PROTOCOL AMENDMENT # 2

LCCC 1632: Phase II multicenter trial of panitumumab, nivolumab, and ipilimumab for *KRAS*/*NRAS*/*BRAF* wild-type MSS refractory metastatic colorectal adenocarcinoma

AMENDMENT INCORPORATES (check all that apply):

_X_ Editorial, administrative changes
___ Scientific changes (IRB approval)
_X_ Therapy changes (IRB approval)
_X_ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

The purpose of this protocol amendment is to provide an administrative change to the risks of nivolumab and ipilimumab to include hemolytic anemia as a possible adverse event, provide additional guidance on managing immune-related adverse events, clarification on panitumumab dosing, update drug information for nivolumab and ipilimumab based on the new investigator brochure, provide clarification on the treatment visit window related to nivolumab dosing, to update multicenter language, and to change the Principal Investigator to Dr. Autumn McRee. Due to changes in the investigator brochure related to risk language, the related eligibility criteria were updated. Changes in therapy administration for nivolumab and ipilimumab were also updated based on the information in the new Investigator's Brochure.

Editorial/Administrative Change

1. The Principal Investigator was changed to Dr. Autumn McRee.
2. Section 4.3.1 and 4.3.2: Clarification on administration of doses of panitumumab over 1000 mg
3. Section 4.4.2, footnote f: Modified to clarify toxicity management guidance
4. Section 4.4.2.1: Added footnote to clarify toxicity management guidance
5. Section 4.4.2.3: Added a section (4.4.2.3.1) to provide guidance on cycle counting relative to treatment delays.
6. Section 4.4.2.4: Adding paragraph related to dosing management. Removed paragraph with repeated information related to toxicity management.
7. Section 4.4.2.5: Added ipilimumab to Discontinuation Criteria. Added paragraph on resuming dosing.
8. Sections 5.2.2, 5.2.4, and 5.2.6: Updated nivolumab packaging, administration and stability information based on the new IB.
9. Sections 5.3.2, 5.3.4: Updated ipilimumab packaging and administration information based on the new IB
10. Section 5.3.4: Updated Section reference.
11. Sections 5.2.8 and 5.3.8: Hemolytic anemia was added as a risk for nivolumab and ipilimumab.
12. Section 6.1, Footnote 2: Added clarification related to the treatment window and the minimum 12-day time span between nivolumab treatments.
13. Title page and Sections 7.3 and 9.4-9.6: Updated multicenter language was added.

14. Section 7.3.3: In the pregnancy subpart, revised the timing of contraceptive use after therapy to be consistent with updated drug information.
15. Section 11.2: Added information related to additional guidance for managing immune-related adverse events.
16. Light mechanical editing throughout

Therapy

1. Section 4.3.1: Updated administration information for ipilimumab based on the new Investigator's Brochure.
2. Section 4.3.1 and 4.3.2 Tables: Updated administration information for nivolumab based on the new Investigator's Brochure.

Eligibility

1. Criteria in 3.1.11, 3.1.12 and 3.2.8 were updated based off updated drug information.

THE ATTACHED VERSION DATED October 01, 2020 INCORPORATES THE ABOVE REVISIONS

ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

PROTOCOL AMENDMENT # 1

LCCC 1632: Phase II multicenter trial of panitumumab, nivolumab, and ipilimumab for *KRAS*/*NRAS*/*BRAF* wild-type MSS refractory metastatic colorectal adenocarcinoma

AMENDMENT INCORPORATES (check all that apply):

X Editorial, administrative changes
___ Scientific changes (IRB approval)
X Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

The protocol was revised to clarify the dose delay and dose modification procedures, to remove duplicate information, add stool specimen collection, and to revise the registration, data management, and single subject/subject exception sections.

In reference to the dose delay and dose modification updates, adverse reaction terms were inadvertently removed from the "Toxicities and Dosing Delays/Dose Modifications" section and have been added back: Infusion-related reactions; Dermatologic reaction; Pulmonary Fibrosis/ILD, Colitis, Pneumonitis, Hypophysitis, Type 1 Diabetes Mellitus, Nephritis and Renal Dysfunction, Rash, Encephalitis, Other. Also included with the updates are the following adverse reaction terms and their corresponding severity and dose modification action: Adrenal Insufficiency, Myocarditis, Infusion Related Reaction, and Uveitis, eye pain, blurred vision. Additionally, Baseline Liver Function Tests were inadvertently removed from the "Nivolumab and/or Ipilimumab Dose Modifications/Delays for Liver Toxicity" table and have been added back: AST or ALT normal, AST or ALT 1.1 to ≤ 2.5 X ULN (Grade 1), Total Bilirubin normal, and Total Bilirubin 1.1 to ≤ 1.5 X ULN (Grade 1).

The registration, data management, and single subject/subject exception procedures were updated to align with current Lineberger Comprehensive Cancer Center procedures. In addition, pregnancy reporting requirements for female partners of male subjects was added.

Lastly, stool specimen collection was added to identify gut microbial composition at baseline and at first restaging.

Editorial and Therapy Changes:

1. For section 1.6, a paragraph regarding stool specimen collection and rationale for addition of a stool specimen was added to this section.
2. For section 2.3, exploratory objective 2.3.5 was added which states "To collect stool specimens to assay gut microbial composition at baseline and longitudinally."
3. For inclusion criterion 3.1.4, "OR CLIA-certified sequencing methodology such as Foundation One" was added as an additional method for Microsatellite stable detection.
4. For section 4.1.1, the sample size was adjusted for accuracy.
5. For section 4.3.1 and 4.3.2, an infusion window of +/- 15 minutes was added for the panitumumab, nivolumab and ipilimumab infusions.

6. For section 4.4.1, the following adverse reaction criteria pertaining to the dosing delays/dose modifications criteria for panitumumab were inadvertently omitted from the table and have been added: Infusion-related reactions; Dermatologic reaction; Pulmonary Fibrosis/ILD.
7. For section 4.4.2, "+/- Ipilimumab" was added to the section header.
8. For section 4.4.2, the following adverse reaction terms and the corresponding severity and dose modification were added to the table: Adrenal insufficiency; Myocarditis; Infusion Related Reaction; Uveitis, eye pain, blurred vision. Additionally, the following adverse reaction terms were inadvertently omitted and have been added to the table: Colitis; Pneumonitis; Hypophysitis; Type 1 Diabetes Mellitus; Nephritis and Renal Dysfunction; Rash; Encephalitis; Other.
9. For section 4.4.2, footnotes b, c, d, e and f were added to the table.
10. For section 4.4.2.1, "and/or Ipilimumab" was added.
11. For section 4.4.2.1, the following terms were inadvertently omitted and have been added to the table under column heading "Baseline Liver Function Test (NCI-CTCAEv4.03 grade)": AST or ALT normal; AST or ALT 1.1 to ≤ 2.5 X ULN (Grade 1); Total Bilirubin normal; Total Bilirubin 1.1 to ≤ 1.5 X ULN (Grade 1).
12. For section 4.4.2.2, dose delay criteria for ipilimumab was added to this section and duplicate criteria was removed as this criteria has been incorporated into sections 4.4.2 and 4.4.2.1.
13. For section 4.4.2.3, "+/- Ipilimumab" was added to the section header.
14. For section 4.4.2.4, section header revised to include immune related events for ipilimumab.
15. Section 4.4.3 and subsections 4.4.3.1, 4.4.3.2 were deleted as this was a duplication of information.
16. For section 4.5, prophylaxis for acneiform skin rash related to panitumumab therapy was clarified.
17. For section 6.1, stool specimen collection was added to the pre-study and D1 Cycle 3-N columns. Additionally, footnote #13 was added indicating the stool specimen should be collected +/- 7 days from C3D1.
18. For section 6.1, footnote #1 was clarified to indicate that other evaluations except for pregnancy test must be performed within 3 weeks prior to Cycle 1 Day 1 (C1D1) of treatment, rather than 2 weeks.
19. For section 6.2, it was clarified that the pre-study assessments are to be conducted within 3 weeks rather than 2 weeks.
20. For section 6.1, prophylaxis for panitumumab-associated rash was clarified in footnote #9.
21. For section 6.2, stool specimen collection was added as pre-study assessment.
22. For section 6.3.5, stool specimen collection was added as a D1 of Cycle 3-N assessment.
23. For section 6.5, information regarding the specimen collection was added to correlative studies.
24. For section 7.3.3, wording was added to clarify that if a female partner of a male subject becomes pregnant, the study personnel at the site must be informed immediately and the pregnancy followed per protocol.

25. For section 9.3, subject registration procedures were updated to reflect current Lineberger Comprehensive Cancer Center procedures.
26. For section 9.4, data monitoring procedures were updated to reflect current Lineberger Comprehensive Cancer Center procedures.
27. For section 9.5.2, wording was revised to indicate that eligibility single subject exceptions are not permitted for Lineberger Comprehensive Cancer Center Investigator Initiated Trials.

THE ATTACHED VERSION DATED JULY 30, 2018 INCORPORATES THE ABOVE REVISIONS

ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

LCCC 1632: Phase II multicenter trial of panitumumab, nivolumab, and ipilimumab for *KRAS*/*NRAS*/*BRAF* wild-type MSS refractory metastatic colorectal adenocarcinoma

Principal Investigator
Autumn McRee, MD
Associate Professor
University of North Carolina at Chapel Hill
Lineberger Comprehensive Cancer Center 170
Manning Rd, CB# 7305
919-966-5902 (PHONE)
919-966-6735 (FAX)
autumn_mcree@med.unc.edu

Biostatistician
Dominic T. Moore
dominic_t_moore@unc.edu
Phone: 919-966-8647
Fax: 919-966-4244

Clinical Protocol Office
Lineberger Comprehensive Cancer Center
The University of North Carolina at Chapel Hill
450 West Drive, 3rd Floor, CB# 7295
Chapel Hill, NC 27599-7295

Multicenter Project Manager:
Phone: 919-966-7359
Fax: 919-966-4300

Sponsor: Lineberger Comprehensive Cancer Center

Funding Source: Amgen, Inc.
Version date: October 01, 2020

IND # 136740

LCCC 1632: Phase II multicenter trial of panitumumab, nivolumab, and ipilimumab for *KRAS*/*NRAS*/*BRAF* wild-type MSS refractory metastatic colorectal adenocarcinoma

Principal Investigator Autumn McRee, MD
Associate Professor
University of North Carolina at Chapel Hill
Lineberger Comprehensive Cancer Center 170
Manning Rd, CB# 7305
919-966-5902 (PHONE)
919-966-6735 (FAX)
autumn_mcree@med.unc.edu

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name:_____

PI Signature: _____

Date:_____

Version date: October, 01, 2020

LIST OF ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
ADCC	Antibody dependent cellular cytotoxicity
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BID	*Bis in die* (twice daily)
BUN	Blood urea nitrogen
BRAF	Murine sarcoma viral oncogene homolog B
CBC	Complete blood count
CEA	Carcinoembryonic antigen
CIN	Chromosome instability
CR	Complete response
CRC	Colorectal cancer
CRP	C-reactive protein
CT	Computer tomography
CTLA-4	Cytotoxic T lymphocyte antigen-4
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DSMC	Data safety monitoring committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
GSEA	Gene set enrichment analysis
g/dL	Grams per deciliter
HIPAA	Health Insurance Portability and Accountability Act
β-HCG	Beta-Human Chorionic Gonadotropin
HBs-Ag	Hepatitis B surface antigen
HBc	Hepatitis B core
HBV	Hepatitis B virus
HCV	Hepatitis C virus
IB	Investigator's brochure
IDS	Investigational drug service
Ig	Immunoglobulin
IgE	Immunoglobulin E
IgG2	Immunoglobulin G2
IHC	Immunohistochemistry
ULN	Upper limit of normal
irRECIST	Immune-related response evaluation criteria in solid tumors
IV	Intravenous
J-STEPP	Japanese skin toxicity evaluation protocol with panitumumab
Kg	Kilograms
Kras	Kirsten rat sarcoma (viral oncogene)
LCCC	Lineberger Comprehensive Cancer Center
LDH	Lactate dehydrogenase
Mabs	Monoclonal antibodies
MAPK	Mitogen activated protein kinase
mCRC	Metastatic colorectal cancer
Mg	Milligrams
Mo	Months
MSI-H	Microsatellite instability - high
MSS	Microsatellite stable

MRI	Magnetic resonance Imaging
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NF-κB	Nuclear factor kappa light-chain enhancer of activated B cells
NK	Natural killer
N-ras	Neuroblastoma sarcoma viral oncogene homolog
ORR	Overall response rate
OS	Overall survival
PABA	Para-aminobenzoic acid
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Programmed cell death-1
PET	Positron Emission Tomography
PFS	Progression free survival
PFT	Pulmonary function test
Pgp	P-glycoprotein
PHI	Personal health information
PK	Pharmacokinetic(s)
PO	*Per os* (by mouth)
PR	Partial response
PRC	Protocol review committee
QD	*Quaque die* (once daily)
Q2wks	Every 2 weeks
RAS	Rat sarcoma (viral oncogene)
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
s.c.	subcutaneous
sCR	Stringent complete response
SD	Stable disease
SPF	Sun protection factor
SLM	Study laboratory manual
STEPP	Skin toxicity evaluation protocol with panitumumab
SUSAR	Serious unexpected adverse reaction
TPF	Tissue Procurement Facility
TRAIL	Tumor necrosis factor related apoptosis inducing ligand
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
UNC	University of North Carolina
USP / USPI	United States Pharmacopeia / US Product Insert
UV	Ultraviolet
VEGFR	Vascular endothelial growth factor receptor
VGPR	Very good partial response
WOCBP	Women of childbearing potential
WT	Wild-type

TABLE OF CONTENTS

1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

We will conduct a single-arm, open-label Phase II clinical trial investigating the combination of nivolumab and ipilimumab with panitumumab in subjects with unresectable, refractory, *KRAS*/*NRAS*/*BRAF* wild-type, microsatellite stable (MSS) metastatic colorectal cancer (mCRC). There will be an initial safety lead-in cohort to ensure the combination is well-tolerated. The primary objective of this study is to estimate the overall response rate (CR + PR) in these subjects at 12 weeks by RECIST 1.1 criteria and also by irRECIST criteria. Secondary objectives include the following: estimating the overall response rate (CR + PR) in these subjects at 12 weeks by irRECIST criteria, estimating the best response rate by both RECIST 1.1 and irRECIST criteria, estimating PFS and duration of response using both RECIST 1.1 and irRECIST criteria, estimating OS, and characterizing the safety issues associated with this regimen. Exploratory objectives involve investigating various biomarkers and peripheral blood and tumor assays.

