3]	Withhold	1st: no dose change 2nd-3rd: decrease by one dose level 4th: discontinue		
	Grade 3[3]	Withhold	1st-2nd: decrease by one dose level 3rd: discontinue		
	Grade 4	Permanently discontinue	N/A		
Hematological toxicitiy[4]	Grade 2 neutropenia or thrombocytopenia on day 1 of each cycle	Withhold	No change in dose		

Table 4 - Dose modification and toxicity management guidelines for AEs associated with copanlisib					
Drug-related AEs	**Grade (CTCAE v5.0) or measurement**	**Action taken to study drugs**	**Retreatment Dose Level**	**AE management**	**Monitor and follow-up**
	Grade ≥ 3	Withhold	Decrease by one dose level at the PI's discretion	• Treatment with transfusion or growth factors allowed at PI's discretion	
Other non-hematological toxicities	Grade 3	Withhold	1st: no dose change 2nd-3rd: decrease by one dose level 4th: discontinue		
	Grade 4 or any toxicity requiring delay for >21 days	Permanently discontinue	N/A		

1. Persistent occurrence is defined as repeated post-infusion blood glucose measurements taken at different times during the cycle despite optimal glucose-lowering therapy in consultation with endocrinologist
2. Infusion may proceed/resume on scheduled day if BP recovers to <150/90 mmHg for 2 consecutive measurements and symptoms (if present) resolve.
3. Despite maximum supportive therapy
4. Thrombocytopenia, neutropenia, febrile neutropenia, anemia, INR or PTT with bleeding

General instructions:

- For situations where drug is withheld due to a copanlisib-related AE, treatment can be resumed after AE has been reduced to Grade 1 or 0 unless otherwise indicated. Treatment should be permanently discontinued if AE does not resolve within 12 weeks of last dose.
- If patient is already on lowest dose level and meets criteria for further decrease, study drug will be discontinued permanently.
- Dose re-escalation may be allowed at the PI's discretion after patient has fully recovered from the toxicity and in the absence of any other adverse events that require dose-reduction, with the exception of non-infectious pneumonitis.
- Abbreviations: SGLT2 = Sodium/Glucose co-transporter 2; DPP4 = Dipeptidyl peptidase 4; PJP= pneumocystis jiroveci pneumonia

In order to standardize the management of AEs for all subjects, treatment management algorithms are included in **Appendix C**. Additional AE treatment management algorithms included in the nivolumab IB might be considered for individual cases.

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

Subjects may resume treatment with study drug when the nivolumab-related AE(s) resolve to grade ≤1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin adverse event
- Treatment-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.
- Treatment-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment, which include grade 2 hyperglycemia, hypothyroidism and thyroiditis.

Subjects should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks.

4.4.2 Toxicity-Related Treatment Discontinuation

In addition to the discontinuation criteria listed in **Table 4** above, permanent discontinuation of study treatment should be considered for any severe or life-threatening treatment-related AEs, including, but not limited to, any of the following (the IND Sponsor and BMS must be notified in the event of these AEs):

- Any grade 2 treatment-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of starting therapy OR requires systemic treatment
- Any grade 3 non-skin, drug-related AE lasting > 7 days, with the following exceptions:
    - Grade 3 treatment-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, myocarditis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
    - Grade 3 treatment-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation. Treatment should be discontinued for grade 3 adrenal insufficiency.
    - Grade 3 treatment-related laboratory abnormalities do not require treatment discontinuation except:
        - Grade 3 treatment-related thrombocytopenia > 7 days **or** that is associated with bleeding requires discontinuation

- Any treatment-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
  - Total bilirubin > 5 × ULN
  - Concurrent AST or ALT > 3 × ULN **and** total bilirubin > 2 × ULN

- Any grade 4 treatment-related AE or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations, or radiographic signs of pancreatitis.
  - Isolated grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
  - Grade 4 lymphopenia and leukopenia.
  - Grade 4 treatment-related endocrinopathy adverse events, such as ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the IND Sponsor.

4.4.3 Infusion Reactions

Nivolumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Infusion-related reactions to copanlisib may also occur. Monitor patients for signs and symptoms of infusion-related reactions from the start of each infusion until at least 30 minutes after the end of the infusion, in an area containing resuscitation equipment and medications necessary for advanced life support and cardiopulmonary resuscitation. Toxicity management guidelines on drug-related infusion reactions are provided in **Table 5**.

Table 5 - Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Monitor vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	Participant may be premedicated at least 30 minutes before infusion of nivolumab with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine) and/or Acetaminophen 325-1000 mg PO (or equivalent dose of analgesic)
Grade 2 Moderate reaction; requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Begin IV normal saline, and treat subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 325-1000 mg; monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate. Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. If symptoms recur, then no further nivolumab will be administered at that visit.	Participant may be premedicated at least 30 minutes before infusion of nivolumab with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). and/or Acetaminophen 325-1000 mg PO (or equivalent dose of analgesic). If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.
Grades 3 or 4 Grade 3: Severe reaction; prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae Grade 4: Life-threatening; urgent intervention indicated	**Stop Infusion.** Begin IV normal saline and treat as follows: Investigators should follow institutional guidelines for the treatment of anaphylaxis. Recommended bronchodilators, epinephrine 0.2-1 mg of a 1:1000 solution for SubQ or a 0.1-0.25 mg of a 1:10,000 solution injected slowly IV (or equivalent), as needed. Subject should be monitored until symptoms resolve and the investigator is comfortable that the symptoms will not recur. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.		

4.4.4 Additional Toxicity Monitoring and Prevention

4.4.4.1 Glucose and Diet Monitoring

Table 6 - Fasting requirements and pre-dose glucose levels		
Period	**Fasting ≥ 12 h required before first glucose measurement**	**Pre-dose glucose levels**
Day 1 of Cycle 1	Yes	<125 mg/dL (non-diabetic patients) <160 mg/dL (diabetic patients)
Subsequent infusions after Cycle 1 Day 1	Yes	<160 mg/dL (fasting) <200 mg/dL (non-fasting)

Fasting refers to a ≥ 12 hour fast. Non-fasting status includes any caloric intake such as meals, juice, snack, as well as other caloric intake not consistently called a meal.

From Cycle 1 Day 1 onwards, glucose measurements may be done either by laboratory analysis or in capillary blood.

Because of its inhibitory effect on the PI3K α-isoform, which is implicated in insulin metabolism, copanlisib infusions could be associated with a temporary increase in blood glucose. Addition of a meal in close proximity to copanlisib infusion may exacerbate glucose increase.

On infusion days a low calorie or low carbohydrate diet is recommended. It is recommended that timing and content of caloric intake as well as additional glucose testing (if clinically indicated) on infusion days is monitored by the investigators based on glucose response patterns during prior treatment days. Consultation with a diabetologist or endocrinologist is advised**.**

All glucose measurements, oral glucose lowering medication and/or insulin administration, if applicable, fasting/non-fasting status, and meal intake timing on infusion days will be collected as part of the clinical source documentation.

Glucose monitoring on study

Management of hyperglycemia and dose delay parameters are outlined in **Table 4**

The following assessments should be performed on Day 1, 8, and 15 of each cycle before receiving copanlisib unless otherwise specified:

- Patients should be fasting for at least 12 hours prior to the pre-dose glucose measurement. For details on fasting requirements and glucose measurement during C1D1 please refer to **Table 6**
- Blood glucose will be measured at 0 hours (pre-dose) and 1 hour after completion of copanlisib (+/- 15min) infusion. If 1 hour post-infusion blood glucose is ≥35 mg/dL higher than pre-dose level, recheck in another hour (2 hours post-infusion) to ensure decline in blood glucose. Additional measurements to be performed as clinically indicated.

NOTE: If patient needs to take a low glycemic meal, then glucose test should be taken prior to meal intake.

- Prior to first cycle, patients should be educated on the signs and symptoms of hyperglycemia, such as frequent urination, increased thirst, blurred vision, headaches and difficulty concentrating and must report these to the investigator or their physician immediately.

4.4.4.2 Blood pressure measurement on treatment days

Blood pressure will be measured every 5 – 10 minutes prior to each copanlisib dose (no more than 4 measurements) until there are two consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. The patient should rest for 5-10 minutes before next blood pressure is recorded.

On infusion days, blood pressure will be measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion), and 1 h and 2 hours after the end of copanlisib infusion

Note: a window of ±15 min is allowed for all BP measurements, except for the 0 h (pre-dose) measurement, which may happen any time prior to infusion on the day of treatment.

4.4.4.3 Hyperlipidemia monitoring

Measurements for cholesterol, LDL and triglycerides.

Total cholesterol, LDL and triglycerides will be tested only at Screening, on Day 1 of every 2nd cycle starting from Cycle 2, and at the EOT visit. On these dates patients must be fasting prior to sampling according to local standards. If a patient can't adhere to fasting requirements, the evaluation of lipid-panels including triglycerides is considered not feasible.

Management of hyperlipidemia

As lipids are monitored for the duration of this study it is recommended to treat significant deviations from normal range with standard interventions and therapy in standard doses according to local medical practice. Goals of therapy are to keep fasting triglycerides < 300 mg/dL (3.4 mmol/L) and low-density lipoproteins (LDL) < 190 mg/dL (4.9 mmol/L) (lower LDL depending on cardiovascular risk) in patients with a life expectancy >1 year. The goals for fasting triglycerides can be raised to < 500 mg/dL (5.6 mmol/L) for patients with life expectancy <1 year (31).

Although there is a paucity of data on the effects of hyperlipidemia and cancer outcomes, these goals have been chosen to decrease risk of established complications of hypertriglyceridemia (pancreatitis) and hypercholesterolemia (cardiovascular events). For evaluation of lipid-panels including triglycerides the patient would be required to be fasted for 11 hours prior to sampling. For patients who cannot adhere to these fasting requirements the evaluation of lipid-panels including triglycerides and determination of

treatment is considered as not feasible

4.4.4.4 Opportunistic Infection (OI) Monitoring

In addition to the weekly clinical review and laboratory tests outlined in the schedule of assessment, the following should be performed in all patients prior to IV infusion of copanlisib:

- Evaluation of any new onset or worsening of pulmonary symptoms (i.e. cough, dyspnea or fever) that includes a lung examination at each visit prior to infusion
- Labs: WBC, Lymphocyte count, CD4 (for patients with signs of infection), blood cultures (per local SOC if patient develops febrile neutropenia or ANC CTCAE of grade 4), PCR for CMV (monthly for first 6 months of treatment and every 3 months thereafter)
    - Note: If PCR test for CMV > 500 IU/mL, treatment should be delayed until level reduces to ≤ 500 IU/mL. Treatment of CMV should be initiated based on local SOC. Re-treatment with copanlisib will be allowed without dose reduction once PCR test for CMV is ≤ 500 IU/mL.

Enhanced monitoring when prior medical history or laboratory parameters could be associated with one of the following risk factors:

- Intensive chemotherapy (≥ 2 lines of myelosupressive cytotoxic therapy)
- History of CMV, herpes
- History of lower respiratory tract infection, history of immunodeficiency in the last 12 months
- Lymphocytes count < 500 while on treatment in clinical study

For patients with identified risk factors and those who developed OI, additional assessments will include:

- CD4 and CD8 count and ratio, CRP, blood cultures
- Any additional laboratory and diagnostic methods according to local SOC reported as unscheduled laboratory and diagnostic methods of assessment
- Radiological imaging (i.e. CXR or CT Scans)

Note: Treatment of developed OI should be based on local standards of care (SOC).

Prophylaxis of OI

Mandatory prophylactic therapy is not recommended in all patients:

- Review of Copanlisib data do not support risk benefit ratio favoring prophylaxis in all patients
- Mandatory prophylaxis may cause a higher risk of side effects associated with supportive treatment where no risks factors are present
- Currently implemented schedule of assessment, and additional enhancements provide frequent monitoring and flexibility for prophylaxis based on local SOC

Although not mandated in all patients, OI prophylaxis may be initiated at the discretion of the treating investigator's judgment of the benefit/risk ratio in any patient, irrespective

of whether a high-risk feature is present, per local SOC. If so, treatment, dosage and route of administration must be reported as concomitant medications.