This treatment regimen will be of clinical interest if the objective response rate increases from the standard of care response rate of 22% with panitumumab alone to approximately 35% with combination therapy (adding nivolumab and ipilumumab to panitumumab).

1.2 Colorectal Cancer Background

CRC is the second most common cause of cancer mortality in the United States, causing an estimated 49,190 deaths in 2016. Mortality is primarily driven by the 20% of CRC subjects with metastatic disease, who suffer 5-year overall survival of only 12.9% [1]. Subjects with mCRC, have experienced improvements in median overall survival (OS), from 14.2 months for those diagnosed in 1990-1997 to over 29 months for those diagnosed after 2004[2]. Much of these improvements are attributable to development of novel therapies. Previously, only fluoropyrimidines were standard options for subjects with CRC, but starting in the mid-2000s, increasing numbers of subjects were treated with novel chemotherapy agents such as irinotecan, oxaliplatin, and novel biologic drugs such as bevacizumab and the monoclonal antibodies targeting the epidermal growth factor receptor (EGFR); subsequent widespread use of these agents has contributed to improvements in survival. Nevertheless, barring surgical resection of oligometastatic disease, inevitably metastatic cancers develop resistance to therapies, thus resulting in clinical progression and ultimately death. There is a great unmet need to better understand biologic mechanisms of resistance to available therapies and use this knowledge to guide future therapy choices for individual subjects with CRC.

While efforts have been extensive to identify molecular markers to guide evidence-based therapy for subjects with CRC, the impact of these efforts thus far

on the standard of care for CRC has been limited. Microsatellite instability high (MSI-H) is a molecular fingerprint of a deficient mismatch repair system that is evident in approximately 15% of CRC that has been recognized since the 1990s[3]. The MSI-H phenotype is a unique subset characterized by less aggressive behavior and a favorable prognosis compared to microsatellite stable (MSS) CRC, at least among subjects with stage II disease[4]. The prognostic value of MSI-H should be evaluated in all stage II CRC subjects regarding chemotherapy as some subjects can be spared adjuvant chemotherapy. Evidence for supporting the preferential efficacy of irinotecan in MSI-H tumors is continuing to emerge but remains inconclusive based on disparate results from clinical trials[3,5,6].

Currently, available biomarkers for CRC are limited to identifying subjects for whom certain treatment is not suited, rather than identifying those who may benefit from treatment[7]. *KRAS* and *NRAS* mutation status provide a basis for subject selection regarding benefit from EGFR targeting antibodies[8] as subjects with *KRAS* or *NRAS* mutations, which are detected in approximately 40% of CRCs, do not derive benefit from these treatments. There are no prognostic or predictive molecular markers for bevacizumab-based therapy which is directed against the vascular endothelial growth factor receptor (VEGF-R) pathway; moreover, due to the heterogeneous nature of CRC, a number of subjects receive little benefit or no benefit from these targeted agents[7]. Although unique subtypes within CRC have been identified as shown in Table 1 below based on a consensus molecular subtyping strategy devised and recently reported by the Colorectal Cancer Subtyping Consortium, [9,10] critical questions remain regarding the pathogenesis and biology of these tumors, and unfortunately, optimal biomarkers for evidence-based therapeutic approaches remain elusive. Key areas of unmet need include optimizing use of EGFR antibodies for *RAS/RAF* wild-type disease and improving treatment for subjects with *RAS* and *RAF* mutations where no proven targeted therapy exists.

Table 1. Proposed taxonomy of CRC reflecting significant biological differences in gene expression-based molecular subtypes (adapted from Nat Med 2015 21(11):1350-1356.)

CRC Molecular subtypes	CMS1 MSI Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
Incidence	14%	37%	13%	23%
	Hypermutation MSI, Braf mutation Immune activation	MSS, CIN WNT/MYC pathway activation, TP53 mutation, EGFR amplification/overexpression	Low CIN Moderate WNT/MYC pathway activation, KRAS, PIK3CA and IGFBP2 mutation	CIN/MSI heterogeneous, Mesenchymal/TGF-beta activation, and NOTCH3/VEGFR2 overexpression
Prognosis	Worse survival After relapse			Worse relapse-free and overall survival

CIN = chromosomal instability; MSI= microsatellite instability; MSS= microsatellite stable

1.3 Panitumumab in CRC

Panitumumab is indicated for treatment of subjects with *KRAS* wild-type mCRC as monotherapy after disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan containing chemotherapy regimens. Panitumumab is a fully human IgG2 antibody that binds the EGFR. The EGFR and proteins involved in its downstream signal transduction play important roles in oncogenesis and tumor progression in CRC. EGFR is a transmembrane receptor tyrosine kinase that homodimerizes upon ligand binding to activate downstream intracellular signal transduction cascades, notably including the mitogen activated protein kinase (MAPK) pathway via RAS, RAF, and MEK, to ultimately promote cell proliferation and survival.[11] There are three human RAS genes that encode homologous proteins, *HRAS*, *NRAS*, and *KRAS.*[12] Mutations in codons 12 and 13 of *KRAS* are found in 37-43% of colorectal cancer subjects,[13,14] and contribute to oncogenesis by driving cell proliferation in a growth factor-independent fashion.[14] Panitumumab, administered at 6 mg/kg IV every 2 weeks, significantly improves progression-free survival (PFS) compared to best supportive care when administered to subjects with chemo-refractory mCRC whose tumors are wild-type in *KRAS* codons 12 and 13 (hazard ratio 0.45, 95% CI 0.34 to 0.59). After additional studies demonstrated that benefit with anti-EGFR therapy was limited to subjects whose tumors are wild-type in exons 2, 3, and 4 of *KRAS* and *NRAS*, consensus guidelines now recommend that only subjects who are wild-type on extended RAS testing receive anti-EGFR therapy[15]. Additional studies have suggested that wild-type *BRAF* is also required for optimal response to anti-EGFR therapy[16]. Thus, while panitumumab is effective for subjects with extended RAS and *BRAF* wild-type mCRC, the duration of benefit is limited, and so improving on panitumumab monotherapy with novel combination therapies is needed to extend the duration of benefit.

1.4 Ipilimumab and Nivolumab in CRC

Therapy with checkpoint inhibitor immunotherapies, such as inhibitory antibodies against cytotoxic T lymphocyte antigen-4 (CTLA-4) or programmed cell death-1 (PD-1) receptors on T cells, relieves tumor immune evasion and allows cytotoxic antitumor immune attack. These therapies have been found to yield durable disease response in several malignancies, including melanoma and non-small-cell lung carcinoma, and are undergoing investigation in a variety of other malignancies. However, efficacy of immune checkpoint inhibitor monotherapy in CRC has been limited, with cases of prolonged disease response initially found only in the rare subjects with MSI-H disease [11,17-20]. Subsequently, in subjects with MSI-H mCRC, nivolumab monotherapy yielded 31% response rate[21], and nivolumab + ipilimumab yielded 33% response rate [20]. Since only 11% of mCRC subjects are MSI-H,[22] this indicates that immune checkpoint inhibitor monotherapy is ineffective in the majority of subjects, who have MSS mCRC.

Indeed, in early clinical trials of nivolumab monotherapy or nivolumab + ipilimumab in subjects with MSS mCRC, there was only 1/20 objective responses [20]. Thus, investigating combinations of immune checkpoint therapy with additional agents to further activate the immune system's antitumor response is necessary in order to improve outcomes in the majority of subjects with mCRC who have MSS disease.

1.5 Rationale for LCCC1632

Monoclonal antibodies (Mabs) targeting the EGFR are commonly used as standard of care in the 40-50% of MSS mCRC subjects with tumors that are wild-type in *KRAS* and *NRAS*.[14] Cetuximab is a chimeric mouse/human IgG1 Mab against EGFR, while panitumumab is a fully human IgG2 anti-EGFR Mab. Although inhibition of downstream signaling transduction from EGFR is an important mechanism of efficacy of these antibody therapies,[23] the ineffectiveness of small molecule EGFR inhibitors in this setting implies that additional mechanisms may explain Mab efficacy. Indeed, Mabs are known to interface with the immune system to trigger antibody-dependent cellular cytotoxicity (ADCC) or facilitate activation of the adaptive immune system. Though the general consensus is that IgG2 Mabs like panitumumab do not trigger classical natural killer (NK) cell-mediated ADCC,[24] panitumumab does recruit myeloid lineage cells, like neutrophils and monocytes, to perform ADCC and impair tumor growth.[25] This observation and others noted below support the hypothesis that anti-EGFR Mab efficacy is also linked to immune modulation.

In addition, immune activation does appear to play an important role in the efficacy of anti-EGFR Mabs in preclinical models. Novel murine xenograft models with reconstituted immune cells demonstrate that cetuximab requires both innate and adaptive immunity to cause tumor regression, including causing proliferation of tumor antigen-specific CD8+ T cells in draining lymph nodes.[26] Furthermore, peripheral blood mononuclear cells (PBMCs) derived from subjects in clinical trials of chemotherapy with cetuximab revealed increases of activated Th1 cytotoxic T-cells, central memory cells, and NK cells.[27] Similarly, head and neck cancer subjects treated with cetuximab had a significant increase in circulating CD8+ T-cells specific to EGFR epitopes.[28] The combination of cetuximab with cytotoxic chemotherapy increased dendritic cell activation and phagocytosis[29] and increased ADCC.[30] However, cetuximab conversely was found to also activate immunosuppressive M2 macrophages, causing upregulation of PD-L1 and contributing further to immune evasion.[31] Indeed, our preliminary data based on gene set enrichment analysis (GSEA) of gene expression microarrays from 68 CRC subjects treated with cetuximab indicates that cetuximab-resistant subjects tend to have an increase in monocyte/macrophage signatures, and also have a signature reflecting PD1-ligated T-cells as compared to control T cells [32] This suggests that while cetuximab can induce ADCC and requires activation of cytotoxic T cells, there is also an immunosuppressive effect triggered by cetuximab that may ultimately limit its activity. Translational studies in subjects treated with panitumumab show similar immunologic effects. Notably,

response to panitumumab in a phase II clinical trial was predicted by a high level of CD8+ tumor infiltrating lymphocytes and tumor FOXP3 expression.[33,34] Furthermore, first-line treatment with panitumumab and chemotherapy yielded increases in all lymphocyte subsets, total dendritic cells, and dendritic cell subsets, suggesting an impact on in vivo T-cell mediated responses.[35] Thus, we hypothesize that the immunosuppressive effect of anti-EGFR Mabs combined with chemotherapy may be overcome and the pro-adaptive immune response may be potentiated by co-administration with immune checkpoint inhibitors.

In studies of immune checkpoint inhibitors in melanoma[36], non-small cell lung cancer[37], and MSI-H CRC,[20] the combination of ipilimumab and nivolumab has yielded greater response rates and PFS than nivolumab alone. Additionally, CTLA4+ regulatory cells may impair cytotoxicity associated with anti-EGFR antibodies in head and neck cancers.[38] Thus, administration of the anti-CTLA-4 antibody ipilimumab may facilitate suppression of the inhibitory regulatory T cells and help activate an immune response driven by enhanced antigen presentation via effective therapy with panitumumab, while anti-PD-1 antibody nivolumab may allow this nascent T cell response to be more effectively unleashed. Given the otherwise poor efficacy of immune checkpoint therapy in MSS mCRC, we propose adding the combination of CTLA-4 inhibition and PD-1 inhibition, through administration of ipilimumab and nivolumab, to treatment with panitumumab.

Though panitumumab and cetuximab have clinically shown comparable efficacy,[39-44] cetuximab has a greater incidence of infusion-related reactions than panitumumab (13% vs 3%), including grade 3-4 reactions (2% vs <0.5%). These hypersensitivity and anaphylactic reactions triggered by cetuximab infusion are particularly relevant in broad swaths of the Southeastern U.S., as grade 3-4 reactions during the first infusion of cetuximab reach rates as high as 22% in this region.[45] These infusion-related reactions are possibly related to geographically prevalent IgE antibodies that target an oligosaccharide present on cetuximab but not panitumumab.[46] There is no cross-reactivity with panitumumab,[47] and consequently panitumumab is used as the standard of care anti-EGFR mAb rather than cetuximab in the Southeastern U.S due to its superior safety profile and equivalent efficacy. Given the limited safety data currently available for the combination of cetuximab with immune checkpoint inhibitors in a geographic region with high rates of grade 3-4 immunologically-mediated hypersensitivity reactions to cetuximab, and the unclear effects of immunotherapy on these anaphylactic reactions, we favor pursuing a clinical trial of nivolumab + ipilimumab combined with panitumumab.

Thus, we propose a single-arm, open-label, multicenter Phase II clinical trial investigating the combination of nivolumab and ipilimumab with panitumumab in subjects with unresectable refractory *KRAS*/*NRAS*/*BRAF* wild-type MSS mCRC. There will be an initial safety lead-in cohort to ensure the combination is well tolerated.

1.6 Correlative Studies

We will collect peripheral blood samples serially to facilitate analyses such as mutation analysis of circulating free tumor DNA and quantitation of circulating cytokines and EGFR ligands including epiregulin and amphiregulin. There is a growing body of evidence that one mechanism of resistance to anti-EGFR Mab therapy is the emergence of mutations or amplification in key components of the MAPK signaling pathways, including in *EGFR*, *KRAS*, and *NRAS*. [48-51] In addition, we have retrospective data indicating that treatment with anti-EGFR Mabs is associated with differential levels of cytokines and growth factors, including epiregulin and TRAIL. [52] These different resistance mechanisms, especially circulating TRAIL levels, are likely to have consequences on immune activation and response, and the association of each of these markers with RR, PFS, and OS will be determined.