Prophylactic treatment of OI should be initiated based on SOC in patients when high risk factors are identified (see above risk factors). For example: Bactrim or equivalent, Acyclovir or equivalent. Treatment, dosage and route of administration must be reported as concomitant medications.

4.4.5 Prohibited and Restricted Therapies

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

- Any non-study anticancer or immunotherapy agent
- Any non-study investigational agents
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an adverse event of suspected immunologic etiology. Steroid treatment should be completed at least 14 days prior to resuming study-related treatments. The use of physiologic doses of corticosteroids may be approved after consultation with the Protocol Chair.
- Strong inhibitors or inducers of CYP3A4/5 (see **Table 7** below for examples)
- Medications that carry a strong risk for QT prolongation
- Herbal medications/preparations except for vitamins (see **Table 7** below for examples)
- Anti-arrhythmic therapy other than beta blockers or digoxin

Table 7: List of prohibited medications during the study

Category	Drug name
Strong CYP3A Inhibitors	Voriconazole, boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, eltegravir/ritonavir, grapefruit juice, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, saquinavir/ritonavir,

	telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin,
Strong CYP3A Inducers	Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum)
Herbal Preparations/ Medications	Herbal preparations/medications are prohibited throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), ginkgo biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

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

4.4.6 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. 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.

Permitted concomitant therapy

- Standard therapies for concurrent medical conditions
- Treatment with non-conventional therapies (for example herbs or acupuncture), and vitamin/mineral supplements is acceptable provided that they do not interfere with the study endpoints, in the opinion of the Investigator. St John's Wort is not permitted.
- Bisphosphonates
- Patients who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that their medication dose and INR/PTT is stable. Close monitoring is recommended according to standard of care. If either of these values is above the therapeutic range, the doses should be modified and the assessments should be repeated weekly until it is stable.
- Antiemetics: Prophylactic anti-emetics may be administered according to standard practice. The routine use of standard antiemetics, including 5-HT3 blockers, such as

granisetron, ondansetron, or an equivalent agent, is allowed as needed. The use of corticosteroids as antiemetics prior to copanlisib administration will be not allowed.

- Palliative and supportive care for the other disease-related symptoms and for toxicity associated with treatment will be offered to all patients in this trial.
- Patients may receive palliative and supportive care for any underlying illness
- Palliative irradiation shall be permitted provided that:
  - In the opinion of the investigator, the patient does not have PD.
  - The radiation field does not encompass a target lesion
  - The radiation field does not encompass a lung field (to reduce the risk of pneumonitis).
- Low-dose aspirin (maximum 100 mg/day) and low-dose heparin are permitted.
- Patients taking narrow therapeutic index medications should be monitored proactively, if these medications cannot be avoided. These medications may include quinidine, cyclosporine, and digoxin
- Calcium channel blockers to control pre-existing hypertension. Non-dihydropyridine calcium channel blockers (Verapamil and diltiazem) are permitted.
- Short term (up to 7 days) systemic corticosteroids above 15 mg prednisone or equivalent will be allowed for the management of acute conditions (e.g. treatment of non-infectious pneumonitis).
- Therapeutic drugs known to be sensitive substrates of the renal drug transporter MATE2K (e.g. metformin, cimetidine, procainamide and N methylnicotinamide) need to be used with caution. Metformin should be interrupted for 48 hours after receiving iodinated contrast media. Please see prescribing information for further information.

4.5 Duration of Therapy and Criteria for Removal from Study Treatment

In the absence of treatment delays due to adverse event(s), treatment may continue indefinitely until one of the following criteria applies. The reason for study treatment removal and the date the patient was removed must be documented in the Case Report Form.

A participant must be discontinued from study treatment but continue to be monitored in the study follow-up for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment
- Confirmed radiographic disease progression outlined in **Section 9** and **Appendix E**
  - As immunotherapy has been shown to cause pseudo-progression, patients are eligible to remain on study after progression if they are clinically stable, if they desire and their treating physician agrees it is in the interest of the patient. If subsequent imaging confirms progression, the patient's date of progression will be the date of first progression
- Clinical progression or deterioration

- Progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Unacceptable adverse experiences as described in **Section 4.4.**2 Exceptions must be approved by the IND Sponsor.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- Investigator's decision to withdraw the subject
- The participant has a confirmed positive serum pregnancy test
- Noncompliance with study treatment or procedure requirements

4.6 End of Treatment (EOT) Visit

After a patient is discontinued from treatment, an End of Treatment (EOT) Visit should be performed approximately 30 days after the last infusion of study medication (or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first). Procedures and assessments performed at this visit and beyond should follow the guidelines described in the Study Calendar in **Section 8** as appropriate. The patient will be monitored for adverse events up to the mandatory Off Study/Safety Follow-Up Visit.

4.7 Duration of Follow Up

Subjects who discontinue from treatment should continue to follow up with their primary oncologist and be contacted every 3 months (+/- 2 weeks) to monitor OS for up to 3 years or death, whichever occurs soonest. Effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, or end of study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are discontinued from the study treatment due to an unacceptable drug-related AE will be monitored for safety until the resolution of the AE to ≤ grade 1, or stabilization, or until initiation of a new therapy for their cancer, whichever occurs first.

All subjects will be followed for at least 30 days after their last dose of study drug for the development of AEs. SAEs that occur within 100 days (+ 14 day reporting window) of the last infusion of nivolumab or before initiation of a new antineoplastic treatment should also be followed and recorded.

5. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

This study will use the descriptions and grading scales found in the revised National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 for adverse event reporting that can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected, recorded, and followed as appropriate.

The PI has the primary responsibility for continuous internal monitoring for safety, protocol compliance, and identification, grading, coding, and required reporting of all anticipated and unanticipated adverse events and protocol problems. Although this responsibility is usually shared among the PI, research nurse, and data manager, the PI is ultimately responsible for grading and attribution of all events.

5.1 Definitions

5.1.1 Adverse Event

An adverse event (AE) is defined as any undesirable sign, symptom or medical condition occurring after starting the study drug (or therapy) even if the event is not considered to be related to the study. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). Medical conditions/diseases present before starting the study treatment are only considered adverse events if they worsen after starting the study treatment (any procedures specified in the protocol). Symptoms / medical conditions occurring before starting the study treatment but after signing the informed consent form will not be recorded as AEs. Additionally, expected progression of the disease being studied will not be recorded as an adverse event.

Laboratory abnormalities: Laboratory abnormalities present at the screening visit will be recorded as pre-treatment signs and symptoms in a medical history CRF. After study treatment administration, all grade 3 and 4 clinical laboratory results that represent an increase in severity from baseline will be reported as adverse events. A grade 1 or 2 clinical laboratory abnormality should be reported as an adverse event only if it is considered clinically significant by the investigator, induces clinical signs or symptoms, or requires therapy.

5.1.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) is an adverse event which:

- Results in death
- Is life threatening (defined as an event in which the subject 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 for exceptions) > 24 hours
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (note: reports of congenital anomalies/ birth defects must also be reported on the Pregnancy Supplemental Form)
- 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 [e.g., 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 (e.g. pathogenic or nonpathogenic) via the study drug is an SAE.

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

Drug induced liver injury (DILI) is defined as:

An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal **and** an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal **and**, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

Events **not** considered to be serious adverse events are hospitalizations for the:

- Admissions as per protocol for a planned medical/surgical procedure or to facilitate a procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission for purpose other than remedying ill health state and was 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 (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

5.1.3 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 SAEs. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

5.2 Relationship

The relationship of an AE to the administration of the study drug is to be assessed by the investigator according to the following definitions:

- No (unrelated, not related, no relation): The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

- Yes (related): The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The following factors should also be considered:

- The temporal sequence from study drug administration - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication - The other medications the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study drug - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

5.3 Assessment of Grade

The investigator will make an assessment of grade for each AE and SAE reported during the study, which will be recorded in the CRF. The assessment will be based on the National Cancer Institute's CTCAE (Version 5.0) and graded as shown below:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living

- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Any AE that changes in grade during its course will have each change of grade recorded on the adverse event case report forms.

5.4 Expectedness

Unexpected adverse event: An adverse event, which varies in nature, intensity or frequency from information on the investigational drug/agent provided in the Investigator's Brochure, package insert or safety reports. Any adverse event that is not included in the informed consent is considered "unexpected".

Expected (known) adverse event: An adverse event, which has been reported in the Investigator's Brochure. An adverse event is considered "expected", only if it is included in the informed consent document as a risk.

5.5 Handling of Expedited Safety Reports

In accordance with local regulations, the IND Sponsor will notify investigators of all SAEs that are unexpected (i.e. not previously described in the Investigator Brochure), and definitely, probably, or possibly related to nivolumab or copanlisib. This notification will be in the form of an expedited safety report (ESR) that is to be faxed to the investigators and the study coordinators. Upon receiving such notices, the investigator must review and retain the notice with the Investigator's Brochure and where required by local regulations, the investigator will submit the ESR to the appropriate IRB. The investigator and IRB will determine if the informed consent requires revision. The investigator should also comply with the IRB procedures for reporting any other safety information.

5.6 Reporting

5.6.1 General

All adverse events (both expected and unexpected) will be captured on the appropriate study-specific case report forms (CRFs).

Adverse events experienced by subjects will be collected and reported from the first dose of the study drug, throughout the study, and will only be followed for 30 days (or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first) unless related to the study drug(s). Adverse events related to the study drug(s) will be monitored for resolution of toxicity to ≤ grade 1, stabilization, or determined to be irreversible by the investigator.

SAEs that occur following the subject's written consent to participate in the study through 100 days (+ 14 day reporting window) after the last infusion of study drug (or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first) will be collected and reported.

All SAEs, regardless of causality to study drug, must be reported within 24 hours of initial notification of the SAE to the IND Sponsor, BMS, and Bayer using the SAE Reporting Form found in **Appendix F**. If this falls on a weekend or holiday, an email notification is acceptable but must be followed by an SAE reporting form on the next business day.

SAE reports and any other relevant safety information are to be sent to:

[redacted]

After the initial SAE report, the investigator is required to proactively follow each subject and provide further information to the safety department in regards to the subject's condition.

All SAE(s) will be followed until:

- Resolution
- The condition stabilizes
- The event is otherwise explained
- The subject is lost to follow-up
- Death

As soon as relevant information is available, a follow-up SAE report will be submitted to the IND Sponsor, BMS, and Bayer.

The Sponsor will reconcile the clinical database SAE cases (case level only) transmitted to BMS Global Pharmacovigilance [redacted].

- The Investigator will request from BMS GPV&E [redacted] the SAE reconciliation report and include the BMS protocol number every 3 months and prior to data base lock or final data summary.
- GPV&E will send the investigator the report to verify and confirm all SAEs have been transmitted to BMS GPV&E.
- 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 [redacted]

5.6.2 Pregnancy Reporting

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner who has provided written consent to provide information regarding pregnancy, that occurs during the trial or within 6 months of completing the trial. All subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious adverse events (Important Medical Events). Pregnancy and non-serious pregnancy outcomes should be reported as Events of Clinical Interest. If the pregnancy continues to term, the outcome (health

[redacted]

5.6.3 Institutional Review Board (IRB)

Participating sites will be responsible for reporting to their IRB. All serious adverse events will be reported to the IRB per institutional standards. Upon receipt, follow-up information will be given to the IRB (as soon as relevant information is available) per institutional standards.

5.6.4 Food and Drug Administration (FDA)

All reporting to the FDA will be completed by the IND Sponsor.

5.6.4.1 Expedited IND Safety Reports:

7 Calendar-Day Telephone or Fax Report:
The IND Sponsor is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the investigational agent. Such reports are to be telephoned or faxe[redacted] to the FDA within 7 calendar days of first learning of the event.

15 Calendar-Day Written Report:
The IND Sponsor is required to notify the FDA of any serious adverse event that is unexpected and possibly related to the investigational agent in a written IND Safety Report.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA within 15 calendar days of first learning of the event. Follow-up information will be submitted to the FDA as soon as relevant information is available.

5.6.4.2 IND Annual Reports

In accordance with the regulation 21 CFR § 312.33, the IND Sponsor shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the adverse events and progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR § 312.33 for a list of the elements required for the annual report. All IND annual reports will be submitted to the FDA by the IND Sponsor.

6. PHARMACEUTICAL INFORMATION

6.1 Nivolumab

6.1.1 Agent Accountability

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.

6.1.2 Mode of Action

Nivolumab is a fully human monoclonal immunoglobulin (Ig) G4 antibody that binds to the PD-1 cell surface membrane receptor, a negative regulatory molecule expressed by activated T and B lymphocytes. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T cell responses to both foreign antigens as well as self-antigens.

6.1.3 Description

Nivolumab Injection, 100 mg/vial (10 mg/mL) is a clear to opalescent, colorless to pale, yellow liquid; light (few) particulates may be present. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriamine pentaacetic acid and polysorbate 80 (Tween™ 80), pH 6.0 and includes a 0.7-mL overfill to account for vial, needle, and syringe (VNS) holdup. It is supplied in 10-cc type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals.

6.1.4 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements. This trial is open-label; therefore, the participant, the trial site personnel, the Sponsor and/or designee are not blinded to treatment.

6.1.5 Preparation

Nivolumab injection should be diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 1 mg/mL. Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyolefin bags have been observed. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves. Detailed instructions on the preparation of nivolumab for administration will be provided in the Investigator's Brochure.

6.1.6 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location. Nivolumab vials must be stored at a temperature of 2°C to 8°C and should be protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton. 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.

6.1.7 Stability

The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°-8°C, 36°-46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period.

6.1.8 Route of Administration

Nivolumab is to be administered as a 30 minute IV infusion, using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified dose. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

6.1.9 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from BMS or designee, the amount dispensed to and returned by the participants 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. BMS will be notified of all destruction of study drug.

6.2 Copanlisib

6.2.1 Agent Accountability

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.

6.2.2 Mode of Action

Copanlisib is a pan-class I phosphatidylinositol 3-kinase (PI3K) inhibitor with predominant and potent activity against the PI3K-δ and PI3K-α isoforms. The PI3K pathway is a

prominent pathway that promotes cellular survival and is found to be constitutively activated in many cancer types. Inhibition of this pathway is expected to lead to impaired cellular uptake of glucose, with a subsequent reactive rise in plasma insulin and glucose levels.

6.2.3 Description

Copanlisib is supplied as lyophilized preparation in a 6-mL injection vial. The total amount of BAY 80-6946 per vial is 60 mg. The solution for IV infusion is obtained after reconstitution of the lyophilisate with 0.9% sodium chloride solution.

6.2.4 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements. Open label kits will be provided for patient dosing.
This trial is open-label; therefore, the participant, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text.

6.2.5 Preparation

Refer to the Pharmacy Manual for preparation instructions.

6.2.6 Storage and Handling Requirements

Copanlisib must be stored between +2°C and +8°C and should not be transported above +30°C. Clinical supplies must be stored in a secure, limited-access location.
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.

6.2.7 Stability

Refrigeration is not required if reconstituted copanlisib is used immediately (within max of 4 hours). If not used immediately, store reconstituted solution in the vials or in the infusion bag at +2°C to +8°C (36°F to 46°F). Allow the product to adapt to room temperature after refrigeration. It takes approximately 60 minutes for a 100 mL dilution filled in bags to return to room temperature after refrigeration. The overall storage time must not exceed 24 hours including preparation and administration. Avoid exposure of the diluted solution to direct sunlight.

6.2.8 Route of Administration

Copanlisib is administered in a normal saline solution, intravenously, over 1 h.
No intravenous glucose preparations should be administered on the days of infusion.

6.2.9 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received

from Bayer or designee, the amount dispensed to and returned by the participants 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.

7. CORRELATIVE/SPECIAL STUDIES

Detailed instructions for collection, processing, and storage of tumor and blood samples are provided in the Laboratory Manual. Results from the sequencing studies will not be released to the patients. These studies are for research purposes only and are not using a clinically validated platform.

7.1 Tumor Tissue

Patients in both phases of the study will have paired biopsies – one prior to treatment and one after six weeks on therapy (4-6 cores per time point). This will be prior to Cycle 2 Day 15 treatment, after two doses of nivolumab and three or five doses of copanlisib (depending on the dose level). Patients will also be asked for an optional biopsy at the time of progression.

Tumor biopsy will not be performed if the tumor is not accessible or if biopsy is considered not in the patient's best interest.

Attempts will be made to obtain archived tissue samples from all subjects. Archived FNA biopsy samples do not contain sufficient tissue and will not be collected.

We will assess tumor immune infiltrate using immunohistochemistry (IHC) and flow cytometry of disaggregated tumor samples. Expression of PD-L1 and of a series of biomarkers will be assessed by IHC. CD8+ T cells will be enriched by magnetic separation from disaggregated tumor samples and stimulated *ex vivo* to query markers of T cell exhaustion and cytokine production. We will also use single cell RNASeq for an unbiased assessment not only of cellular composition but also of functional status as assessed by gene expression profiles. From single cell expression data, we hope to identify gene expression profiles of tumor cells that are correlated with response to therapy.

Tumor Sample Requirements:

Slides
- H&E
- 10 unstained FFPE

Tissue
- 50mg fresh (flow cytometry)
- 50mg fresh (*ex vivo* T cell stimulation)
- 25 mg fresh/frozen (single cell RNASeq)

7.2 Peripheral Blood Mononuclear Cells (PBMCs)

Up to 100 cc of whole blood for isolation of PBMCs will be collected at baseline prior to first dose of study drug, at 2 weeks after first dose, on Day 1 of each odd cycle, and at progression or EOT visit. Phenotypic and functional analysis of PBMCs via flow cytometry will be performed.

7.3 Plasma

Up to 20 cc whole blood for plasma will be collected at baseline prior to first dose of study drug, at 2 weeks after first dose, on Day 1 of each odd cycle, and at progression or EOT visit.

Peripheral Cytokines will be measured by standard luminex assays from patient plasma. We will measure cytokine levels from peripheral blood including but not limited to IFNγ, TNFα, TGFβ, IL-10, CXCL9, CCL2, IL-6, IL-12, IL-2 and IL-17.

7.4 Diagnostic Tissue Samples

Tissue, fluid, or blood may be collected from standard of care procedures used to treat or diagnose immune-related toxicities.

7.5 Planned Analyses

7.5.1 PI3K mutation assessment

PI3K mutation assessment will be performed centrally in batched analysis using NGS and PCR based testing by a CLIA certified lab. All PI3K mutations will be noted, but the patient will be considered to have PI3K mutations if they have a known-activating mutation of PIK3 as defined in **Table 8**. Additional mutations may be added to this definition in the face of emerging discovery.

Table 8 – Activating PIK3 Mutations

G106R
R108H
P124L
V344G
N345K
C420R
E542K
E543_I459del
E545K, E545A, E545Q, E545G
Q546K
Q546R, Q546P
H1047R, H1047L
G1049R

7.5.2 Determining effect of copanlisib on tumor immune subpopulations.

Expected results include 1) an increase in the number of infiltrating CD8+ T cells following treatment with copanlisib and nivolumab and/or 2) a decrease in immunosuppressive cells including CD4+, FOXP3+ Treg cells or functional myeloid derived suppressor cells (MDSCs). Objectives related to tumor immune subsets will be accomplished by three techniques, and tissue prioritized as below. Intended comparisons are between paired biopsy specimens from the same patient, where a change in populations can be correlated with treatment, as well as inter-patient comparisons for correlation with clinical response.

1. Multiplex IHC/IF

A series of biomarkers will be assessed on tissue from this study. A sample of immune and other markers in **Table 9** will be the stains of high priority for these exploratory investigations, in order of priority based on amount and quality of tissue obtained. Briefly, tumor samples will be stained on a quantitative multiplex immunohistochemical platform developed at Johns Hopkins Sidney Kimmel Comprehensive Cancer Center that was previously published[22]. This technology incorporates a computational image processing workflow, including image cytometry, that enables simultaneous evaluation of 12 biomarkers in one formalin fixed paraffin-embedded tissue section. This platform is readily adaptable to assess a variety of markers including lymphoid and myeloid lineage markers, in addition to those listed in **Table 9**. After staining, slides will be analyzed in the Cell Imaging Core Facility at Johns Hopkins Sidney Kimmel Comprehensive Cancer Center to quantitate the percentage and intensity of cells for each marker(s) in the TME. The biomarker data will be captured for samples according to a digital image workflow. Briefly, this encompasses three steps: image preprocessing, visualization, and quantitative image analysis using state-of-the-art software in the Core Lab. This system allows for true quantitative data on dual staining in patient samples. These IHC and IF analyses will be conducted under the guidance o[redacted] To ensure the rigor of these analyses, samples will be batch run when possible, with appropriate positive (i.e. tonsil tissue for immunostains) and negative controls (secondary Ab only) along with serial sections from a single archival colon carcinoma tumor specimen as a qualitative control to for intensity and any batch-to-batch variability between reagents used in IHC or IF assays.

Table 9 - Planned Immunohistochemical (IHC) and Immunofluorescence (IF) analysis (*denotes primary biomarker)

Immunohistochemistry	**Immunofluorescence**	
CD8*, CD4, PD-L1, PTEN	CD8+, Ki67+, CD8+Nur77+, CD4+FoxP3+	Priority 1
CD11c, CD19, CD68, CD163, CTLA4, PD-1, PD-L2, IDO1, LAG3, p-AKT	CD33+S100+, CD4+IL-17+	Priority 2

2. Flow cytometry

When adequate fresh tissue can be obtained, tumor will be disaggregated using a combination of enzymatic and mechanical disruption[23]. Resulting suspension will be analyzed by flow cytometry with markers shown in **Table 10**. Included in this panel is analysis of a subset of CD8+ T cells identified by [redacted]

(CD8+Ki67+) that displays a proliferative burst after PD-1 blockade and may be a potential biomarker of response to anti-PD-1 therapy[24]. Populations will be normalized to tumor weight using counting beads.

Table 10 - Planned markers for flow cytometry of disaggregated tumor biopsies.

Cell population	**Marker**
CD8+ T cell	CD8, GZMB, PD-1, Tim3, Lag3, 2B4, Ki67
Regulatory CD4+ FOXP3+ T Cell	CD4, FOXP3
MDSC	CD11b, HLA-DR, CD14, CD15, CD33, Lin-(CD3/14/15/19/56)
NK	CD56
B cell	CD19

3. Single cell/nuclei RNASeq
Single cell RNASeq will provide an unbiased assessment of cellular composition and of functional status as assessed by individual cell gene expression profiles. Single cell sequencing of tumor biopsies will be performed using droplet technology (10X genomics), whereby single cells from tumor suspensions are partitioned and a unique transcriptome barcode applied prior to lysis and whole transcriptome amplification. High-quality data will be generated from 6-10,000 tumor and immune cells from each biopsy. Each biopsy will contain both tumor, stromal and immune cells, which will allow the broadest analysis of the tumor microenvironment. Initial analysis based on signature enrichment will allow the deconvolution of tumor vs. non-tumor (stroma, immune cell) populations. Subsequent analyses will include reconstruction of TCR sequences and tracking of TCR clones throughout subpopulations[25], arrangement of cells in pseudotemporal space with Monocle[26], differential expression analysis based on mixture models to account for the zero-inflation of single cell transcriptional data[27], and calculation of cell-by-cell gene-set signature scores[28] to probe for pathway and phenotype-level differences between subpopulations.

7.5.3 Determining Effect of Copanlisib on CD8 T cell function

CD8+ T cells are expected to not only increased in number in copanlisib-treated tumors but to also be more functional, as measured by cytokine production and decreased expression of inhibitory ligands. CD8+ T cells will be enriched by magnetic separation from disaggregated tumor samples and stimulated *ex vivo.* Production of cytokines IFNγ and TNFα will be measured by flow cytometry. Inhibitory ligands commonly expressed on exhausted T cells including PD-1, Tim3, Lag3, and 2B4 will be measured by flow cytometry as described above.