We will also plan to perform peripheral blood immune monitoring, such as assessment of ADCC and T cell activity, and can consider sequencing peripheral blood mononuclear cells for FcγRIIa and FcγRIIIa polymorphisms. There have been conflicting studies regarding the prognostic utility of FcγRIIa or FcγRIIIa polymorphisms and anti-EGFR Mab efficacy,[25,53-59] though the largest study to date showed no significant association in KRAS wild-type subjects with mCRC.[60] Since these factors may affect immune activation, sequencing for polymorphisms in *FCGR2A* and *FCGR3A* may be informative. Additionally, isolation of T cells and NK cells from subject-derived PBMCs to perform ex vivo ADCC assays and interferon γ release assays would provide important data on the activation of adaptive and innate immune cells.

Additionally, we will include optional serial tumor biopsies to identify potential biomarkers for immune checkpoint inhibitors and anti-EGFR antibodies. These could include integrated genomic analysis with multiplex next generation DNA and RNA sequencing for baseline mutation analysis, and gene expression analyses. This approach can also facilitate sequencing of low-diversity B cell and T cell receptors, both at baseline and serially in subjects who opt to undergo serial biopsies, which may aid in discovery of future potential targets for intervention.

Finally, we will collect stool specimens to identify gut microbial composition at baseline and at first restaging. Several studies have shown significant associations between gut microbial dysbiosis and lack of efficacy of immune checkpoint inhibitors, and we will perform exploratory studies to determine the association between baseline gut microbiome and efficacy of therapy.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the clinical efficacy of panitumumab/nivolumab/ipilimumab or panitumumab/nivolumab therapy in subjects with unresectable refractory *KRAS*/*NRAS*/*BRAF* wild-type MSS mCRC, by determining overall response rate (ORR) at 12 weeks by RECIST 1.1 criteria.

2.2 Secondary Objectives

2.2.1 To determine the best overall response associated with panitumumab/nivolumab/ipilimumab or panitumumab/nivolumab therapy in subjects with unresectable refractory *KRAS*/*NRAS*/*BRAF* wild-type MSS metastatic colorectal adenocarcinoma based on both RECIST1.1 and irRECIST criteria.

2.2.2 To determine the overall response rate (ORR) associated with panitumumab/nivolumab/ipilimumab or panitumumab/nivolumab therapy in subjects with unresectable refractory *KRAS*/*NRAS*/*BRAF* wild-type MSS metastatic colorectal adenocarcinoma at 12 weeks by irRECIST criteria.

2.2.3 To determine PFS associated with panitumumab/nivolumab/ipilimumab or panitumumab/nivolumab therapy in subjects with unresectable refractory *KRAS*/*NRAS*/*BRAF* wild-type MSS metastatic colorectal adenocarcinoma based on both RECIST 1.1 and irRECIST criteria.

2.2.4 To determine OS of subjects with unresectable refractory *KRAS*/*NRAS*/*BRAF* wild-type MSS metastatic colorectal adenocarcinoma treated with panitumumab/nivolumab/ipilimumab or panitumumab/nivolumab therapy.

2.2.5 To determine the duration of response of subjects with unresectable refractory *KRAS*/*NRAS*/*BRAF* wild-type MSS metastatic colorectal adenocarcinoma treated with panitumumab/nivolumab/ipilimumab or panitumumab/nivolumab therapy based on both RECIST1.1 and irRECIST criteria

2.2.6 To evaluate the toxicity of panitumumab/nivolumab/ipilimumab in subjects with unresectable refractory *KRAS*/*NRAS*/*BRAF* wild-type MSS mCRC, by determining the number of treatment-emergent grade 3 and 4 toxicities as defined by National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03).

2.3 Exploratory Objectives

2.3.1 [redacted]

[redacted]

2.4 Endpoints

2.4.1 Primary Endpoint

ORR is defined as the percentage of subjects with unresectable refractory *KRAS*/*NRAS*/*BRAF* wild-type MSS mCRC who achieve a complete response or a partial response (CR+PR) by 12 weeks to panitumumab/nivolumab/ipilimumab or panitumumab/nivolumab therapy per RECIST 1.1 criteria.

2.4.2 Secondary Endpoints

2.4.2.1 The best overall responses for both RECIST 1.1 and irRECIST are defined as the best response achieved across all time points prior to progression (for example, a subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). Please Note: In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 12 weeks from initiation of treatment.

2.4.2.2 The immune-related response rate is defined as the percentage of subjects with unresectable refractory *KRAS*/*NRAS*/*BRAF* wild-type MSS mCRC who achieve a CR+PR by 12 weeks to panitumumab/nivolumab/ipilimumab or panitumumab/nivolumab therapy per irRECIST criteria. (See section 6.7.5.1)

2.4.2.3 Assessment of immune-related PFS is defined as starting from the first day of treatment or Day 1 (D1) until the event of disease progression as defined by irRECIST, or death from any cause in subjects with unresectable refractory *KRAS*/*NRAS*/*BRAF* wild-type MSS mCRC (See section 6.7.5.1). Any subject that has not had a documented event at the time of analysis will be censored. Assessment of PFS (as defined by RECIST 1.1) is defined from D1 of treatment until the event of disease progression occurs or death from any cause in subjects with unresectable refractory *KRAS*/*NRAS*/*BRAF* wild-type MSS mCRC. Any

subject that has not had a documented event at the time of analysis will be censored.

2.4.2.4 OS is defined as the time from D1 of treatment until death from any cause. Any subject that has not died by the analysis date will be censored.

2.4.2.5 The duration of response as defined by RECIST 1.1 will be defined as the time elapsed from first scan documenting partial response or complete response until the event of disease progression occurs. Any subject that has not had a documented progression at the time of analysis will be censored. The duration of response as defined by irRECIST will be defined as the time elapsed from first scan documenting partial response or complete response until the event of disease progression occurs. Any subject that has not had a documented progression at the time of analysis will be censored.

2.4.2.6 Treatment-related adverse events will be assessed per NCI-CTCAE v4.03.

3.0 SUBJECT ELIGIBILITY

3.1 Inclusion Criteria

Subjects must meet all of the inclusion criteria as listed below to participate in this study.

3.1.1 Histologically or cytologically confirmed colorectal adenocarcinoma, with unresectable metastatic or locally advanced disease documented on diagnostic imaging studies.

3.1.2 Previously received 1-2 prior lines of therapy. Subjects who relapse within 6 months of adjuvant chemotherapy comprised of oxaliplatin and a fluoropyrimidine will have their adjuvant therapy count as one prior line of therapy.

3.1.3 Confirmed wild-type in KRAS and NRAS codons 12, 13, 59, 61, 117, and 146; and BRAF codon 600, by standard of care testing of tumor specimen. Tissue used for testing may have been collected from primary or metastatic site.

3.1.4 Microsatellite stable as detected by PCR-based assay OR CLIA-certified sequencing methodology such as Foundation One; OR mismatch repair proficient as detected by immunohistochemistry showing intact nuclear staining of MLH1, MSH2, MSH6, and PMS2.

3.1.5 Radiographically measurable disease present per RECIST 1.1

3.1.6 Age ≥ 18 years at the time of consent.

3.1.7 Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.

3.1.8 Blood counts performed within 3 weeks prior to starting study therapy must have absolute neutrophil count ≥ 1,500/mm^3, platelets ≥ 100,000/mm^3, and hemoglobin ≥ 9 g/dL.

***Note**: Hematology and other lab parameters that are ≤ grade 2 BUT still meet criteria for study entry are allowed. Furthermore, changes in laboratory parameters during the study should not be considered adverse events unless they meet criteria for dose modification(s) of study medication outlined by the protocol and/or worsen from baseline during therapy.

3.1.9 Liver function tests performed within 3 weeks prior to starting study therapy must have total bilirubin ≤ 1.5 x upper limit of normal (ULN), alanine aminotransferase and aspartate aminotransferase ≤ 3 x ULN, and albumin ≥ 2.5 g/dL.

3.1.10 Serum creatinine performed within 3 weeks prior to starting study therapy must be ≤ 1.5 x ULN, or have calculated creatinine clearance (using Cockcroft-Gault formula provided in Appendix 11.3) of ≥ 50 mL/minute.

3.1.11 Females of childbearing potential must have a negative serum pregnancy test within 24 hours prior to receiving the first dose of study medication. Females of childbearing potential must agree to use 2 methods of effective contraception or abstain from heterosexual sex throughout the treatment period and for 5 months after the last dose of study treatment. Females of childbearing potential are women who have not been surgically sterilized (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or have not been free of menses for >1 year.

3.1.12 Male subjects with female partners must have had a prior vasectomy or agree to use an adequate method of contraception (i.e., double barrier method: condom plus spermicidal agent) starting with the first dose of study therapy through 6 months after the last dose of study treatment.

3.1.13 Written informed consent and HIPAA authorization for release of personal health information. NOTE: HIPAA authorization may be included in the informed consent or obtained separately.

3.1.14 An adequate amount of archival tumor tissue must be available at baseline to be eligible for enrollment in the study. If archival tissue is not available or is inadequate, then the subject must consent to undergo a mandatory biopsy at baseline in order to participate in the study.

3.2 Exclusion Criteria

3.2.1 Past treatment with an antibody targeting EGFR including cetuximab or panitumumab.

3.2.2 Past treatment with an antibody targeting immune checkpoints including CTLA-4, PD-1, PD-L1, PD-L2, or CD137.

3.2.3 Known untreated brain metastasis or brain metastasis treated within 3 months prior to enrollment in this trial.

3.2.4 Has evidence of interstitial lung disease or active, non-infectious pneumonitis.

3.2.5 Has a known additional malignancy that is active and/or progressive requiring treatment; exceptions include basal cell or squamous cell skin cancer, in situ cervical or bladder cancer, or other cancer for which the subject has been disease-free for at least five years.

3.2.6 Treatment within 21 days of the first dose of study drug with any other chemotherapy, immunotherapy, biologic therapy, vaccine therapy, or investigational treatment for the treatment of malignancy, or failure to recover from adverse effects of prior therapies administered over 4 weeks prior to Study Day 1. All toxicities from prior therapies must be ≤ Grade 1 (or ≤ Grade 2 for alopecia or peripheral neuropathy). Prior systemic treatment in the adjuvant setting is allowed. See note above under inclusion 3.1.8

3.2.7 Any serious and/or unstable pre-existing medical disorder (aside from malignancy exception above), psychiatric disorder, or other conditions that could interfere with subject's safety, obtaining informed consent, or compliance to the study procedures.

3.2.8 Pregnant or planning to become pregnant within 6 months after the end of treatment. (NOTE: breast feeding and storage of breast milk is not allowed while mother is being treated, and for up to 5 months after stopping nivolumab, 2 months after stopping panitumumab and/or ipilumumab.

3.2.9 History of organ allograft or other history of immunodeficiency, or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days before the first dose of investigational treatment.

3.2.10 Inability or unwillingness to comply with study and/or follow-up requirements.

3.2.11 Any major surgery, extensive radiotherapy, chemotherapy with clinically significant delayed toxicity, biologic therapy, or immunotherapy within 21 days

prior to randomization and/or daily or weekly chemotherapy without the potential for delayed toxicity within 14 days prior to randomization.

3.2.12 Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to study drug.

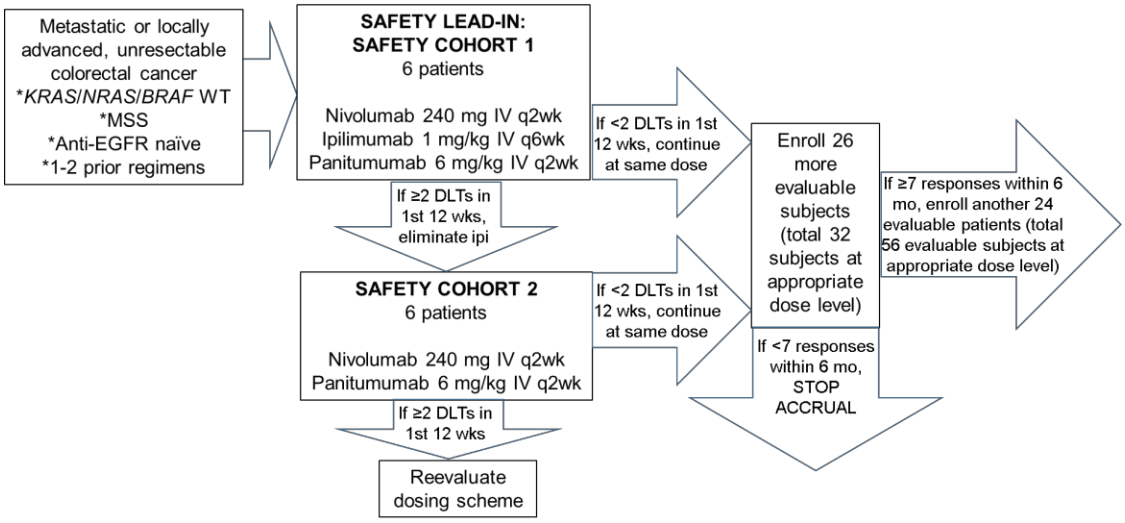
3.2.13 Known Human Immunodeficiency Virus (HIV), Hepatitis B virus (HBV), or Hepatitis C virus (HCV) infection. Subjects with laboratory evidence of cleared HBV and HCV infection will be permitted.

3.2.14 Active autoimmune disease requiring systemic treatment in the past 3 months (for example with disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators, local steroid injections, or inhaled or topical steroids would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjogren's syndrome will not be excluded from the study.