7.5.4 Determining Effect of Copanlisib on Peripheral Blood Immune Subsets

Peripheral blood mononuclear cells will be isolated from blood samples following removal of the plasma layer. This will be accomplished via standard methods using density gradient

centrifugation with ficoll-paque plus[29]. Following isolation PBMCs will be resuspended in PBS, counted via trypan blue exclusion and aliquoted into tubes for phenotypic and functional analysis via flow cytometry staining per standard techniques. Markers and cell populations analyzed will be the same as indicated in **Table 9**.

7.5.5 Determining Effect of Copanlisib on Peripheral Blood Cytokines

Cytokine levels from peripheral blood including but not limited to IFNγ, TNFα, TGFβ, IL-10, CXCL9, CCL2, IL-6, IL-12, IL-2 and IL-17 will be measured by standard luminex assays from patient plasma.

7.6 Investigator Responsibilities for Translational Research

[redacted]

that we will have approximately 40 paired biopsies (75% success rate based on previous studies) as well as ~6-12 time points for blood draws to assess changes in circulating immune parameters. We estimate 20% of patients would allow a progression biopsy.

8. STUDY SCHEDULE

8.1 Study Calendar – Phase I

Procedure	Baseline[1] (-28 to 0)	Treatment (1 cycle = 28 days)						EOT[21]	Survival Follow-Up[22]
		Cycle 1			Cycle 2 and higher				
		D1 (±3 days)	D8 (+1 day)	D15 (+3 days)	D1 (±3 days)	D8 (+1 day)	D15 (+3 days)	30 days (+/-4 days) after last study drug	Q12 weeks (± 2 weeks)
Administrative Procedures									
Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Demographics and Med Hx[2]	X								
Copanlisib		X	X	X	X	X	X		
Nivolumab		X			X				
Post-study anticancer therapy and survival status									X
Clinical Assessments									
Physical Examination, ECOG[3]	X	X	X	X	X		X	X	
Vital Signs[4]	X	X	X	X	X	X	X	X	
Blood Pressure (infusion days)[5]		X	X	X	X	X	X		
Weight	X	X			X			X	
Height (may be from prior visit)	X								
Review Adverse Events		X	X	X	X	X	X	X	
Con Med Review	X	X	X	X	X	X	X	X	
Laboratory Assessments									
CBC with Differential[6, 16]	X	X	X	X	X	X	X	X	
Chemistry Panel[7, 16]	X	X	X	X	X	X	X	X	
Glucose[8]		X	X	X	X	X	X		
Hemoglobin A1C[16]	X				X[9]			X	
Lipid Panel[10, 16]	X	X	X	X	X(even cycles)			X	
TSH[11, 16]	X	X		X	X		X	X	
PT, INR and aPTT[16]	X								
HBsAg, HCV Ab, HIV[12]	X								
CMV PCR[13,16]	X				X				
Pregnancy Test[14, 16]	X	X			X			X	
Urinalysis[15, 16]	X				X(even cycles)				
Urine protein:creatinine ratio (UPCR)	X								
12-lead ECG	X							X	
MUGA or echocardiogram[17]	X							X	
CEA	X	X			X			X	
Efficacy Assessments									
Tumor Imaging[18]	X				X(odd cycles)			X	
Tissue and Blood for Correlative Studies									
Fresh Tumor Biopsy[19]	X						X	X	
Archival Tumor Sample	X								
Blood for PBMC (180cc)[20, 16]		X		X	X(odd cycles)			X	

	Baseline[1]	Treatment (1 cycle = 28 days)						EOT[21]	Survival Follow-Up[22] Q12 weeks (± 2 weeks)
		Cycle 1			Cycle 2 and higher				
Procedure	(-28 to 0)	D1 (±3 days)	D8 (+1 day)	D15 (+3 days)	D1 (±3 days)	D8 (+1 day)	D15 (+3 days)	30 days (+/-4 days) after last study drug	
Blood for plasma (20 cc) [20, 16]		X		X	X(odd cycles)			X	

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in-person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

1. Baseline evaluations should occur within 28 days prior to registration, unless otherwise noted. No window applies to demographics, consent, or height at baseline.
2. Includes history of lung disease, cardiovascular disease, diabetes, HIV, hepatitis B or C infection, and complete cancer history, including primary site of cancer, gross location of primary tumor, histology, histologic grade, date of initial diagnosis, date of metastatic diagnosis, prior cancer therapy regimens
3. A complete physical exam will be performed at baseline; focused physical exams will be done thereafter. Physical exams and AE assessments can be done up to 3 days prior to dosing.
4. Temperature, pulse, blood pressure, respiratory rate, and pulse oxygen will be collected at baseline, and prior to each dose of study drug, and at EOT visit.
5. Blood pressure will be measured every 5-10 minutes prior to each copanlisib dose (no more than 4 measurements) until there are 2 consecutive results ≤ 150/90 mmHg. If the blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention e.g. administration of dihydropyridine calcium channel blocker), or delaying the infusion of the study drug. Blood pressure will be measured at pre-dose, 30 min (mid-infusion), 60 min (end of infusion), and 1h and 2h after the end of copanlisib infusion (±15 minute window for all BP measurements).
6. CBC with differential includes: absolute neutrophil count, absolute lymphocyte count, absolute eosinophil count, and platelet count
7. Chemistry panel includes: albumin, alkaline phosphatase, total bilirubin (direct bilirubin if total bili is > ULN), bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, LDH, magnesium, phosphorus, uric acid. Amylase and lipase to be down at screening and Day1 of every cycle.
8. **Fasting** glucose will be measured at 0h (pre-dose), and 1 hour (+/- 15 min) after completion of copanlisib infusion and subsequently if clinically indicated at the discretion of the investigator. NOTE: if patient needs to take a low glycemic meal on infusion days, then glucose test should be taken prior to meal intake. Glucose measurements may be done by laboratory analysis or in capillary blood.
9. HbA1c to be tested at screening, on Day 1 of every three cycles (4, 7, 10, etc) starting at cycle 4, and at the EOT visit
10. HDL, LDL, triglycerides, total cholesterol; performed at Screen, Cycle 1 Day 1, Day 8, and Day 15; then Day 1 of every other cycle (starting at Cycle 2)

11. If TSH is abnormal, T3 and FT4 will be assessed.
12. Patients with positive tests for HBsAg or HIV are excluded from study. Patients with positive test for anti-HCV antibody will be eligible if they are negative for HCV-RNA. These patients should perform HCV RNA test with PCR monthly through treatment and 6 months thereafter. If viral load becomes positive, patient should be withdrawn from the study.
13. CMV PCR may be done up to 7 days prior to each Day 1 visit. CMV PCR should be done with every cycle through cycle 6, then every 3 cycles thereafter.
14. Serum or urine pregnancy test required for WOCBP only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test is required
15. Bilirubin, hemoglobin, glucose, ketones, leukocytes, nitrite, pH, color, protein, RBC and WBC count, and specific gravity. Performed at baseline and Day 1 of every other cycle (starting at cycle2).
16. Labs and research blood should be collected within a window of 3 days prior to dosing. Labs may be repeated prior to dosing if needed.
17. MUGA scan or echocardiogram to measure LVEF; the method chosen at baseline must be the same throughout the whole study period (baseline and EOT); at EOT visit must be done if not previously done within 4 weeks
18. Radiologic evaluations and tumor measurements will be performed at baseline (within 28 days of dosing), prior to each odd cycle (up to 1 week prior), and at End of Treatment visit. If patient comes off study for reasons other than disease progression, subject may have additional radiologic evaluations every 8 weeks until progression or start of new anti-cancer therapy. CT of the chest/abdomen/pelvis with contrast will be used, however, non-contrast CT chest and MRI abdomen/pelvis will be done for patients with contrast allergies.
19. Biopsy to be collected at baseline and 6 weeks after first dose of study drug (± 3 days, but before Cycle 2 Day 15 study drug administration). An optional biopsy may be performed at the time of progression. Approximately 6 core biopsy specimens will be obtained at each biopsy.
20. Blood for PBMC and plasma will be collected at baseline/prior to first dose, 2 weeks after first dose, on Day 1 of each odd cycle, and at progression or EOT visit.
21. EOT Clinical assessments do not need to be repeated if they were done within last 7 days. Hemoglobin A1C, 12-lead ECG, and MUGA or echocardiogram do not need to be repeated if they were done within the last 4 weeks.
22. Subjects who discontinue treatment will be followed (by phone, email or visit) every 12 weeks (± 2 weeks) after completion of EOT visit for up to 2 years or study closure to monitor overall survival. Information on other cancer therapies and disease status will also be collected. In addition, SAEs that occur within 100 days (+14 day reporting window) of the end of treatment or before initiation of a new antineoplastic treatment should also be followed and recorded.

8.2 Study Calendar – Phase II

Procedure	Screen[1]	Treatment (1 cycle = 28 days)						EOT[21]	Survival Follow-Up[22]
		Cycle 1			Cycle 2 and higher				
	D -28 to 0	D1 (±3 days)	D8 (+1 day)	D15 (+3 days)	D1 (±3 days)	D8 (±1 day)	D15 (-1/+3 days)	30 days (+/-4 days) after last study drug	Q12 weeks (± 2 weeks)
Administrative Procedures									
Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Demographics and Med Hx[2]	X								
Copanlisib		X	X	X	X	X	X		
Nivolumab		X			X				
Post-study anticancer therapy and survival status									X
Clinical Assessments									
Physical Examination, ECOG[3]	X	X		X	X		X	X	
Vital Signs[4]	X	X	X	X	X	X	X	X	
Blood Pressure (infusion days)[5]		X	X	X	X	X	X		
Weight	X	X			X			X	
Height	X								
Review Adverse Events		X	X	X	X	X	X	X	
Con Med Review	X	X	X	X	X	X	X	X	
Laboratory Assessments									
CBC with Differential[6, 16]	X	X	X	X	X	X	X	X	
Chemistry Panel[7, 16]	X	X	X	X	X	X	X	X	
Glucose[8]		X	X	X	X	X	X		
Hemoglobin A1C[16]	X				X[9]			X	
Lipid Panel[10, 16]	X				X(even cycles)			X	
TSH[11, 16]	X	X		X	X		X	X	
PT, INR and aPTT[16]	X								
HBsAg, HCV Ab, HIV[12]	X								
CMV PCR[13,16]	X				X				
Pregnancy Test[14, 16]	X	X			X			X	
Urinalysis[15, 16]	X				X(even cycles)				
Urine protein:creatinine ration (UPCR)	X								
12-lead ECG	X							X	
MUGA or echocardiogram[17]	X							X	
CEA	X	X			X			X	
Efficacy Assessments									
Tumor Imaging[18]	X				X(odd cycles)			X	
Tissue and Blood for Correlative Studies									
Fresh Tumor Biopsy[19]	X						X	X	
Archival Tumor Sample	X								
Blood for PBMC (100cc)[20, 16]		X		X	X(odd cycles)			X	
Blood for plasma (20 cc) [20, 16]		X		X	X(odd cycles)			X	

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in-person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

1. Baseline evaluations should occur within 28 days prior to registration, unless otherwise noted. No window applies to demographics, consent, or height at baseline.
2. Includes history of lung disease, cardiovascular disease, diabetes, HIV, hepatitis B or C infection, and complete cancer history, including primary site of cancer, gross location of primary tumor, histology, histologic grade, date of initial diagnosis, date of metastatic diagnosis, prior cancer therapy regimens
3. A complete physical exam will be performed at baseline; focused physical exams will be done thereafter. Physical exams and AE assessments can be done up to 3 days prior to dosing.
4. Temperature, pulse, blood pressure, and respiratory rate, and pulse oxygen will be collected at baseline, and prior to each dose of study drug, and at EOT visit.
5. Blood pressure will be measured every 5-10 minutes prior to each copanlisib dose (no more than 4 measurements) until there are 2 consecutive results ≤ 150/90 mmHg. If the blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention (e.g. administration of dihydropyridine calcium channel blocker), or delaying the infusion of the study drug. Blood pressure will be measured at 0h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion), and 1h and 2h after the end of copanlisib infusion (±15 minute window for all BP measurements).
6. CBC with differential includes: absolute neutrophil count, absolute lymphocyte count, absolute eosinophil count, and platelet count
7. Chemistry panel includes: albumin, alkaline phosphatase, total bilirubin (direct bilirubin if total bili is > ULN), bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, LDH, magnesium, phosphorus, uric acid. Amylase and lipase to be down at screening and Day1 of every cycle.
8. **Fasting** glucose will be measured at 0h (pre-dose), and 1 hour (+/- 15min) after completion of copanlisib infusion and subsequently if clinically indicated at the discretion of the investigator. NOTE: if patient needs to take a low glycemic meal on infusion days, then glucose test should be taken prior to meal intake. Glucose measurements may be done by laboratory analysis or in capillary blood.
9. HbA1c to be tested at screening, on Day 1 of every three cycles (4, 7, 10, etc) starting at cycle 4, and at the EOT visit.
10. HDL, LDL, triglycerides, total cholesterol; performed at Screen and Day 1 of every other cycle (starting at Cycle 2)
11. If TSH is abnormal, T3 and FT4 will be assessed.
12. Patients with positive tests for HBsAg or HIV are excluded from study. Patients with positive test for anti-HCV antibody will be eligible if they are negative for HCV-RNA. These patients should perform HCV RNA test with PCR monthly through treatment and 6 months thereafter. If viral load becomes positive, patient should be withdrawn from the study.
13. CMV PCR may be done up to 7 days prior to each Day 1 visit. CMV PCR should be done with

every cycle through cycle 6, then every 3 cycles thereafter.

14. Serum or urine pregnancy test required for WOCBP only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test is required.
15. Bilirubin, hemoglobin, glucose, ketones, leukocytes, nitrite, pH, color, protein, RBC and WBC count, and specific gravity. Performed at baseline and Day 1 of every other cycle (starting at cycle2).
16. Labs and research blood should be collected within a window of 3 days prior to dosing. Labs may be repeated prior to dosing if needed.
17. MUGA scan or echocardiogram to measure LVEF; the method chosen at baseline must be the same throughout the whole study period (baseline and EOT); at EOT visit must be done if not previously done within 4 weeks.
18. Radiologic evaluations and tumor measurements will be performed at baseline (within 28 days of dosing), prior to each odd cycle (up to 1 week prior), and at End of Treatment visit. If patient comes off study for reasons other than disease progression, subject may have additional radiologic evaluations every 8 weeks until progression or start of new anti-cancer therapy. CT of the chest/abdomen/pelvis with contrast will be used, however, non-contrast CT chest and MRI abdomen/pelvis will be done for patients with contrast allergies.
19. Biopsy to be collected at baseline and 6 weeks after first dose of study drug (± 3 days, but before Cycle 2 Day 15 study drug). An optional biopsy may be performed at the time of progression. Approximately 6 core biopsy specimens will be obtained at each biopsy. Tumor biopsy will not be performed if the tumor is not accessible or if biopsy is considered not in the patient's best interest.
20. Blood for PBMC and plasma will be collected at baseline/prior to first dose, 2 weeks after first dose, on Day 1 of each odd cycle, and at progression or EOT visit.
21. EOT Clinical assessments do not need to be repeated if they were done within last 7 days. Hemoglobin A1C, 12-lead ECG, and MUGA or echocardiogram do not need to be repeated if they were done within the last 4 weeks.
22. Subjects who discontinue treatment will be followed (by phone, email or visit) every 12 weeks (± 2 weeks) after completion of EOT visit for up to 2 years or study closure to monitor overall survival. Information on other cancer therapies and disease status will also be collected. In addition, SAEs that occur within 100 days (+14 day reporting window) of the end of treatment or before initiation of a new antineoplastic treatment should also be followed and recorded.

9. MEASUREMENT OF EFFECT

9.1 Definitions

Evaluable for toxicity. All subjects are evaluable for toxicity after receiving first dose of study treatment.

Evaluable for objective response. All patients who have received at least one dose of study drug at any time during the study will be considered evaluable for response, with the exception of patients that withdraw consent prior to disease re-evaluation. Patients who withdraw consent before disease re-evaluation may be replaced. Patients who come off study prior to disease re-evaluation with imaging due to clinical deterioration will be coded as progressing. Response criteria will be classified by RECIST 1.1 criteria (**Appendix E)**

9.2 Methods for Evaluation of Measurable Disease

Imaging should include the chest, abdomen, and pelvis. Tumor imaging is strongly preferred to be acquired by computed tomography (CT). For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when local practice mandates it. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging. Body scans should be performed with breath-hold scanning techniques, if possible.

All baseline evaluations should be performed as closely as possible to the beginning of treatment and no more than 28 days before the beginning of the treatment. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1. Subjects will be evaluated for anti-tumor effect by follow-up imaging as outlined in the study calendar. All subsequent scans (post-treatment) will be compared to the same pretreatment scan that was used prior to initiating of study treatment.

All measurements should be taken and recorded in metric notation using a ruler or calipers.

The definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

10. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event guidelines and instructions for AE reporting can be found in **Section 5**.

Dr. Nilofer Azad will hold the IND for this study. She will comply with all regulated reporting requirements to the FDA.

10.1 Data Management

All information will be collected on study-specific case report forms (CRFs) by study staff. These data will be reviewed for completeness and accuracy by the Principal Investigator at each site.

Protocol Chair

The Protocol Chair and/or designee is responsible for performing the following tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments.
- Assuring that all participating institutions are using the correct version of the protocol.
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study.
- Reviewing and ensuring reporting of SAE
- Reviewing data from all sites.

Coordinating Center (Johns Hopkins University)

The Coordinating Center (or its representative) is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first subject registration at that site, and maintaining copies of IRB approvals from each site.
- Monitoring subject registration.
- Collecting and compiling data from each site.
- Establishing procedures for documentation, reporting, and submitting of AE's and SAE's to the Protocol Chair, and all applicable parties.
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

Participating Sites

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, and the guidelines of Good Clinical Practice (GCP).
- Submitting data to the Coordinating Center.
- Consent subjects promptly and enroll eligible subjects in EDC.
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol.
- Maintaining regulatory binders on site and providing copies of all required documents to the Coordinating Center.
- Collecting and submitting data according to the schedule specified by the protocol.

10.2 Safety Meetings

Scheduled meetings will occur on a regular basis with the frequency dependent on the rate of subject accrual and the progress of the study. Meetings will include the protocol principal investigator, study coordinator(s), data manager(s), lead research nurses(s), sub-investigators (as appropriate), collaborators (as appropriate), and biostatisticians (as appropriate) involved with the conduct of the protocol. During these meetings matters related to the following will

be discussed: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for objectives.

Monthly teleconferences will be scheduled to include the Coordinating Center and the clinical trial sites. During these meetings, the Coordinating Center and clinical trial sites shall discuss the following: study protocol updates, safety data, enrollment status, and progress of data for objectives.

10.3 Monitoring

Eligibility for all sites will be monitored by the Protocol Chair. The protocol will be monitored internally by the Principal Investigator at each site. Data monitoring of this protocol will occur on a regular basis with the frequency dependent on the rate of subject accrual and the progress of the study. External monitoring will occur according to the following guidelines:

Johns Hopkins SKCCC: The SKCCC Compliance Monitoring Program will provide external monitoring for JHU-affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will determine the level of patient safety risk and level/frequency of monitoring.

Participating site(s): The protocol will be monitored at each participating site by a member of the Johns Hopkins study team regulatory staff. A report of the reviews will be submitted to the Johns Hopkins principal investigator and SKCCC CRO.

11. STATISTICAL CONSIDERATIONS

11.1 Sample Size

Phase I will be enrolled in a standard 3+3 design with up to 18 patients. For the purposes of dose finding, DLTs will be evaluated during the first cycle for each patient. An initial cohort of 3 patients will be enrolled. If 0-1/3 have a DLT then 3 additional patients will be enrolled at the same dose level. If 2-3/3 DLTs are observed, then the dose will be considered too toxic and the next lower dose level will be enrolled. The RP2D is the dose at which ≤ 1/6 patients have a DLT (i.e. if 0/3 of the initial patients have a DLT then an additional 3 will be recruited at the highest feasible dose to establish the RP2D).

During Phase II 42 patients will be recruited: 21 patients with colorectal cancer with PIK3CA mutation (cohort A) and 21 with WT PIK3CA with known lack of sensitivity to immune checkpoint inhibitor therapy (cohort B). ORR (CR+PR) at 6 months the primary endpoint and will be evaluated separately in each cohort. Enrollment will be carried out in 2 stages so that the study can terminate early if the combination of copanlisib and nivolumab is not sufficiently effective. A design similar to Simon's minimax design with relaxed futility stopping will be employed to test the null hypothesis that the true ORR is 5% or less.[30-31] In the first stage, 12 subjects will be accrued in each cohort. If there are no responders among the first 12 patients, the study will be terminated for futility. Otherwise, 9 additional patients will be accrued for a

total of 21 treated subjects. Patients who withdraw consent before disease re-evaluation will not be considered evaluable for response and may be replaced. Patients who come off of study prior to disease re-evaluation with imaging due to clinical deterioration will be considered evaluable for response and will be coded as progressing. If ≥3 out of the 21 patients have a response, then the trial will be considered a success for that cohort. If the true response rate is 20% (alternative hypothesis rate), then the probability of a declaring the treatment a success is 0.80 (power). If the true response rate is 5% (null hypothesis rate), then the probability of declaring the treatment a success is 0.08 (type I error).

11.2 Statistical Analyses

Data will be summarized descriptively within each phase overall and by subgroups of interest (e.g. cohort). The descriptive summary including demographics and baseline variables will include counts and percentages for categorical variables and means, medians, standard deviations, and quartiles for continuous variables.

ORR at 6 months, the primary outcome for Phase II, will be summarized using counts and percentages. Logistic regression will be used to compare the ORR between the two cohorts as well as to identify risk factors associated with ORR. Other binary outcomes (e.g. disease control at 6 months (SD+PR+CR) and immunologic response) will be analyzed using the same methods.

Time to event outcomes include overall survival (OS) and progression free survival (PFS). Overall survival is defined as the time from the first dose until death. Individuals without an event will be censored at the date of last contact. Progression free survival is defined as the time from the first dose until progression or death. Individuals who die will be counted as having progressed. Individuals without an event will be censored at the date of the last evaluation for progression. Kaplan-Meier curves will be use to graphically summarize the survival function and to estimate the median time to event and the proportion event-free at key intervals (e.g. 6 months) along with 95% confidence intervals. Cox proportional hazards models will be used to compare Cohorts A and B and to identify risk factors associated with OS and PFS. Graphical techniques (e.g. log-log plots) and formal statistical testing (e.g. Schoenfield tests) will be used to assess the proportional hazards assumption. If necessary, alternate models (e.g. incorporating a time variable) will be considered.

Safety will be monitored continuously throughout the study, including the phase II component. Weekly team meetings and a minimum of monthly investigator calls will be conducted to review ongoing and resolved toxicity.

Exploratory correlative outcomes are an important part of the study. Paired tumor biopsies will be collected prior to and after initial treatment. Continuous measurements (e.g. density of immune cells, peripheral blood cytokine expression, percentage of CD8+ Tcells expressing >= 2 inhibitory receptors, and CD8+ cytokine expression) will be evaluated graphically (e.g. histograms) and numerically (e.g. means, medians) to determine whether or not a transformation (e.g. log) is appropriate. Once the appropriate scale has been determined, graphical techniques, including but not limited to boxplots spaghetti plots, will be used to summarize the values at each time point and the change from pre-to post- treatment. The

means and 95% confidence intervals of each of these quantities will be estimated. A variety of tools including Wilcoxon rank-sum tests and linear regression, with the change as the outcome variable, will be used to determine whether there is a significant change within each group, whether the changes differ between cohorts, and the association between immunologic parameters and response status (CR/PR or SD vs PD). Linear mixed effects models, which account for the correlation between repeated measurements from an individual and allow the inclusion of additional time points, will also be explored. The baseline and change scores will also be considered as potential risk factors for ORR, OS, and PFS using the analysis techniques described above. Serial samples of PBMC and plasma will be evaluated in a similar manner with greater emphasis on the longitudinal modeling due to the greater abundance of repeat measurements.