3.2.15 Active infection requiring intravenous systemic therapy.

4.0 TREATMENT PLAN

4.1 Schema



4.1.1 Rationale for Doses Selected

We plan to perform a single-arm, open-label, multicenter Phase II clinical trial of nivolumab 240 mg IV q2wk), ipilimumab (1 mg/kg IV q6wk), and panitumumab (6 mg/kg IV q2wk), after a safety lead-in cohort of a total of 6 subjects has completed 12 weeks of combination therapy at the proposed starting doses. The starting doses and schedule were carefully selected after consideration of existing clinical studies and preclinical data. The efficacy of ipilimumab monotherapy is dose-dependent, but the rate and severity of immune-related adverse events is also dose-dependent [61]. The FDA-approved dose of combination ipilimumab and nivolumab in management of metastatic melanoma is ipilimumab 3 mg/kg IV q3wk for four doses combined with nivolumab 1 mg/kg IV q3wk; followed by nivolumab monotherapy 240 mg flat dose IV q2wk. Notably, studies of combination ipilimumab and nivolumab have started both antibodies concurrently, with the rationale that preclinical models showed that the combination is synergistic only when administered concurrently rather than sequentially[62], and so we plan to administer the investigational drugs concurrently as well. Subsequent clinical trials have investigated combinations of ipilimumab and nivolumab that would attenuate the frequency and severity of immune-related adverse events without mitigating efficacy. The efficacy and toxicity profiles of more infrequent dosing of ipilimumab combined with nivolumab were studied in a phase I study in subjects with chemotherapy-naïve recurrent stage IIIB or IV NSCLC, CheckMate 012. In this study, treatment with ipilimumab 1 mg/kg q6wk combined with nivolumab 3 mg/kg q2wk was much better tolerated than treatment with ipilimumab 1 mg/kg q3wk combined with nivolumab 3 mg/kg q3wk. Additional dosing combination regimens tested revealed inferior efficacy when nivolumab dosing was decreased to 1 mg/kg. Treatment with ipilimumab 1 mg/kg q6wk combined with nivolumab 3 mg/kg q2wk resulted in a 33% rate of grade 3-4 treatment-related AEs, but only 13% rate of treatment-related AEs leading to study drug discontinuation[63] (compared to 19% grade 3-4 treatment-related AEs and 10% treatment-related AEs leading to discontinuation in nivolumab 3 mg/kg IV q2wk arm).[29] The FDA has determined that based on population pharmacokinetics models, there is a negligible difference in overall exposure between nivolumab 240 mg IV q2wk and 3 mg/kg IV q2wk. Consequently, we plan the ipilimumab and nivolumab dosing within safety cohort 1 to be ipilimumab 1 mg/kg IV q6wk plus nivolumab 240 mg IV q2wk. The dose of panitumumab selected within dose level 1 is the FDA-approved monotherapy dose.

If DLTs occur in no more than one subject in the first 6 subjects treated during the 12 week assessment period in the first safety cohort, then the trial would continue enrolling subjects to the remainder of the first stage of the phase II portion to complete enrollment to 32 subjects to assess efficacy of panitumumab, ipilimumab and nivolumab (3-drug combination). This would then be followed by interim analysis to determine whether the second stage would merit enrollment. If the 3-drug combination is not well tolerated, then 6 additional subjects will be enrolled into safety cohort 2 and receive panitumumab and nivolumab (2-drug combination). If no more than one subject experiences a DLT in safety cohort 2, then the trial will continue enrolling subjects into the phase II portion and the 2-

drug combination of panitumumab and nivolumab will be evaluated for efficacy. Subjects may continue combination treatment as long as they are benefitting from therapy until disease progression, unacceptable toxicity or withdrawal for other reasons as deemed necessary by the investigator.

DLT definitions applicable to the safety assessment run-in are defined in section 4.2. Subjects will undergo disease evaluation every 6 weeks for the first year, and will continue on this disease assessment schedule if they are at least stable but have less than a CR. If subjects continue on study after one year with a CR, then disease evaluations may occur every 12 weeks from that point forward.

4.2 Dose Limiting Toxicities for Safety Lead-in

The safety lead-in DLT assessment period is defined as the first 12 weeks (84 days) of ipilimumab/nivolumab/panitumumab therapy. An event will be considered a DLT if it occurs within the first 84 days of combination therapy and meets one of the following criteria.

- Grade 4 neutropenia lasting ≥ 5 days
- Febrile neutropenia
- Grade 4 thrombocytopenia
- Grade 4 anemia
- Grade 2 drug-related uveitis that does not respond to topical therapy and does not improve to Grade 1 severity within 6 weeks OR requires systemic treatment
- Grade 3 drug-related uveitis
- Grade 3-4 pneumonitis
- Grade 3-4 bronchospasm
- Grade 3-4 diarrhea
- Grade 3-4 colitis
- Grade 3-4 neurologic adverse event
- Grade 3-4 adrenal insufficiency
- Grade 3-4 hypersensitivity reaction
- Grade 3-4 infusion reaction of any duration
- Grade 3 non-skin, drug-related non-hematologic toxicity per NCI-CTCAE criteria 4.03 lasting over 7 days
- Grade 4 non-hematologic toxicity per NCI-CTCAE criteria 4.03 (excluding alopecia, isolated electrolyte disturbances that responds to correction within 72 hours of onset, isolated amylase or lipase abnormalities that are not associated with symptoms or clinical signs of pancreatitis and decrease to < Grade 4 within 1 week of onset)

4.3 Treatment Dosage and Administration

Dosing should be based on the subject's baseline weight on day 1 of cycle 1, as measured according to institutional standards; doses will be adjusted for subjects who experience a ≥10% change in weight during the study.

4.3.1 Safety Cohort 1 Schedule (3-drug combination)

REGIMEN DESCRIPTION –Safety Cohort 1)					
Agent	**Premedications; Precautions**	**Dose/Frequency**	**Route**	**Schedule**	**Cycle Length**
Panitumumab	See Section 4.5 and 4.5.1	6mg/kg every 2 weeks	IV (specific details below)	D1, D15, D29 of each cycle	
		For doses ≤ 1000 mg	IV over 60 (± 15) minutes		
		For doses >1000 mg,	IV over 90 (± 15) minutes		
Ipilimumab	See Section 4.5.3	1 mg/kg every 6 weeks	IV over 30 (± 15) minutes	D1 of each cycle	
Nivolumab	See sections 4.5.2 and 4.5.3	240 mg every 2 weeks	IV over 30 (± 15) minutes	D1, D15, D29 of each cycle	

4.3.2 Safety Cohort-2 Schedule (2-drug combination)

REGIMEN DESCRIPTION – Safety Cohort 2					
Agent	**Premedications; Precautions**	**Dose/Frequency**	**Route**	**Schedule**	**Cycle Length**
Panitumumab	See Section 4.5 and 4.5.1	6mg/kg every 2 weeks	IV(specific details below)	D1, D15, D29 of each cycle	
		For doses ≤1000 mg,	IV over 60 (±15) minutes		
		For doses >1000 mg,	IV over 90 (± 15) minutes		
Nivolumab	See section 4.5.2	240 mg every 2 weeks	IV over 30 (± 15) minutes	D1, D15, D29 of each cycle	

If the 3-drug combination is not tolerated in Cohort 1, then ipilimumab will be omitted and panitumumab in combination with nivolumab will be evaluated for safety. If no more than 1 subject out of 6 experiences DLTs after 12 weeks on therapy, then additional subjects will be enrolled to evaluate the safety and efficacy of panitumumab and nivolumab (2-drug combination). If neither the 3-drug or 2-drug combination is well-tolerated, the dosing approach for these agents will be reconsidered.

4.4 Toxicities and Dosing Delays/Dose Modifications

4.4.1 Panitumumab Dosing Delays/Dose Modifications

Toxicity grades per NCI-CTCAE Criteria v 4.03

Adverse Reaction	Severity	Dose Modification
Infusion-related reactions	Grade 1 or 2	Reduce infusion rate by 50%
	Grade 3 or 4	• Terminate the infusion • Depending on the severity and /or persistence of the reaction, permanently discontinue panitumumab
Dermatologic reaction	Grade 3 – 1st occurrence	Withhold 1 or 2 doses of Panitumumab, if reaction improves to < grade 3, reinitiate at original dose
	Grade 3 – 2nd occurrence	Withhold 1 or 2 doses of Panitumumab, if reaction improves to < grade 3, reinitiate at 80% of the original dose
	Grade 3 – 3rd occurrence	Withhold 2 doses of panitumumab, if reaction improves to < grade 3, reinitiate at 80% of the original dose
	Grade 3 - 4th occurrence	Permanently discontinue panitumumab
	Grade 3 reaction that not recover after withholding 1 or 2 doses **OR** Grade 4	Permanently discontinue panitumumab
Pulmonary Fibrosis/ILD	Acute onset of pulmonary symptoms	Interrupt panitumumab until resolution
	ILD confirmed	Permanently discontinue panitumumab
Ocular toxicities	Acute or ulcerative keratitis	Interrupt panitumumab or permanently discontinue panitumumab for acute or worsening keratitis
Warnings		
Electrolyte depletion/Monitoring	Monitor subjects for hypomagnesemia and hypocalcemia prior to initiating panitumumab and periodically during panitumumab treatment, and for up to 8 weeks after the completion of therapy. Replete magnesium with oral or IV supplements as indicated.	

4.4.2 Nivolumab +/- Ipilimumab Dosing Delays/Dose Modifications

Toxicity grades per NCI-CTCAE Criteria v 4.03

Adverse Reaction	Severity	Dose Modification
Adrenal Insufficiency[f]	Grade 2 adrenal insufficiency	Withhold dose[a]
	Grade 3-4 adrenal insufficiency	Permanently discontinue[e]
Myocarditis	Grade 3-4 myocarditis	Permanently discontinue
Infusion Related Reaction	Grade 1-2 infusion related reaction	See section 4.5.2 for guidance
	Grade 3-4 infusion related reaction or anaphylaxis	Permanently discontinue
Uveitis, eye pain, blurred vision	Grade 2 that does not respond to topical therapy and does not improve to grade 1 severity within re-treatment period OR requires systemic treatment	Permanently discontinue
	Grade 3-4 uveitis or eye pain or blurred vision	Permanently discontinue
Colitis[f]	Grade 2 diarrhea or colitis	Withhold dose[a]
	Grade 3 diarrhea or colitis	Withhold dose[a]
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis[f]	Grade 2 pneumonitis	Withhold dose[a]
	Grade 3 or 4 pneumonitis	Permanently discontinue
Hypophysitis[f]	Grade 2hypophysitis	Withhold dose[a]
	Grade 3-4 hypophysitis	Permanently discontinue[e]
Type 1 Diabetes Mellitus[f]	Grade 3 hyperglycemia	Withhold dose[a]
	Grade 4 hyperglycemia	Permanently discontinue[e]
Nephritis and Renal Dysfunction[f]	Serum creatinine more than 1.5 and up to 6X ULN	Withhold dose[a]
	Serum creatinine more than 6X ULN	Permanently discontinue
Rash[f]	Grade 3 rash	Withhold dose[a]
	Grade 4 rash	Permanently discontinue
Encephalitis[f]	New-onset moderate or severe neurologic signs or symptoms	Withhold dose[a]
	Immune-mediated encephalitis	Permanently discontinue
Hepatitis	See section 4.4.2.1 for guidance	
Other[f]	Other Grade 3 adverse reaction [b] First occurrence Recurrence of same Grade 3 adverse reaction	 Withhold dose[a] Permanently discontinue
	Life-threatening or Grade 4 adverse reaction[d]	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer[c]	Permanently discontinue

a) Resume treatment when adverse reaction returns to Grade 0 or 1. If toxicity persists > 6 weeks, permanently discontinue nivolumab +/- ipilimumab. May discuss with Medical Monitor.

b) Except for grade 3 lymphopenia, leukopenia, isolated laboratory abnormalities without clinical significance, or amylase or lipase abnormality that is not associated with symptoms or clinical

manifestations of pancreatitis.

c) Except for grade 2 fatigue, some subjects with baseline grade 1 LFT abnormalities who have grade 2 elevation of AST/ALT/bilirubin as described in 4.4.2.3, or subjects with grade 2-3 endocrine toxicities not described elsewhere in the table that are adequately treated with physiologic hormone replacement (e.g. hypothyroidism)

d) Except for grade 4 lymphopenia, leukopenia, isolated electrolyte abnormalities without clinical significance that are corrected with supplementation/appropriate management within 72 hours of onset, or amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis and decreases to <grade 4 within 1 week of onset.

e) Selected subjects with transient episodes of grade 3-4 endocrine toxicities who are adequately treated and stabilized on physiologic hormone replacement or other supportive medications with improvement to grade 1-2 may not require discontinuation after discussion with and approval from the Medical Monitor.

f) For additional management, including monitoring and use of corticosteroids or additional immunosuppressant therapies, recommend using guidelines for management of immunotherapy related toxicities, primarily the NCCN Management of Immunotherapy-Related Toxicities Version 1.2020. Section 11.2 has algorithms for possible management of selected toxicities, but management does not have to follow direction of Section 11.2.

4.4.2.1 Nivolumab and/or Ipilimumab Dose Modifications/Delays for Liver Toxicity

Recognizing that mCRC is often associated with the presence of liver metastases at baseline, the following criteria will be used for dose modifications/delays of nivolumab and/or ipilimumab for liver toxicity.

Baseline Liver Function Test (NCI-CTCAEv4.03 grade)	Adverse Reaction Severity	Dose Modification *
AST or ALT normal	AST or ALT ≥ 3 X ULN to ≤ 5 X ULN	Withhold dose[a]
	AST or ALT > 5 X ULN	Permanently discontinue
AST or ALT 1.1 to ≤ 2.5 X ULN (Grade 1)	AST or ALT ≥ 5 X ULN to ≤ 8 X ULN	Withhold dose[a]
	AST or ALT > 8 X ULN	Permanently discontinue
Total Bilirubin normal	> 1.5 to ≤ 3 X ULN	Withhold dose[a]
	> 3 X ULN	Permanently discontinue
Total Bilirubin 1.1 to ≤ 1.5 X ULN (Grade 1)	≥ 3 to 5 X ULN	Withhold dose[a]
	> 5 X ULN	Permanently discontinue

a) Resume treatment when adverse reaction returns to Grade 0 or 1. If toxicity persists > 6 weeks, permanently discontinue nivolumab +/- ipilimumab

* For additional management, including monitoring and use of corticosteroids or additional immunosuppressant therapies, recommend using guidelines for management of immunotherapy related toxicities, primarily the NCCN Management of Immunotherapy-Related Toxicities Version 1.2020. Section 11.2 has algorithms for possible management of selected toxicities, but management does not have to follow direction of Section 11.2.