Genomic sequencing library construction, whole genome/exome sequencing, whole transcriptome sequencing, microbial sequencing, neoepitope prediction, mutation burden, and bioinformatic analysis may be performed either at an on-campus laboratory or at an off-campus sequencing service. All the samples will be de-identified before sending to any laboratory for sequencing. The FASTQ files, BAM files and VCF files will be generated and analyzed. Other sequencing assays may be performed on a subset of samples according to specific requirements of collaboration projects. Genomic sequencing data will be stored and computations conducted using a JH IT managed subscription of Azure.

11.3 Safety Analyses

AE data will be listed individually and incidence of AEs will be summarized by system organ class and preferred terms within a system organ class for Phase I and Phase II (overall and within each cohort). When calculating the incidence of AEs, each AE will be counted only once for a given subject. In analyses of grade and causality, if the same AE occurs on multiple occasions, the highest grade and strongest relationship to study drug will be assumed. If 2 or more AEs are reported as a unit, the individual terms will be reported as separate experiences. Incidence, measured as time to first AE, will be analyzed for all AEs and by type using the methods described above. In addition, the event rates (which incorporate multiple AEs of the same type) will be analyzed using Negative Binomial regression.

Changes in vital signs, hematology and clinical chemistry parameters from baseline to the end of the study will be examined. Toxicity will be tabulated by type and grade. Toxicities will be characterized according to the CTCAE version 5.0. Treatment-emergent changes from normal to abnormal values in key laboratory parameters will be identified. Incidence and rate evaluations will follow the methods described for AEs.

11.4 Safety Monitoring

The proportion of treated subjects with unacceptable toxicity will be monitored using a Bayesian stopping guideline within each cohort (Cohort A: colorectal cancer with PIK3CA mutation and Cohort B: WT PIK3CA with known lack of sensitivity to immune checkpoint inhibitor therapy) separately during Phase II. A $\beta(1.5, 5.5)$, representing a toxicity rate of 21%, the slightly higher than the expected toxicity rate, was used in the development of our guidelines. These guidelines will recommend that recruitment be halted and the trial be

reassessed if the posterior probability that the unacceptable toxicity rate exceeds the maximum allowable rate (33%) is greater than 0.55. Once the initial 6 patients are recruited, toxicity will be monitored continuously. **Table 11** summarizes the stopping boundaries for unacceptable toxicities.

Table 11: The number of toxicities needed to trigger stopping guidelines throughout the course of the study within each cohort.

Number of Subjects Per Cohort	**Number of toxicities needed to trigger re-evaluation**
6-8	4
9-11	5
12-14	6
15-17	7
18-20	8
21	9

The probability of triggering the stopping guidelines was assessed for a range of possible true toxicity rates using simulations with 10,000 replicates (**Table 12**). The probability of stopping to re-evaluate was 9.5% if the true proportion with an unacceptable toxicity was 20%, the expected level. In comparison, the probability of stopping early is 54% and 70% if the true proportion with an unacceptable toxicity was 35% or 40%, i.e. above the 33% threshold.

Table 12: Probability of triggering a re-evaluation based upon the proportion with an unacceptable toxicity for a range of true toxicity probabilities.

True probability of unacceptable toxicity	Probability of triggering stopping guidelines
5%	< 0.1%
10%	0.8%
15%	3.1%
20%	9.5%
25%	21%
30%	37%
35%	54%
40%	70%

12. REFERENCES

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APPENDIX A: Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active 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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - Defined as no menses for 12 months without an alternative medical cause.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following for the duration of the study and for 7 months after last dose of study drug:

- Agree to be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 8 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
  - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Note: male participants will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in **Table 13** for the duration of the study and for 5 months after last dose of study drug:

Table 13 - Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of < 1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b, c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b, c] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 120 days after the last dose of study treatment. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test. Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected, after the last dose of study treatment, and as required locally.

APPENDIX C: Management Algorithms

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the IND Sponsor. The guidance applies to all immuno-oncology (I-O) 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.

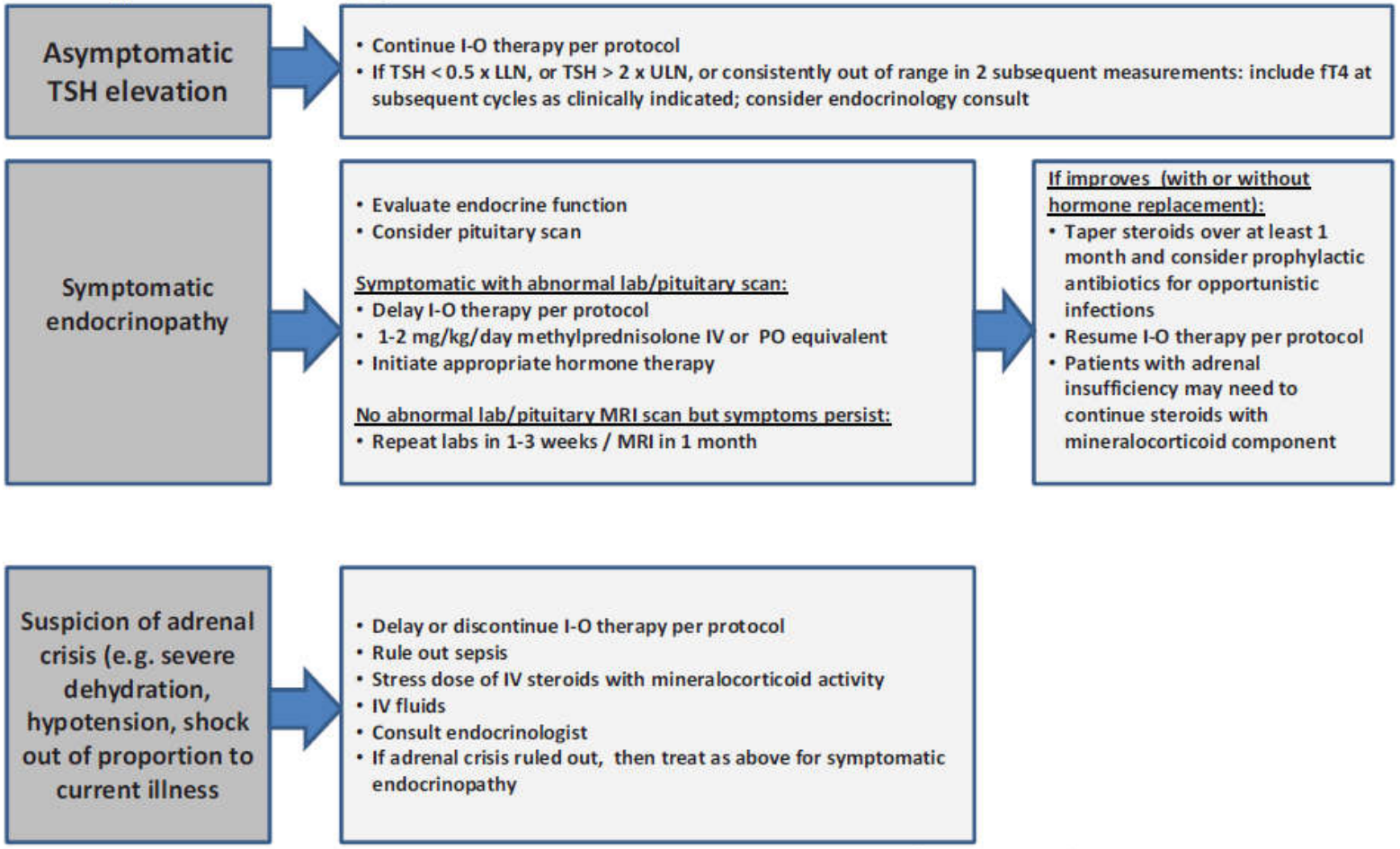
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory subjects with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

Endocrinopathy Management Algorithm

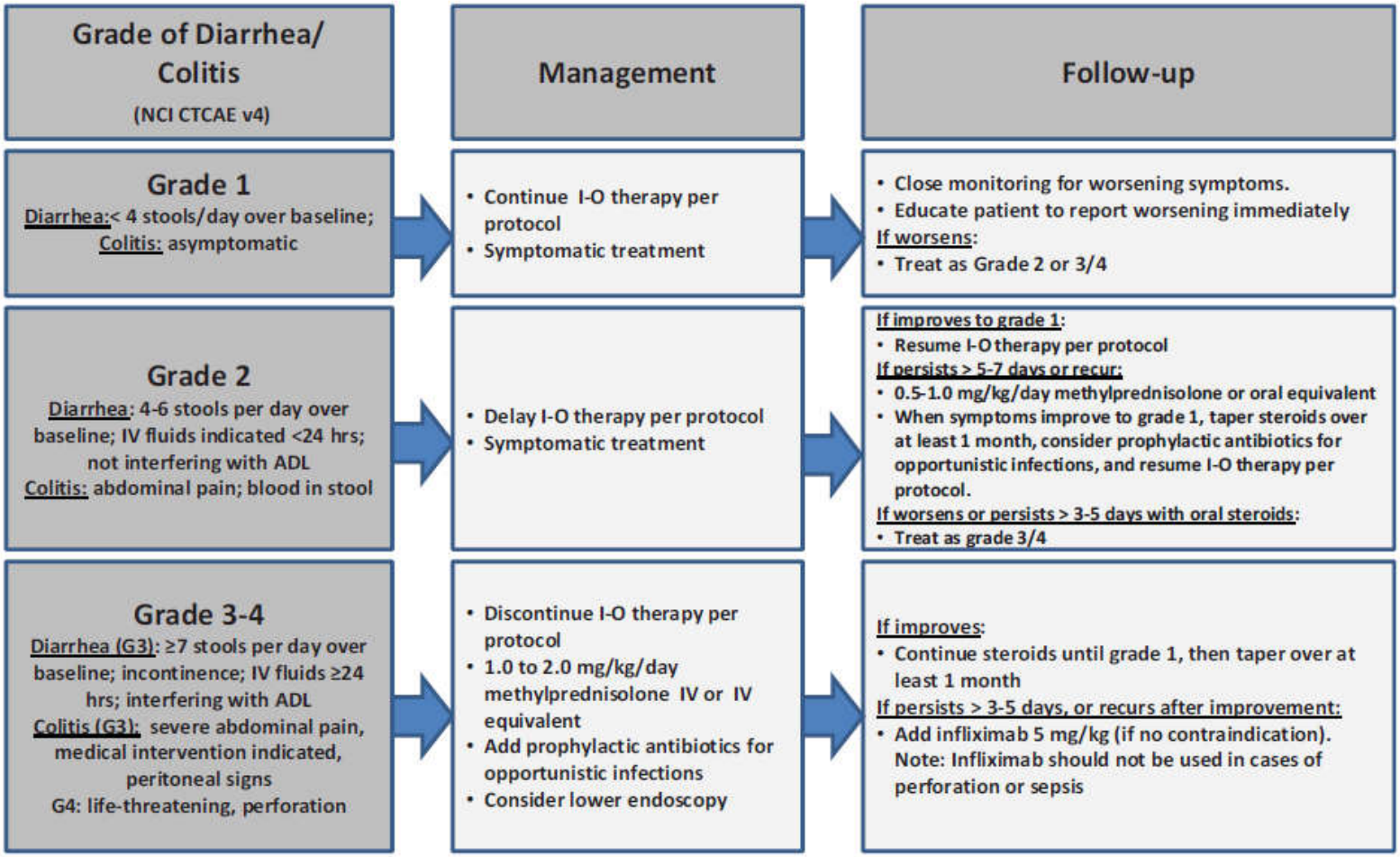
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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.