4.4.2.2 Dose Delay Criteria for Nivolumab +/- Ipilimumab

Because of the potential for clinically meaningful nivolumab-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected AEs of selected categories [see current Investigator Brochure and Appendix 11.2]. Hepatotoxicity guidelines are provided in the section above.

Dose delay criteria apply for all drug-related adverse events related to nivolumab and/or ipilimumab (regardless of whether or not the event is attributed to nivolumab, ipilimumab, or both). If both nivolumab and ipilimumab are being administered, both must be delayed until treatment can resume.

Nivolumab +/- ipilimumab administration should be delayed per the criteria in 4.4.2 and 4.4.2.1.

Additionally, nivolumab +/- ipilimumab should be held in the event of any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

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

4.4.2.3 Criteria to Resume Nivolumab +/- Ipilimumab Treatment

Subjects may resume treatment with study drug when the drug-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 toxicity
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if investigator allows.
- Subjects with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment if the investigator allows it, but this should be documented clearly in the electronic case report form (eCRF).

4.4.2.3.1 Guidance on Cycle Counting after Treatment Delay

If the criteria to resume treatment are met, and treatment was delayed for up to one week (≤ 7 days), make up the missed treatment visit. If treatment was delayed for 8-42 days, skip the missed treatment(s) and resume treatment at the next relevant cycle/day treatment visit, unless the subject is ≥ 42 days from the last dose of ipilimumab, in which case resume treatment at day 1 of the next treatment cycle.

If treatment is delayed or interrupted for > 6 weeks due to toxicity, adverse effect, or medical comorbidity, the subject must be permanently discontinued from study therapy, except as specified in the discontinuation section 4.4.2.5.

4.4.2.4 Management Algorithms for Immune-related Events for Nivolumab +/- Ipilimumab

Guidelines for the management of immune-related events can be found in the current Nivolumab Investigator Brochure AND in the approved USPI in the US.

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered an I-O agent in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

For mandatory guidance on dosing of nivolumab and/or ipilimumab with specified immune related adverse events, please refer to section 4.4.2 and

section 4.4.2.1. For additional management, including monitoring and use of corticosteroids or additional immunosuppressant therapies, recommend using guidelines for management of immunotherapy related toxicities, primarily the NCCN Management of Immunotherapy-Related Toxicities Version 1.2020. Section 11.2 has algorithms for possible further management of selected toxicities, but management does not have to follow direction of Section 11.2. Instead, these algorithms are only an additional resource to complement other guidelines and the Investigator's medical judgment.

4.4.2.5 Discontinuation Criteria for Nivolumab and/or ipilimumab

Treatment with nivolumab and ipilimumab should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, and infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except those noted below
- Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
- Any drug-related liver function test (LFT) abnormality that meets the following criteria requires discontinuation:
  - If baseline AST or ALT is within normal limits, AST or ALT > 5 x ULN
  - If baseline AST or ALT is Grade 1, AST or ALT > 8 x ULN

  - If baseline total bilirubin is within normal limits, total bilirubin ≥ 3x ULN
  - If baseline total bilirubin is Grade 1, total bilirubin > 5 x ULN

- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset.
  - 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 or leucopenia
  - Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, 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 Investigator
- Any dosing interruption lasting > 6 weeks with the following exceptions:
  - Dosing delays or interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted or delayed
  - Dosing interruptions or delays lasting > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab and ipilimumab dosing

Additionally, after any immune related adverse event that does not meet the mandatory discontinuation requirement, the treating investigator should carefully consider the safety of resuming nivolumab and/or ipilimumab. In select cases, like for colitis, it would be appropriate to discontinue ipilimumab but continue nivolumab. This should be discussed with the medical monitor, and decisions should use guidelines for rechallenge after immune-related adverse events, such as found in the NCCN Management of Immunotherapy-Related Toxicities Version 1.2020.

4.5 Concomitant Medications/Treatments

Subjects on the trial are allowed to receive all supportive care therapy needed to alleviate symptoms related to CRC or other medical problems at the investigator's discretion. No treatments should be withheld due to a subject's participation in this study. Prophylaxis for infusion-related reactions should be employed per institutional guidelines.

Infusion-related reactions (including anaphylaxis) may occur during the infusion of nivolumab. Infusion-related reactions are also associated with panitumumab treatment, but no prophylaxis measures are suggested. The infusion of nivolumab (and panitumumab) should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. Monitor subjects during infusion. If anaphylaxis occurs immediately and permanently discontinue administration of the study medication and administer appropriate medical therapy per institutional standards. If a mild or moderate infusion-related reaction occurs, the infusion should be interrupted, or the rate of infusion slowed, and appropriate medical management instituted. Subjects who experienced a prior infusion-related reaction to nivolumab should be pre-medicated for subsequent infusions per institutional standards. Premedication may include acetaminophen, an antihistamine and a corticosteroid.

Brief (up to 7 days) and episodic use of systemic corticosteroids for other general conditions (e.g. pre-medication for radiographic imaging due to IV contrast allergy, COPD exacerbation, poison ivy, etc.) is allowed.

4.5.1 Prophylaxis for acneiform skin rash related to panitumumab therapy

Subjects receiving panitumumab should receive prophylactic management for EGFR-I associated skin toxicity in accordance with the strategies employed in the STEPP and J-STEPP randomized clinical trials. Subjects should be educated thoroughly on avoiding sun exposure as able. If sun avoidance is not possible, subjects should be advised to wear a hat with brim and to cover extremities with non-restrictive UV protectant clothing.

All subjects should be prescribed prophylactic oral tetracycline antibiotic (Doxycycline 100mg PO BID or Minocycline 100mg PO Daily).

Additionally, the following measures are suggested for rash prophylaxis/management:

1. Skin moisturizer applied to face, hands, feet, neck, back and chest both in the morning on rising and evening (bedtime)
2. Sunscreen (PABA Free, UVA and UVB protectant, SPF 25 or higher) applied to potentially sun-exposed areas before going outdoors.
3. Topical steroids (0.5% Hydrocortisone Cream) applied to face, hands, feet, neck, back and chest both in the morning on rising and evening (bedtime)

Prophylactic management with the above regimen was continued for 8 weeks in the STEPP and J-STEPP studies (or until the development to intolerance to a component of the prophylactic regimen). Treatment with the above regimen can be continued for the duration of panitumumab-containing therapy at the discretion of the treating physician.

While skin toxicity management is employed pre-emptively per the J-STEPP regimen described above, emergent skin toxicity may still occur. Additional measures for the alleviation of emergent skin toxicity grade 2 or higher will be at the discretion of the treating physician. Treatment strategies/agents selected may include higher-potency topical steroids, oral steroids, and additional topical or systemic antibiotics. Grade 3 rash is considered to be at the panitumumab treatment threshold, and panitumumab dose reduction or delay are implemented also at the discretion of the treating physician. Dermatology consultation is recommended for subjects being considered for dose reduction or cessation due to skin toxicity. Referral to dermatologist should also be recommended for grade 3 or 4 toxicity, skin toxicity that is difficult to manage employing the measures above or does not improve within 1-2 weeks, and any skin toxicity that is severely symptomatic or has an uncharacteristic appearance or distribution.

4.5.2 Treatment of Therapy-Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. Panitumumab caused grade 3-4 infusion reactions in <0.5% of subjects[44]. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms of allergic-like reactions.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAEv4.03 guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

For Grade 1 symptoms during panitumumab infusion: (Mild reaction; infusion interruption not indicated; intervention not indicated). Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and 325 to 1000 mg acetaminophen at least 30 minutes before additional therapeutic antibody administrations. Decrease the infusion rate of panitumumab to 50% of the original infusion rate.

For Grade 1 symptoms during nivolumab infusion: (Mild reaction; infusion interruption not indicated; intervention not indicated). Remain at bedside and

monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and 325 to 1000 mg acetaminophen at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms during panitumumab infusion: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti- inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for 24 hours).

Stop the panitumumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and 325 to 1000 mg acetaminophen; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve. Monitor subject closely. If symptoms recur, then no further panitumumab will be administered at that visit. Administer diphenhydramine 50 mg IV and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and 325 to 1000 mg acetaminophen should be administered at least 30 minutes before additional NVB administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 2 symptoms during nivolumab infusion: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti- inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for 24 hours).

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and 325 to 1000 mg acetaminophen; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and 325 to 1000 mg (acetaminophen)

should be administered at least 30 minutes before additional NVB administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms of panitumumab or nivolumab: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]). Grade 4: (life threatening; pressor or ventilatory support indicated).

Immediately discontinue infusion of the therapeutic antibody. Begin an IV infusion of normal saline and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. The offending therapeutic antibody will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

4.5.3 Special warnings and precautions

- Nivolumab and ipilimumab are associated with immune-related AEs. Subjects should be monitored continuously (at least up to 5 months after the last dose) as an AE with nivolumab/ipilimumab may occur at any time during or after discontinuation of therapy.

- For suspected immune-related reactions, adequate evaluation should be performed to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab/ipilimumab should be withheld and corticosteroids administered. If immunosuppression with corticosteroids is used to treat an AE, a taper of at least 1-month duration should be initiated upon improvement. Rapid tapering may lead to worsening of the AE. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use.

4.6 Duration of Therapy

Subjects should continue protocol therapy as described until:

- Disease progression (Note: treatment should continue until progression is confirmed by repeat scan approximately 6 weeks later to rule out pseudoprogression based on investigator discretion)
- Inter-current illness prevents further administration of treatment
- Unacceptable adverse event(s)

- Subject decides to withdraw from the study, OR
- General or specific changes in the subject's condition render the subjects unacceptable for further treatment in the judgment of the investigator.

4.7 Duration of Follow Up

Subjects will be followed for up to 3 years after removal from study treatment for determination of OS. Subjects removed from study treatment for unacceptable AEs will be followed for resolution or stabilization of the adverse event(s). All subjects (including those withdrawn for AEs) should be followed after removal from study treatment as stipulated in the protocol.

4.8 Removal of Subjects from Protocol Therapy

Subjects will be removed from protocol therapy and the PI notified when any of the criteria listed in section 4.6 apply. The reason for discontinuation of protocol therapy will be documented on the eCRF.

In case a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if she or he may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.

Excessive subject withdrawals from protocol therapy or from the study can render the study un-interpretable; therefore, unnecessary withdrawal of subjects should be avoided.

4.9 Study Withdrawal

If a subject decides to withdraw from the study (and not just from protocol therapy) an effort should be made to complete and report study assessments as thoroughly as possible. At the time of withdrawal, the investigator should attempt to establish as completely as possible the reason for the study withdrawal.

- The subject should be asked if they are willing to allow for the abstraction of relevant information from their medical record in order to meet the long term follow up (e.g., survival) objectives outlined in the protocol.
- A complete final evaluation at the time of the subject's study withdrawal should be obtained with an explanation of why the subject is withdrawing from the study.
- If the subject is noncompliant and does not return for an end of study follow up assessment, this should be documented in the eCRF.
- If the reason for removal of a subject from the study is an adverse event, the principal specific event will be recorded on the eCRF.

Excessive subject withdrawals from protocol therapy or from the study can render the study un-interpretable; therefore, unnecessary withdrawal of subjects should be avoided.

5.0 DRUG INFORMATION

5.1 Panitumumab (Vectibix®)

For additional information, refer to the Panitumumab Investigator's Brochure (IB) and the prescribing information for Vectibix® (panitumumab) available at the link provided: http://pi.amgen.com/united_states/vectibix/vectibix_pi.pdf

5.1.1 Description, Packaging and Labeling

Panitumumab is supplied as a sterile, colorless, preservative-free solution containing 20 mg/mL panitumumab in a single-use vial. Panitumumab is a sterile, colorless, pH 5.6 to 6.0 liquid for intravenous (IV) infusion, which may contain a small amount of visible translucent-to-white, amorphous, proteinaceous, panitumumab particulates.

Panitumumab is provided in 12 units/kit and 6 units/kit. Each single-use 10 mL vial contains 200 mg of panitumumab, 58 mg sodium chloride, 68 mg sodium acetate, and Water for Injection, USP. Each single-use 20 mL vial contains 400 mg of panitumumab, 117 mg sodium chloride, 136 mg sodium acetate, and Water for Injection, USP. Panitumumab kit description is as follows:

- (200mg) Panitumumab, 20 mg/ml, 10 ml vial, 12 units/kit
- (400mg) Panitumumab, 20mg/ml, 20ml vial, 6 units/kit

5.1.2 Storage and Handling

Store vials in the original carton under refrigeration at 2^0 to 8^0C (36^0 to 46^0F) until time of use. Protect from direct sunlight. DO NOT FREEZE. Since panitumumab does not contain preservatives, any unused portion remaining in the vial must be discarded.

5.1.3 Dose, Schedule and Administration

See section 4.3

5.1.4 Preparation

See the panitumumab prescribing information for preparation instructions.

5.1.5 Stability

The diluted infusion of panitumumab should be used within 6 hours of preparation if stored at room temperature, or within 24 hours of dilution if stored at 2^0 to 8^0C (36^0 to 46^0F). DO NOT FREEZE.

5.1.6 Return and Retention of Panitumumab

Unused vials will be handled per instructions from Amgen, Inc. Partially used and completely used vials will be destroyed per institutional guidelines.

5.1.7 Adverse Events Associated with Panitumumab

The most common adverse events (≥20%) with panitumumab monotherapy are skin rash with variable presentations, paronychia, fatigue, nausea, and diarrhea. The adverse events listed below have been reported in subjects receiving panitumumab. See section 4.4.1 for further instruction on the management adverse events associated with panitumumab therapy.