GI Adverse Event Management Algorithm

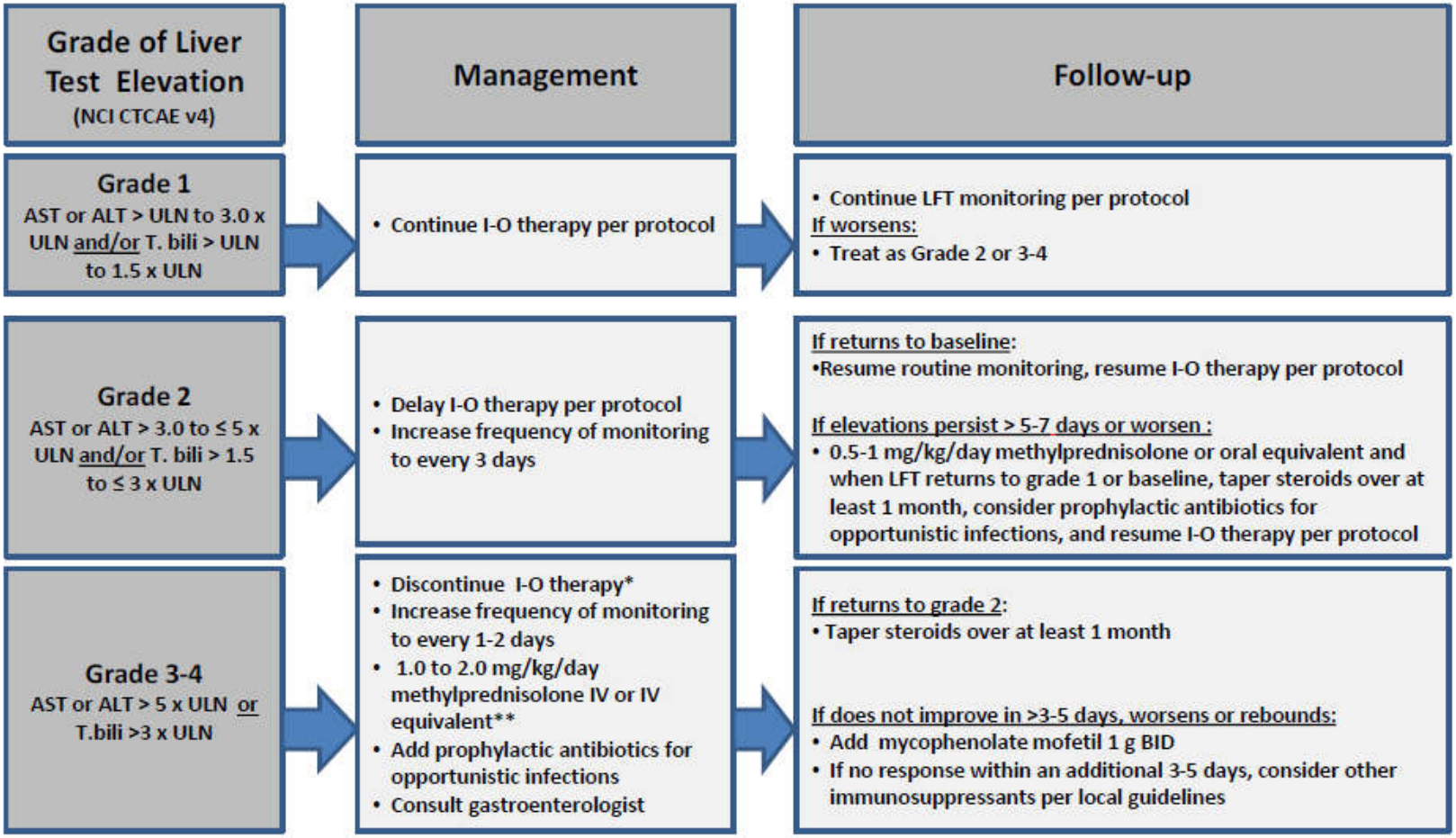
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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.

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.



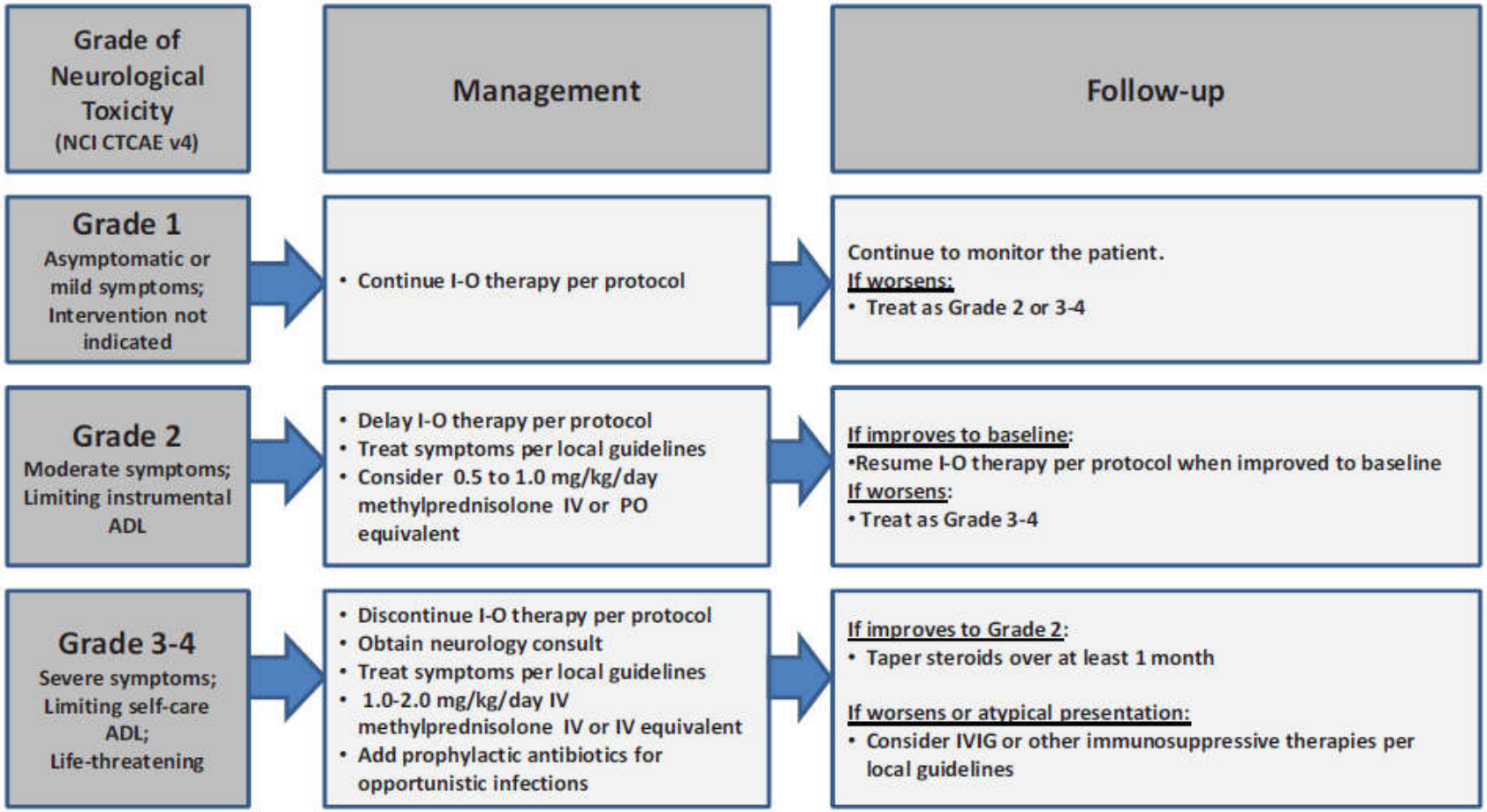
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Neurological Adverse Event Management Algorithm

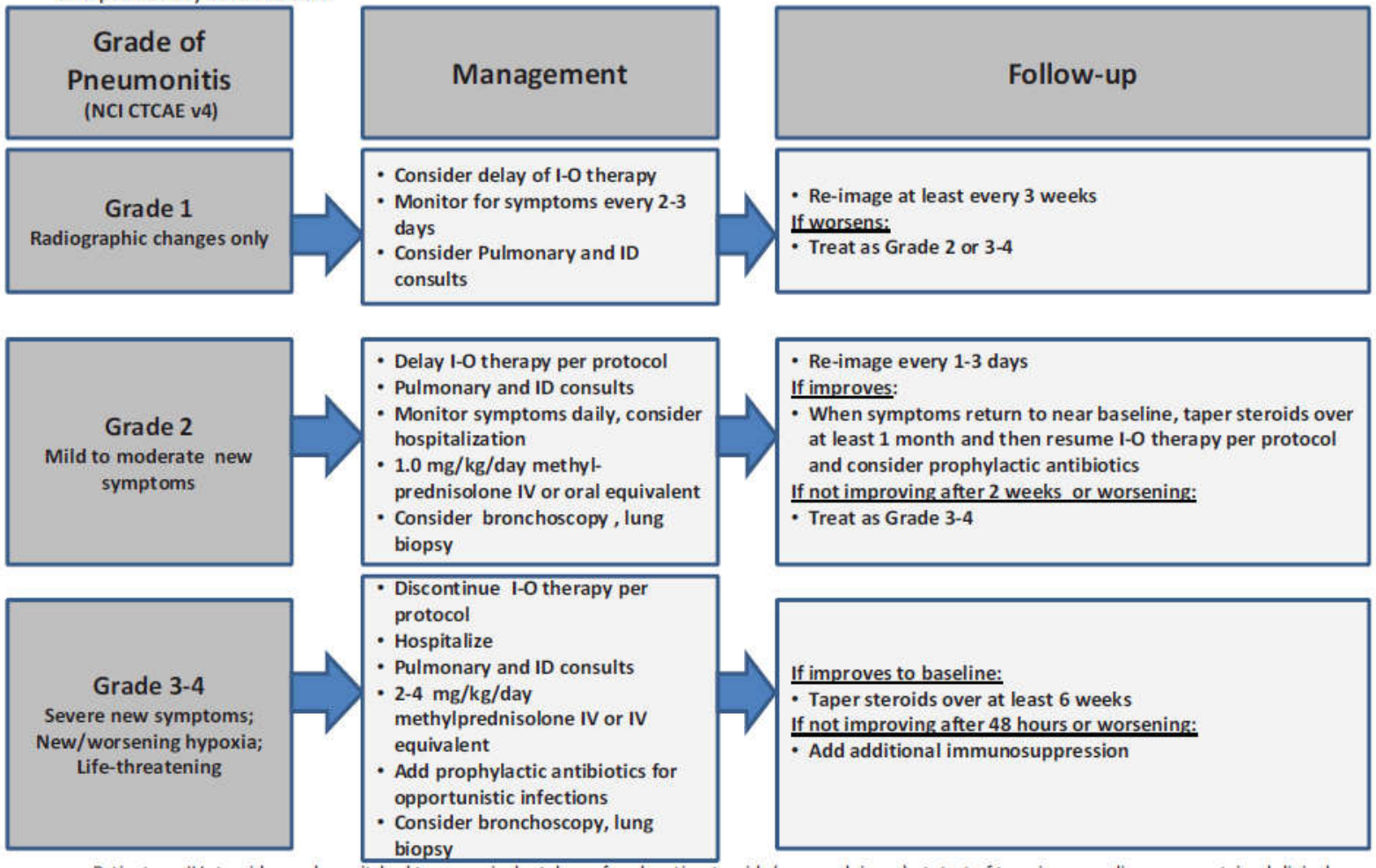
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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.

Pulmonary Adverse Event Management Algorithm

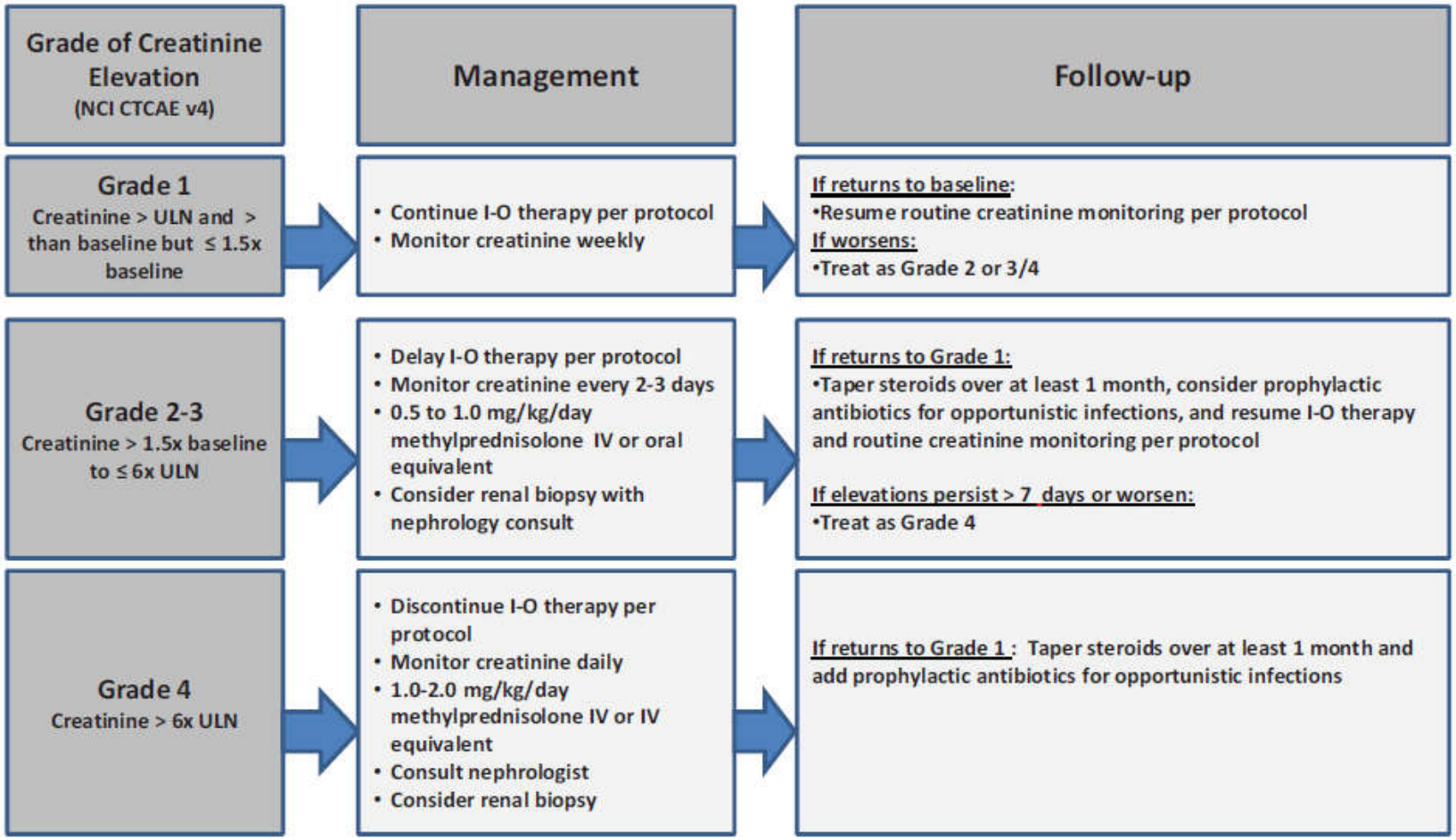
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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.

Renal Adverse Event Management Algorithm

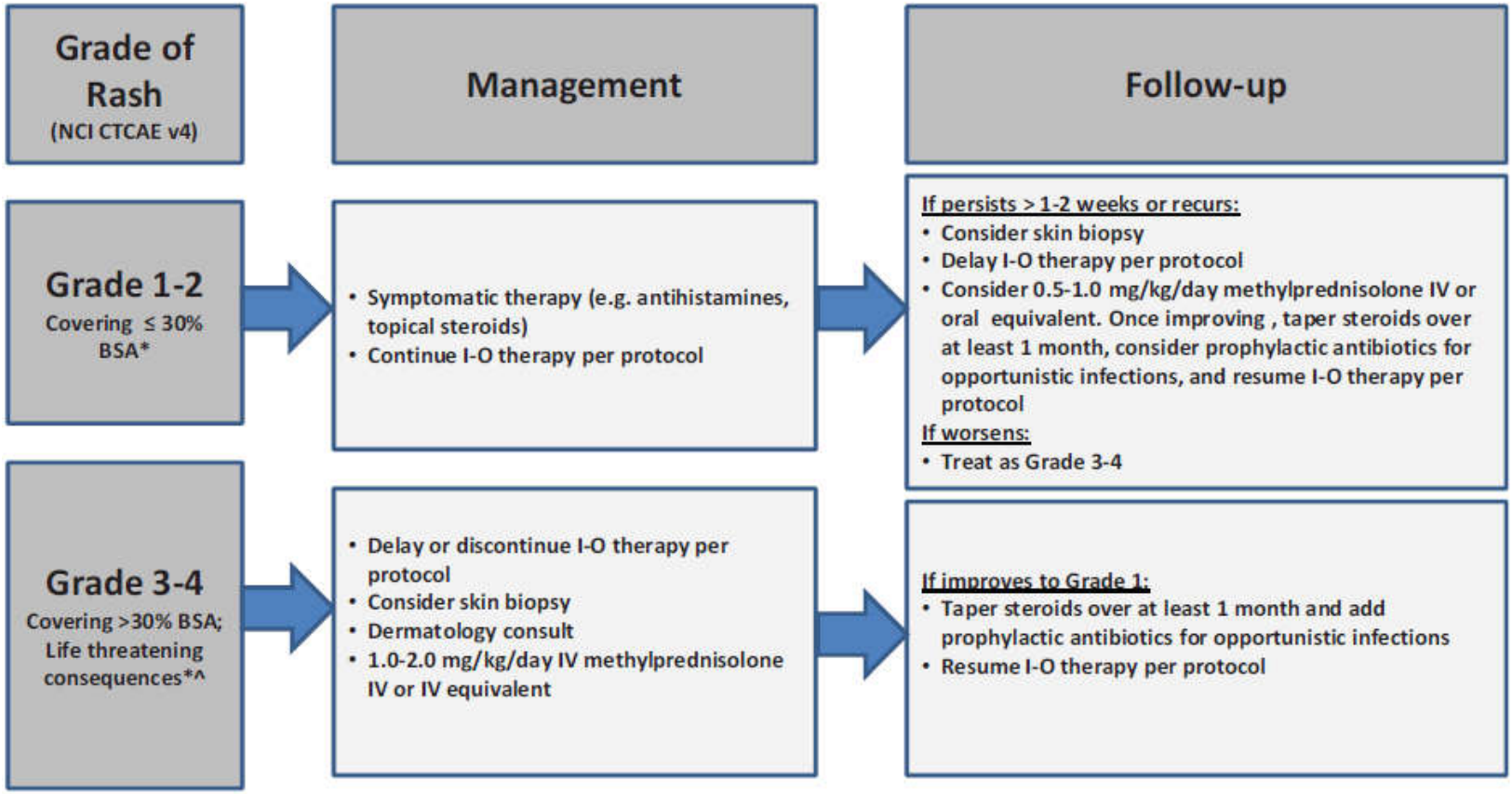
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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.

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.

APPENDIX D: Average Glycemic Index of Common Foods

The average Glycemic Index of common foods derived from multiple studies by different laboratories

Foods are categorized as having a low-glycemic index if the glucose reference index is ≤ 55. High-Glycemic Index foods have a glucose reference index >55. The summary table below contains glucose reference for common foods.

High-carbohydrate foods		Breakfast cereals		Fruit and fruit products		Vegetables	
White wheat bread*	75 ± 2	Cornflakes	81 ± 6	Apple, raw†	36 ± 2	Potato, boiled	78 ± 4
Whole wheat/whole meal bread	74 ± 2	Wheat flake biscuits	69 ± 2	Orange, raw†	43 ± 3	Potato, instant mash	87 ± 3
Specialty grain bread	53 ± 2	Porridge, rolled oats	55 ± 2	Banana, raw†	51 ± 3	Potato, french fries	63 ± 5
Unleavened wheat bread	70 ± 5	Instant oat porridge	79 ± 3	Pineapple, raw	59 ± 8	Carrots, boiled	39 ± 4
Wheat roti	62 ± 3	Rice porridge/congee	78 ± 9	Mango, raw†	51 ± 5	Sweet potato, boiled	63 ± 6
Chapatti	52 ± 4	Millet porridge	67 ± 5	Watermelon, raw	76 ± 4	Pumpkin, boiled	64 ± 7
Corn tortilla	46 ± 4	Muesli	57 ± 2	Dates, raw	42 ± 4	Plantain/green banana	55 ± 6
White rice, boiled*	73 ± 4			Peaches, canned†	43 ± 5	Taro, boiled	53 ± 2
Brown rice, boiled	68 ± 4			Strawberry jam/jelly	49 ± 3	Vegetable soup	48 ± 5
Barley	28 ± 2			Apple juice	41 ± 2		
Sweet corn	52 ± 5			Orange juice	50 ± 2		
Spaghetti, white	49 ± 2						
Spaghetti, whole meal	48 ± 5						
Rice noodles†	53 ± 7						
Udon noodles	55 ± 7						
Couscous†	65 ± 4						

Dairy products and alternatives		Legumes		Snack products		Sugars	
Milk, full fat	39 ± 3	Chickpeas	28 ± 9	Chocolate	40 ± 3	Fructose	15 ± 4
Milk, skim	37 ± 4	Kidney beans	24 ± 4	Popcorn	65 ± 5	Sucrose	65 ± 4
Ice cream	51 ± 3	Lentils	32 ± 5	Potato crisps	56 ± 3	Glucose	103 ± 3
Yogurt, fruit	41 ± 2	Soya beans	16 ± 1	Soft drink/soda	59 ± 3	Honey	61 ± 3
Soy milk	34 ± 4			Rice crackers/crisps	87 ± 2		
Rice milk	86 ± 7						

Data are means ± SEM. *Low-GI varieties were also identified. †Average of all available data.

APPENDIX E: Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1 will be used in this study for assessment of tumor response. While either CT or MRI may be used utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable unless there is evidence of progression in the irradiated site. Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be

recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Evaluation of Target Lesions

Complete Response (CR):Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

Complete Response (CR):Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD):Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Subjects with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

Reference

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

APPENDIX F: Serious Adverse Event (SAE) Reporting Form

Serious Adverse Event Reporting Form

[redacted]

Protocol Title:	A phase I/II study of PI3Kinase inhibition (copanlisib) and anti-PD-1 antibody nivolumab in relapsed/refractory solid tumors with expansions in MSS colorectal cancer		
Protocol #: [redacted]	**Principal Investigator:**	**Signature of PI:**	**Date:**
Report Type: ☐Initial ☐Follow-up ☐Final Follow-up ☐Death ☐Addendum to:	**Serious Criteria / Outcome (check all that apply):** ☐Death ☐Life-threatening ☐ Hospitalization or Elongation of Existing Hospitalization ☐ Persistent or Significant Disability ☐ Congenital / Birth Defect ☐ Other Important Medical Event ☐ New Cancer ☐ AE associated with Overdose	**Hospital Admission Date:** **Hospital Discharge Date:** **Date Event Discovered:**	

Section A: Subject Information

Subject ID:	**Age (years):**	**Gender:** ☐Male ☐Female

Section B: Event and Study Drug Information

Event diagnosis or symptoms:		**Copanlisib**	**Nivolumab**
	Dose and Route:		240mg IV
	Dx for Use (indication):		
	Date of First Dose:		
	Date of Last Dose Prior to Event:		
	# of Total Doses:		
Event Grade:	**Action Taken w/ study drug**	☐None ☐Interrupted ☐Discontinued ☐Delayed	☐None ☐Interrupted ☐Discontinued ☐Delayed
	Event Abated after use stopped/ reduced?	☐Yes ☐No ☐N/A	☐Yes ☐No ☐N/A
	Event Reappeared After Reintroduction?	☐Yes ☐No ☐N/A	☐Yes ☐No ☐N/A

Event Onset Date:	**Event End Date:**

Relationship to:	**Copanlisib**	**Nivolumab**	**Underlying Disease**
Unrelated	☐	☐	☐

Related	☐	☐	☐

Section C: Brief Description of the Event

Section D: Relevant Tests/Laboratory Data

Section E: Relevant Medical History

Section F: Concomitant Drug (Not related to SAE)

Name of the Drug	Start Date	Stop Date	Route	Dose	Frequency

Section G: Comments

Additional Documents Attached (labs, scans, notes, etc): ☐ Please specify, including dates