- Dermatologic and soft tissue toxicity
- Increased tumor progression, increased mortality, or lack of benefit in *RAS*- and *KRAS*-mutant mCRC
- Electrolyte depletion
- Infusion reactions
- Acute renal failure in combination with chemotherapy
- Pulmonary fibrosis/interstitial lung disease
- Photosensitivity
- Ocular toxicities
- Increased mortality and toxicity with panitumumab in combination with bevacizumab and chemotherapy

5.2 Nivolumab (Opdivo®)

See the Nivolumab Investigator's Brochure (IB) and the prescribing information for Opdivo® (Nivolumab) at http://packageinserts.bms.com/pi/pi_opdivo.pdf for more detailed information.

5.2.1 Description

Nivolumab (BMS 936558-01*) injection drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 100mg/10 mL. The vials supplied contain 100 mg. Nivolumab is a sterile, preservative-free, non-pyrogenic clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles for IV administration. Nivolumab will be supplied by Bristol-Myers Squibb (BMS) at no charge to study subjects.

*Nivolumab may be labeled as BMS936558-01 solution for injection.

5.2.2 Packaging and Labeling

Primary Packaging (Volume)/Label type: Carton of 5
Secondary Packaging (Qty)/Label type: 10-cc Type 1 flint glass vials stoppered with butyl stoppers and sealed with aluminum seals.

5.2.3 Storage and Handling

Store nivolumab under refrigeration at 2^0C to 8^0C (36^0F-46^0F) in the original package until time of use. Protect from light and freezing. Do not shake the vial.

If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For additional details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the BMS-936558 (nivolumab) Investigator Brochure section for "Recommended Storage and Use Conditions".

The investigator should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as per product information and the Investigator Brochure and per local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

5.2.4 Dose, Schedule and Administration

See section 4.3

Nivolumab will be given every two weeks at a dose of 240 mg, to be administered as a 30-minute IV infusion.

Subjects may be dosed no less than 12 days from the previous dose of drug. There are no premedications recommended for nivolumab on the first cycle.

The dosing calculations should be based on the actual body weight at baseline. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the original dose, the dose must be recalculated. All doses should be rounded to the nearest milligram. There will be no dose modifications allowed.

Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to institutional guidelines (See section 4.5.2).

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment.

5.2.5 Preparation

See the nivolumab prescribing information for preparation instructions. Nivolumab Injection, 100 mg/10 mL (10 mg/mL) is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding polyether sulfone membrane in-line filter at the protocol-specified dose. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be

infused undiluted (10 mg/mL) or 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 antimicrobial preservative or bacteriostatic agent.

5.2.6 Stability

After preparation of infusion, from a microbiological point of view, the product should be used immediately. If not used immediately, chemical and physical in-use stability of nivolumab has been demonstrated for 24 hours at 2ºC to 8ºC protected from light and a maximum of 8 hours at 20°C-25°C and room light (this 8-hour period of the total 24 hours should be inclusive of the product administration period).

5.2.7 Return and Retention of Nivolumab

Unused vials will be handled per instructions from BMS. Partially used and completely used vials will be destroyed per institutional guidelines.

5.2.8 Adverse Events Associated with Nivolumab

The adverse events listed below have been reported in subjects receiving NVB. See section 4.4 for further instruction on the management of adverse events associated with nivolumab therapy.

- Immune-mediated pneumonitis: Defined as requiring use of corticosteroids and no clear alternate etiology, including fatal cases have occurred with nivolumab treatment.
- Immune-mediated colitis: Defined as requiring use of corticosteroids and no clear alternate etiology, including fatal cases have occurred with nivolumab treatment.
- Immune-mediated hepatitis: Defined as requiring use of corticosteroids and no clear alternate etiology have occurred with nivolumab treatment.
- Immune-mediated endocrinopathies: Hypophysitis, adrenal insufficiency, hypo- and hyper-thyroidism, and type I diabetes mellitus have occurred with nivolumab treatment.
- Immune-mediated nephritis and renal dysfunction: Defined as renal dysfunction or ≥Grade 2 increased creatinine, requirement for corticosteroids, and no clear alternate etiology, can occur with nivolumab treatment.
- Immune-mediated rash: Severe rash (including rare cases of fatal toxic epidermal necrolysis) can occur with nivolumab treatment.
- Immune-mediated encephalitis: Withhold nivolumab in subjects with new-onset moderate to severe neurologic signs or symptoms.
- Other immune-mediated adverse reactions: Monitor for as described in section 4.4.2
- Infusion reactions: Severe infusion reactions have been reported in <1.0% of subjects in clinical trials of nivolumab. See section 4.5.2 for information on the management of nivolumab-related infusion reactions.
- Other events may occur. One event that has been observed is hemolytic anemia

5.3 Ipilimumab (Yervoy®)

See the Ipilimumab Investigator's Brochure (IB) and the prescribing information for Yervoy® (Ipilimumab) at http://packageinserts.bms.com/pi/pi_yervoy.pdf for more detailed information.

5.3.1 Description

Ipilimumab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution of IV infusion, which may contain a small amount of visible translucent-to-white, amorphous ipilimumab particulates. It is suppled in single-use vials of 50 mg/10mL and 200 mg/40 mL.

5.3.2 Packaging and Labeling

Primary Packaging (Volume)/Label type: Carton of 6 (50 mg/10 mL) or 4 vials (200 mg/40 mL)

5.3.3 Storage and Handling

Store ipilimumab under refrigeration at 2^0C to 8^0C (36^0F-46^0F) in the original package until time of use. Protect from light. Do not freeze.

Store the diluted solution for no more than 24 hours under refrigeration 2^0 to 8^0C (36^0 to 46^0F) or at room temperature 20^0 to 25^0C (68^0 to 77^0F).

5.3.4 Dose, Schedule and Administration

See section 5.3.4

The recommended dose of ipilimumab for metastatic melanoma is 3mg/kg administered over 90 minutes every 3 weeks for a maximum of 4 doses. The recommended dose for adjuvant treatment of melanoma is 10 mg/kg administered over 90 minutes every 3 weeks for 4 doses followed by 10mg/kg every 12 weeks for up to 3 years.

In this trial, ipilimumab will be given at a dose of 1mg/kg administered over 30 minutes every 6 weeks if DL1 is tolerated as outlined in the study schema and described in section 4.3.

5.3.5 Preparation

See the ipilimumab prescribing information for preparation instructions. Do not shake the product. Inspect for particulate matter or discoloration prior to administration. Discard vial if solution is cloudy, there is pronounced discoloration (solution may have pale yellow color) or there is foreign particulate matter other than translucent-to-white, amorphous particles.

5.3.6 Stability

Store the diluted solution for no more than 24 hours under refrigeration 2^0 to 8^0C (36^0 to 46^0F) or at room temperature 20^0 to 25^0C (68^0 to 77^0F).

5.3.7 Return and Retention of Ipilimumab

Unused vials will be handled per instructions from BMS. Partially used and completely used vials will be destroyed per institutional guidelines.

5.3.8 Adverse Events Associated with Ipilimumab

The adverse events noted here have been reported in subjects receiving ipilimumab. See section 4.4.3 for further instruction on the management of adverse events associated with ipilumumab in combination with nivolumab therapy.

- Common adverse events occurring in ≥ 5% of subjects on ipilimumab are fatigue, diarrhea, pruritus, rash, and colitis.
- Additional common adverse reactions at the 10mg/kg dose (≥ 5%) include nausea, vomiting, headache, weight loss, pyrexia, decreased appetite, and insomnia.
- Other events may occur. One event that has been observed is hemolytic anemia

5.4 Return and Retention of Study Drug

The investigator is responsible for keeping accurate records of the clinical supplies received from the study, the amount dispensed to the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used and completely used vials of investigational product will be destroyed per UNC IDS drug destruction policy for drug received by UNC. All unused drug will be handled per instructions provided by the manufacturer. In general, 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.

6.0 EVALUATIONS AND ASSESSMENTS

6.1 Time and Events Table

Assessment	Pre-Study[1]	D1[2] Cycle 1	D15[2] Cycle 1	D29[2] Cycle 1	D1[2] Cycle 2	D15[2] Cycle 2	D29[2] Cycle 2	D1[2] Cycle 3-N	D15[2] Cycle 3-N	D29[2] Cycle 3-N	End of Treatment[3]	30-day Follow up[3]	100-day Follow up[3]	Long term Follow up[3]
Informed Consent	X													
History[4]	X	X	X	X	X	X	X	X	X	X	X	X		
Physical exam	X	X	X	X	X	X	X	X	X	X	X	X		
Performance Status	X	X	X	X	X	X	X	X	X	X	X			
Tumor measurement[5]	X							X[5]						
Pregnancy test[6]	X	X[6]			X[6]			X[6]			X[6]	X[6]		
Hematology[7]	X	X	X	X	X	X	X	X	X	X	X			
Serum Chemistries[7]	X	X	X	X	X	X	X	X	X	X	X			
TSH, Free T3/T4[8]	X				X			X			X			
ACTH/Amylase/Lipase[8]	X				X			X			X			
CEA[8]	X				X			X			X			
Toxicity Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Meds[9]	X	X	X	X	X	X	X	X	X	X	X	X		
Ipilimumab IV (if DL1 safe)[10]		X			X			X						
Nivolumab IV[10]		X	X	X	X	X	X	X	X	X				
Panitumumab IV[10]		X	X	X	X	X	X	X	X	X				
Request archival or Perform mandatory biopsy	X[11]													
Blood sample[12]		X			X			X			X			
Stool specimen	X							X[13]						
On treatment Tumor biopsy (Optional; goal n=15)	X			X[14]										
Survival analysis													X	X

1. Radiological assessments and physical exam may be performed within 4 weeks prior to day 1 of treatment. Other evaluations except for pregnancy test must be performed within 3 weeks prior to Cycle 1 Day 1 (C1D1) of treatment. Serum or urine β-HCG must be performed **within 24 hours prior** to first dose of study medication for women of child-bearing potential. Other screening labs performed within 72 hours prior to Cycle 1 Day 1 do not need to be repeated on C1D1.

2. Treatment cycles are to be repeated every 42 days until progression. A window of +/- 3 days applies to all study visits unless otherwise specified. While the treatment window is +/- 3 days, a minimum of 12 days must pass before the next dose of nivolumab.

3. The end of treatment visit should only occur when subjects permanently stop study treatment. Subjects who have an ongoing ≥grade 2 or serious AE (SAE) at this visit will continue to be followed until the event is resolved or deemed irreversible by the investigator. The 30-day (+/- 7 days) follow up visit after stopping study treatment should be performed to check for ongoing toxicity. Subsequently, subjects should be contacted by telephone at approximately 100 days (+/- 7 days) after discontinuing study treatment for the emergence of SAEs (including checking for pregnancy) and to ensure contraceptive guidelines are followed as stipulated in inclusion criteria 3.1.11 and 3.1.12. Subsequent long-term follow-up for survival, defined as every 90 days thereafter (+/- 15 days) for up to 3 years or until death (whichever is first) may be conducted via telephone or chart review and/or clinic visit. Long term survival follow up will be limited to history of any subsequent cancer treatments, an assessment of any SAEs (including checking for pregnancy) considered to be possibly or probably related to study treatment until resolution, and survival status.

4. Complete history at baseline only, thereafter focused history on symptoms/toxicity; physical exam to include height (baseline only), examination of the skin, weight, and vital signs. Note that starting with cycle 7, only include assessment by physician on days 15 and 29 if clinical signs and symptoms warrant MD consult

5. Tumor imaging should remain consistent throughout study and should include those thought by investigator to best capture status of disease. Disease assessments should include contrasted computed tomography (CT) of the chest and either contrasted CT of abdomen and pelvis or MRI of abdomen and pelvis. Repeat tumor imaging every 12 weeks (+/- 1 week).

6. Urine or serum β-HCG must be performed within 24 hours prior to first dose of study medication for women of child-bearing potential. The test result must be confirmed as negative prior to dosing with study medication. A serum or urine pregnancy test must be repeated every 6 weeks while receiving study medications and repeated approximately 30 days after discontinuing the study medications.

7. Hematology: CBC with differential including Hgb, and platelet count. Serum chemistries will include a complete metabolic panel (ie, BUN, creatinine, sodium (Na), potassium (K), Chloride (Cl), Bicarbonate (CO_2), glucose, calcium (Ca), albumin, total protein, total bilirubin, ALT, AST, and alkaline phosphatase) + magnesium (Mg) and phosphorus.

8. Thyroid function test: TSH and free T3/T4 should be assessed prior to initiating study treatment and performed every 6 weeks +/- 3 days during study treatment and at the end of treatment. ACTH, amylase and lipase should be measured at baseline (pre-study) and

then on D1 of each cycle. CEA should be measured pre-study and then on D1 of each cycle.

9. Please note all subjects should receive prophylaxis for panitumumab-associated rash with a tetracycline antibiotic (like doxycycline or minocycline) and continue for at least the duration of the first cycle of study combination treatment (i.e., 6 weeks), as described in section 4.5.1

10. Ipilimumab dosing will be halted and will not be given if the triple combination is determined to be unsafe during the safety run-in period (Cohort 1). If this is the case then subjects will be dosed with panitumumab and nivolumab in (Cohort 2) as described in section 4.3.2

11. Fixed paraffin-embedded blocks or slides from the original diagnostic specimen or from a metastatic or recurrent site must be requested for subjects at baseline. Subjects with inadequate archival specimens must undergo a mandatory biopsy prior to initiating study medications.

12. Blood samples will be collected for correlative studies on D1 of each cycle prior to dosing, and at the end of treatment visit.

13. Stool specimen should be collected +/- 7 days from C3D1.

14. We will collect fresh on-treatment biopsies (optional) in consenting patients for correlative studies in up to 15 patients. The on-treatment biopsy will be performed during cycle 1 on or between days 28 and 35.

6.2 Pre-Study Assessments

Pre-study evaluations are to be conducted within 3 weeks prior to start of protocol therapy. Scans for tumor evaluation must be done within 4 weeks prior to the start of therapy. Pre-study assessments include:

Complete medical history and physical examination (including height and weight)
ECOG Performance Status (see appendix 11.1)
Laboratory evaluations:

- Hematology: CBC with differential
- Complete Metabolic Panel (plus Mg and Phosphorus)
- TSH/Free T3/Free T4
- ACTH/Amylase/Lipase
- CEA
- Serum or urine pregnancy test in women of childbearing potential (**Note**: pregnancy test to be done within 24 hours of day 1 of treatment)

Concomitant medication(s): All concomitant medications will be recorded.
Tumor evaluation: Contrasted computed tomography (CT) of the chest, and either contrasted CT of abdomen and pelvis or MRI of abdomen and pelvis.
Tissue (archival and/or fresh biopsy): Obtain archival tissue from diagnostic regimen for correlative studies if available. If insufficient tissue available, subject must agree to mandatory pretreatment biopsy to participate in the clinical trial.
Stool Specimen: Collect pre-treatment stool specimen from patients as described in

Laboratory manual.
Toxicity evaluation: Use NCI CTCAEv4.03 for notation of any baseline toxicity

6.3 Treatment Assessments

6.3.1 D1 of Cycle 1

Focused history and physical examination (including weight)
ECOG Performance Status (see appendix 11.1)
Laboratory evaluations:

- Hematology: CBC with differential
- Complete Metabolic Panel (plus Mg and Phosphorus)
- Blood sample for correlatives
- Serum or urine pregnancy test in women of childbearing potential (**Note**: pregnancy test to be done within 24 hours of day 1 of treatment)

Concomitant medication(s): All concomitant medications will be recorded.
Toxicity evaluation: Use NCI CTCAEv4.03 for notation of any baseline toxicity
Administer Study Medications according to Safety Cohort 1 or 2 schedule as depicted in sections 0 and 4.3.2, respectively.

6.3.2 D15 of Cycles 1 and 2

Focused history and physical examination (including weight)
ECOG Performance Status (see appendix 11.1)
Laboratory evaluations:

- Hematology: CBC with differential
- Complete Metabolic Panel (plus Mg and Phosphorus)

Concomitant medication(s): All concomitant medications will be recorded.
Toxicity evaluation: Use NCI CTCAEv4.03 for notation of any baseline toxicity
Administer Study Medications according to Safety Cohort 1 or 2schedule as depicted in sections 0 and 4.3.2, respectively

6.3.3 D29 of Cycles 1 and 2

Focused history and physical examination (including weight)
ECOG Performance Status (see appendix 11.1)
Laboratory evaluations:

- Hematology: CBC with differential
- Complete Metabolic Panel (plus Mg and Phosphorus)
- Tumor biopsy (optional): **Applies to cycle 1 days 28-35 only**

Concomitant medication(s): All concomitant medications will be recorded.
Toxicity evaluation: Use NCI CTCAEv4.03 for notation of any baseline toxicity
Administer Study Medications according to Safety Cohort 1 or 2 schedule as depicted in sections 4.3.1 and 4.3.2, respectively

6.3.4 D1 of Cycle 2

Focused history and physical examination (including weight)
ECOG Performance Status (see appendix 11.1)
Laboratory evaluations:

- Hematology: CBC with differential
- Complete Metabolic Panel (plus Mg and Phosphorus)
- TSH/Free T3/Free T4
- ACTH/Amylase/Lipase
- CEA
- Serum or urine pregnancy test in women of childbearing potential (within 24 hours of dosing with study medications
- Blood sample for correlative studies

Concomitant medication(s): All concomitant medications will be recorded.
Toxicity evaluation: Use NCI CTCAEv4.03 for notation of any baseline toxicity
Administer Study Medications according to Safety Cohort 1 or 2 schedule as depicted in sections 0 and 4.3.2, respectively

6.3.5 D1 of Cycle 3-N

Focused history and physical examination (including weight) /
ECOG Performance Status (see appendix 11.1)
Laboratory evaluations:

- Hematology: CBC with differential
- Complete Metabolic Panel (plus Mg and Phosphorus)
- TSH/Free T3/Free T4
- ACTH/Amylase/Lipase
- CEA
- Serum or urine pregnancy test in women of childbearing potential (within 24 hours of dosing with study medications
- Blood sample for correlative studies

Concomitant medication(s): All concomitant medications will be recorded.
Tumor evaluation: Contrasted computed tomography (CT) of the chest, and either contrasted CT of abdomen and pelvis or MRI of abdomen and pelvis on cycles 3, 5, 7, etc. **Note**: Repeat tumor imaging every 12 weeks (+/- 1 week).
Stool Specimen: Collect stool specimen from patients as described in Laboratory manual +/- 7 days from Day 1 of Cycle 3 only.
Toxicity evaluation: Use NCI CTCAEv4.03 for notation of any baseline toxicity
Administer Study Medications according to Safety Cohort 1 or 2 schedule as depicted in sections 4.3.10 and 4.3.2, respectively

6.3.6 D15 of Cycles 3-N

Focused history and physical examination (including a weight) / **Note**: after 6 cycles completed, only include assessment by physician if clinical signs and symptoms warrant MD consult
ECOG Performance Status (see appendix 11.1)
Laboratory evaluations:

- Hematology: CBC with differential
- Complete Metabolic Panel (plus Mg and Phosphorus)

Concomitant medication(s): All concomitant medications will be recorded.
Toxicity evaluation: Use NCI CTCAEv4.03 for notation of any baseline toxicity
Administer Study Medications according to Safety Cohort 1 or 2 schedule as depicted in sections 4.3.1 and 4.3.2, respectively

6.3.7 D29 of Cycles 3-N

Focused history and physical examination (including a weight) / **Note**: after 6 cycles completed, only include assessment by physician if clinical signs and symptoms warrant MD consult
ECOG Performance Status (see appendix 11.1)
Laboratory evaluations:

- Hematology: CBC with differential
- Complete Metabolic Panel (plus Mg and Phosphorus)

Concomitant medication(s): All concomitant medications will be recorded.
Toxicity evaluation: Use NCI CTCAEv4.03 for notation of any baseline toxicity
Administer Study Medications according to Safety Cohort 1 or 2 schedule as depicted in sections 4.3.1 0and 4.3.2, respectively

6.4 Post-Treatment/Follow-up Assessments

6.4.1 End of treatment

Focused history and physical examination (including weight)
ECOG Performance Status (see appendix 11.1)
Laboratory evaluations:

- Hematology: CBC with differential
- Complete Metabolic Panel (plus Mg and Phosphorus)
- TSH/Free T3/Free T4
- ACTH/Amylase/Lipase
- CEA
- Serum or urine pregnancy test in women of childbearing potential
- Blood sample for correlative studies

Concomitant medication(s): All concomitant medications will be recorded.
Toxicity evaluation: Use NCI CTCAEv4.03 for notation of any baseline toxicity.
Note: Subjects who experienced a grade 3 or 4 event or SAE during the treatment phase will be contacted every 2 weeks until the event is resolved or deemed irreversible by the investigator.

6.4.2 30-day follow up

Focused history and physical examination (including weight)
Laboratory evaluations:

- Serum or urine pregnancy test in women of childbearing potential

Concomitant medications
Toxicity evaluation: Use NCI CTCAEv4.03 for notation of any baseline toxicity.
Note: Subjects who experienced a grade 3 or 4 event or SAE during the treatment phase will be contacted every 2 weeks until the event is resolved or deemed irreversible by the investigator.

6.4.3 100-day follow up

Survival and Toxicity evaluation: Use NCI CTCAEv4.03 for notation of any baseline toxicity. **Note**: Subjects who experienced a grade 3 or 4 event or SAE during the treatment phase will be contacted every 2 weeks until the event is resolved or deemed irreversible by the investigator.

6.4.4 Long-term follow up

Subsequent long-term follow-up visits should occur per standard of care, defined as every 90 days thereafter (+/- 15 days) for up to 3 years or until death (whichever is first) and may be conducted via telephone, medical record check, and/or via clinic visit. These visits will be limited to history of any subsequent cancer treatments, an assessment of any SAE's considered to be possibly or probably related to study treatment until resolution, and survival status.

6.5 Correlative Studies Procedures

Blood samples will be collected for correlative studies on D1 of each cycle and at the end of treatment visit. Collection details will be provided in the study laboratory manual.

Stool specimens will be collected during screening and on approximately Cycle 3 Day 1 (see 6.1 for details on timing of collection). Collection details will be provided in the study laboratory manual.

Handling of Biospecimens Collected for Correlative Research

Biospecimens collected for this study will be stored in the Lineberger Comprehensive Cancer Center (LCCC) Tissue Procurement Facility (TPF), or if needed, in a secure off-site storage facility. All biospecimen samples will be obtained in accordance with procedures outlined in the LCCC 1632 Study Laboratory Manual and stored in containers with controlled access. Each sample will be assigned a unique code number and no identifiable personal health information (PHI) will be on the specimen label. Information about the subject's disease will be linked to the specimens stored in the repository database. TPF-associated research staff, LCCC Bioinformatics staff who support the TPF database and the LCCC Data Warehouse, and researchers with IRB-approval for access to PHI for each subject in this study will be able to link specimens to relevant medical information. Some results from laboratory analyses that occurred during the subject's participation in the clinical study may also be included. This information may be important for understanding how the subject's cancer developed and responded to treatment.

All the planned correlative research studies will be performed by laboratories affiliated with UNC-Chapel Hill (for additional details please consult the laboratory manual).

Storage Time:

The biospecimen will be used first and foremost for research purposes outlined within the confines of this protocol. Samples will be discarded/destroyed after relevant data are collected for this study,

unless consent was obtained from the subject to use tissue for other research purposes (e.g., TPF consent form was signed by the subject). In this circumstance, there is no time limit on how long biospecimens may be stored.

- The investigator must agree to abide by policies and procedures of the TPF facility and sign a letter of research agreement for ethical and appropriate conduct of their research that utilizes specimens obtained from the TPF facility (e.g., Use of leftover specimens will require a protocol outlining the research plan for biospecimen use).

Compliance Statement

Biospecimen collection for this study will be conducted in full accordance to all applicable University of North Carolina (UNC) Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, and the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. Any episode of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent (unless a waiver is granted), and will report unexpected problems in accordance with The UNC IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

6.6 Assessment of Safety

Any subject who receives at least one dose of study therapy on this protocol will be evaluable for toxicity. Each subject will be assessed periodically for the development of any toxicity according to the Time and Events table. Toxicity will be assessed according to the NCI CTCAEv4.03.

6.7 Assessment of Efficacy

Efficacy will be assessed per RECIST 1.1 Criteria in the next section and by irRECIST as described in Section 6.7.5.1.

6.7.1 Assessment of Disease-Tumor Measurement Based on RECIST 1.1

See the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for additional details on RECIST1.1.

Measurable disease will be defined as the presence of at least one measurable lesion that can be accurately measured in at least one dimension with the longest diameter a minimum size of:

- $\geq$10mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest x-ray.

For malignant lymph nodes to be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5mm). At baseline and in follow-up, only the short axis will be measured and followed.

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions, will be considered non-measurable. Lesions considered truly non-measurable include: leptomeningeal disease; ascites; pleural/pericardial effusion; inflammatory breast disease; lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesions is recommended.

6.7.2 Baseline Documentation of Target and Non-Target Lesions

All measurable lesions up to a maximum of 5 lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longer diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

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, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as “present” or “absent”, or in rare cases “unequivocal progression”.

6.7.3 Evaluation of Target Lesions using RECIST 1.1 Criteria

NOTE: In addition to the information below, also see section 4.3.2 in the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

Complete response (CR)−Disappearance of all target lesions. Any pathological lymph node (LN) (whether target or non-target) must have decreased in short axis to <10mm.

Partial response (PR)−At least a 30% decrease in the sum of the LD of the target lesions taking as reference the baseline sum LD.

Progressive Disease (PD)−At least a 20% increase in the sum of the LD of the target lesions taking as reference the smallest sum LD recorded since the treatment started including baseline 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 5mm. The appearance of one or more new lesions also constitutes PD.

Stable disease (SD)−Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD since the treatment started.

6.7.4 Evaluation of Non-Target Lesions using RECIST 1.1 Criteria

Complete response (CR)−Disappearance of all non-target lesions and normalization of tumor marker levels. All LN must be non-pathological in size (<10mm short axis).

Non-complete response (non-CR)/non-progression (non-PD)−Persistence of one or more non-target lesion(s) or/and 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.

NOTE: Any progressive disease as defined by RECIST1.1 in subjects that are asymptomatic without signs or symptoms of impending visceral crisis SHOULD be confirmed by repeat scan to rule out "tumor flare" (pseudoprogression) related to immune response. In these subjects and per MD discretion, study therapy should be continued in these subjects until the repeat scan is performed approximately 4 weeks but no more than 6 weeks later. If PD is confirmed, subjects will be withdrawn from study. If tumor flare confirmed, subjects may continue therapy as per protocol. Subjects that have clear progressive disease as defined by RECIST 1.1 should be withdrawn from treatment and a repeat scan is not necessary.

6.7.4.1 Evaluation of Best Overall Response - The best overall responses for both RECIST 1.1 and irRECIST are defined as the best response achieved across all time points prior to progression (for example, a subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). Please Note: In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 12 weeks from initiation of treatment.

The best overall response will be defined according to the following table:

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[1]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE[2]	SD provided minimum criteria for SD duration met, otherwise, NE[2]
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE[2]	SD provided minimum criteria for SD duration met, otherwise, NE[2]
NE	NE[2]	NE[2]

[1] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.
[2] NE=inevaluable

6.7.5 Other Efficacy Parameters (Immune Response Criteria)

6.7.5.1 Evaluation of Response by irRECIST

Secondary objectives of this study involve assessment of ORR and PFS based in immune response criteria as outlined below (see Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Wolchok JD et al. Clin Cancer Res 2009;15(23):7412-20, Nishino et al. Clin Cancer Res 19(14):3936-43, and Bohnsack O. et al., *Adaptation of the immune related response criteria: irRECIST.* Annals of Oncology (2014) 25 (suppl_4): iv361-iv372. 10.1093/annonc/mdu342, 2014).

irRECIST criteria are based on irRC criteria (Wolchok et al) adapted for unidimensional measurement as outlined by Nishino et al. The adaptation described by Bohnsack et al. further aligns irRECIST to allow for assessment of

baseline non-target lesions and new non-measurable lesions and discusses the impact of those lesions on the overall tumor response assessment. The adaptation by Bohnsack et al. allows for evaluation of subjects with non-target disease only and subjects in the adjuvant setting (not applicable for this study in subjects with metastatic disease).

Overall response using the irRECIST is based on tumor burden as follows:

irCR	Complete disappearance of all lesions (whether measurable or not, and no new lesions) Lymph nodes must decrease to < 10 mm in short axis. Confirmation of response is not mandatory.
irPR	Decrease in tumor burden ≥30% in TMTB relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation, non-target lesions are irNN, and no equivocal progression of new non-measurable lesions.
irSD	Not meeting criteria for irCR, irPR, in absence of irPD
irPD	Increase in tumor burden ≥20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions confirmed by a repeat, consecutive assessment no less than 4 weeks from the date first documented
irNN	No target disease was identified at baseline and at follow-up the subject fails to meet criteria for irCR or irPD.

irNN = irNon-CR/Non-PD
TMTB = Total measureable tumor burden

7.0 ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a drug) in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE unless it is attributable by the investigator to the study therapy.

7.1.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the drug is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study drug exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than once occurrence from one or multiple studies would be needed before the sponsor could determine that there is *reasonable possibility* that the drug caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the drug treatment group than in a concurrent or historical control group

7.1.3 Unexpected AE or SAR

An AE or SAR is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., Investigator's Brochure (IB) for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious AE or SAR

An AE or SAR is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);

- Requires in subject hospitalization (>24 hours) or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.
- Potential drug induced liver injury (DILI) is also considered an important medical event.
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.
- Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

Pregnancy that occurs during the study must also be reported as an SAE.

7.2 Documentation of non-serious AEs or SARs

For non-serious AEs or SARs, documentation must begin from day 1 of study treatment and continue through the 100-day follow-up period after treatment is discontinued.

Collected information should be recorded in the electronic Case Report Forms (eCRF) for that subject. Please include a description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least monthly.

7.3 SAEs or Serious SARs

7.3.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g. SAEs related to invasive procedures such as biopsies, medication washout).

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin from day 1 of study treatment and continue through the 100-day follow-up period after treatment is discontinued.

7.3.2 Documentation and Notification

SAEs or Serious SARs must be recorded in the SAE console within Oncore™ for that subject within 24 hours of learning of its occurrence. Additionally, the Regulatory Associate and Medical Monitor must also be notified via email of all SAEs within 24 hours of learning of its occurrence.

7.3.3 Reporting

IRB Reporting Requirements:

UNC**:**

- The UNC-IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting system within 7 days of the Investigator becoming aware of the problem. These events must be reported to the sponsor within 24 hours of learning of the occurrence.

Affiliate sites:

- For affiliate sites using a local IRB of record, please submit adverse events per local IRB policy.
- For affiliate sites relying on the UNC-IRB, an aggregated list of all SAEs will be submitted to the UNC IRB annually at the time of study renewal according to the UNC IRB policies and procedures. In addition, any SAEs that qualify as an Unanticipated Problem will be entered into Oncore by the affiliate site and reported to the UNC IRB by the Multicenter Regulatory Associate using the IRB's web-based reporting system within 7 days of the Investigator becoming aware of the problem.

Pregnancy

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject or a female partner of a male subject occurring while the subject is on study, or within the period stipulated for continued contraceptive use for WOCBP (5 months) and sexually active men (6 months) after the subject's last dose of study medication should be recorded as SAEs. The female subject is to be discontinued immediately from the study for a pregnancy event.

For Affiliate sites, the pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Multicenter Project Manager immediately (within 24 hours) at CPOMultiCenter@med.unc.edu (primary route of submission) or facsimile (919) 966-4300 (back-up)). The Multicenter Project Manager will then report the event to the Funding Source (see requirements below). The female subject or the female partner of a male subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject or female partner of a male subject until completion of the pregnancy, and must document the outcome of the pregnancy (either normal or abnormal outcome) and report the condition of the fetus or newborn to the Multicenter Project Manager. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE.

Note if the female subject or female partner of a male subject has received nivolumab, the investigator must immediately notify Worldwide Safety @BMS of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures. The nivolumab IB notes that non-clinical safety findings of adverse pregnancy outcomes and infant losses in the absence of maternal toxicity have been reported. Findings in monkeys suggest a potential risk to human pregnancy if there is continued treatment with nivolumab during pregnancy.

Laboratory Test Abnormalities

The following laboratory abnormalities should be documented and reported appropriately:

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

Overdose

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

Other Safety Considerations

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

Funding Source Amgen Reporting Requirements:

Safety Data	Timeframe for Submission to Amgen
Suspected Unexpected Serious Adverse Reaction	Sent to Amgen at time of regulatory submission
Serious Adverse Events (SAEs)	Not required, unless contractually specified per study
Adverse Events not meeting serious criteria	Not required, unless contractually specified per study
Events of Interest	Not required, unless contractually specified per study
Pregnancy/Lactation	Within 10 calendar days of Sponsor awareness
Event listing for reconciliation	As specified per contract

*Specific requirements are to be outlined in the Research Agreement

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-772-6436) or Food and Drug Administration (FDA) at 1-800-FDA-1088 or www.fda.gov/medwatch.

For all studies – aggregate reports*:

Safety Data	**Timeframe for submission to Amgen**
Annual Safety Report (eg, EU Clinical Trial Directive [CTD] Annual Safety Report, and US IND Annual Report)	**Annually**
Other Aggregate Analyses (any report containing safety data generated during the course of a study)	**At time of ISS sponsor submission** to any body governing research conduct (eg, RA, IRB, etc)
Final (End of Study Report, including: • Unblinding data for blinded studies • Reports of unauthorized use of a marketed product	**At time of ISS sponsor submission** to any body governing research conduct (eg, RA, IRB, etc) but not later than 1 calendar year of study completion

*Specific requirements are to be outlined in the Research Agreement

Bristol-Myers Squibb (BMS) Reporting Requirements

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

Wordwide.safety@bms.com

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

All SAEs should simultaneously be faxed or e-mailed to BMS at:
Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

FDA Expedited Reporting requirements for studies conducted under an IND:
A sponsor (in this case the LCCC) must report any suspected adverse reaction that is both serious and unexpected to the FDA. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g. tendon rupture);
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

The sponsor must submit each IND safety report on FDA Form 3500A. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division that has the responsibility for review of the IND. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

Timing
FDA must be notified of potential serious risks within 15 calendar days after the sponsor determines the event requires reporting. FDA must be notified of unexpected fatal or life-threatening suspected adverse reactions as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information. The sponsor must be notified by the investigator within 24 hours of the event. For Multicenter trials, Lineberger is the sponsor, therefore, the Multicenter Project Manager must be notified of the SAE within 24 hours of the event. If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable is reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

Follow-up

The sponsor must promptly investigate all safety information it receives. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and as such the Multicenter Project Manager should be updated within 24 hours of the information being available via a follow-up MedWatch Form 3500A.

Notification of Investigators

The sponsor must notify all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

Process

If the sponsor deems that an event is both a serious SAR AND unexpected, it must also (in addition to Oncore) be recorded on the MedWatch Form 3500A. Unexpected adverse events or adverse reaction refers to an event or reaction that is not listed in the investigator's brochure/IND or is not listed at the specificity or severity that has been observed; or if an investigator's brochure is not required or available, is not consistent with the risk information described in the general investigation plan or elsewhere in the current IND application.

The MedWatch 3500A form and supporting documents defining the event and causality should be sent to the electronic mailbox (CPOMultiCenter@med.unc.edu; primary route of submission) (or facsimile (919) 966-4300 (back-up)) of the Multicenter Project Manager along with supporting documentation defining the event and causality. The Multicenter Project Manager will then send the report to the Funding Source. The MedWatch 3500a form can be accessed at: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm.

(Please be sure and access form 3500a, and not form 3500).

Once the UNC Principal Investigator determines an event is a serious SAR AND unexpected, the MedWatch 3500A form will be submitted to the FDA. If the event is serious, unexpected and considered to be possibly-, probably- or definitely-related to the study treatment, the Multicenter Project Manager will inform the Regulatory Associate at UNC and IND Specialist. The MedWatch form will be submitted according to LCCC SOP for safety reporting for a multi-site study.

All IND safety reports must be submitted on Form 3500A and be accompanied by Form 1571. The FDA must be notified or any unexpected or life-threatening suspected adverse reactions as soon as possible, but no later than 7 calendar days of learning of the event.

The Multicenter Project Manager will also be responsible for informing each Affiliate site of all serious and unexpected SARs reported to the FDA via fax as soon as possible.

Additional Reporting Requirements

The following additional items must be reported via IND safety report:

- *Findings from other studies.* The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk to humans exposed to the drug.
- *Findings from animal or in vitro testing.* The sponsor must report any findings from animal or *in vitro* testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity t or near the expected human exposure.
- *Increased rate of occurrence of serious suspected adverse reactions.*

Additional Guidance

Please refer to 21CFR312.32 and "Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies" for additional information and reporting requirements. All IND Safety Reports will be submitted in accordance with these regulations/guidances.

7.4 Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of subject safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC).

Meetings/teleconferences will be held at a frequency dependent on study accrual, and in consultation with the study Biostatistician. These meetings will include the investigators as well as protocol nurses, clinical research associates, regulatory associates, data managers, biostatisticians, and any other relevant personnel the principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, data collection, etc.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight (Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

The UNC LCCC Data and Safety Monitoring Committee (DSMC) will review the study on a regular (quarterly to annually) basis, with the frequency of review based on risk and complexity as determined by the UNC Protocol Review Committee. The UNC PI will be responsible for submitting the following information for review: 1) safety and accrual data including the number of subjects treated; 2) significant developments reported in the literature that may affect the safety of participants or the ethics of the study; 3) preliminary response data; and 4) summaries of team meetings that have occurred since the last report. Findings of the DSMC review will be disseminated by memo to the UNC PI, PRC, and the UNC IRB and DSMB.

8.0 STATISTICAL CONSIDERATIONS

8.1 Study Design/Study Endpoints

This study will be a prospective, single arm, multicenter, open-label phase II clinical trial investigating the combination of nivolumab and ipilimumab with panitumumab in subjects with unresectable, refractory, *KRAS*/*NRAS*/*BRAF* wild-type, microsatellite stable metastatic colorectal cancer. The primary objective of this study is to estimate the ORR (CR + PR) in these subjects at 12 weeks by RECIST 1.1 criteria. Secondary objectives include the following: estimating the ORR (CR + PR) at 12 weeks by irRECIST criteria, estimating the best response rate by both RECIST 1.1 and irRECIST criteria, estimating PFS and duration of response using both RECIST 1.1 and irRECIST criteria, estimating OS, and characterizing the safety issues associated with this regimen. Exploratory objectives involve investigating various biomarkers and peripheral blood and tumor assays.

8.2 Sample Size and Accrual

Power and sample size considerations for this study are based on the primary objective. The historical overall response rate (CR+PR) of *KRAS* wild-type mCRC to panitumumab is approximately 22%. The proposed treatment regimen is expected to increase the response rate to a clinically relevant rate of at least 35%. A Simon two-stage minimax design will be used, with an alpha=0.10, and power of 80%, to evaluate the efficacy of this treatment regimen. The null and alternative hypothesis overall response rates (CR + PR) are 22% and 35%, respectively. In the first stage, 32 evaluable subjects will be enrolled and treated. If 6 or less of these 32 first stage subjects are ‘responders’ (i.e., either a CR or a PR), the trial will be suspended and study investigators will consult with the study funding sources (BMS and Amgen) and with the DSMC about whether or not to continue accruing subjects to the study. However, if 7 subjects or more are found to be responders, another 24 evaluable subjects will be accrued for a total of at least 56 evaluable subjects. If a total of 17 (or more) responders are observed

among the total of 56 evaluable subjects, then this treatment regimen would be considered of clinical interest and therefore would justify further development.

We expect to accrue subjects at a rate of approximately 4 subjects per month. At this rate, we expect total accrual to this study to take approximately 30 months, allowing for up to 6 month assessment period for response between the first and second stages.

8.3 Toxicity Monitoring

Toxicity will be assessed using NCI CTCAE version 4.03. Subjects will be monitored for excessive toxicity over the duration of the study. A toxicity rate due to the study regimen greater than 35% would be considered unacceptable. Toxicity events that will be monitored will be those that call for discontinuation of therapy, as defined in Section 4.4.

Pocock-type boundaries will be utilized as described in Ivanova, A., et al. Biometrics. 2005; 61(2):540-5. If a toxicity boundary is reached, accrual for the study will be suspended and the Data Safety and Monitoring Committee (DSMC) will be alerted. The DSMC (in consultation with the Principal Investigator and the drug company) will evaluate the toxicity events to help determine whether or not to terminate the study.

Accrual to the trial is to be suspended if the number of protocol defined toxic events is equal to or larger than boundary in the table below.

Number of Subjects	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary	-	-	-	-	5	6	6	7	7	8	9	9	10	10	11	11	12	12	13	13
Number of Subjects	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Boundary	13	14	14	15	15	16	16	17	17	18	18	19	19	19	20	20	21	21	22	22
Number of Subjects	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
Boundary	22	23	23	24	24	25	25	26	26	26	27	27	28	28	28	29	29	30	30	31
Number of Subjects	61	62	63	64	65	66														
Boundary	31	31	32	32	33	33														

8.4 Data Analysis Plans

ORRs and best response rates will be determined using both the RECIST 1.1 and irRECIST criteria will be reported along with their corresponding 95% confidence intervals. Wilson's method will be used to calculate confidence intervals for these rates (reported as percentages). PFS and the duration of response estimates using both the RECIST 1.1 and irRECIST criteria will be calculated using the Kaplan-Meier (or product-limit) method. OS will also be calculated using the Kaplan-Meier (or product-limit) method. These time to event estimated functions will be plotted, and median time to estimates will be reported along with their 95%

confidence intervals. The confidence intervals for these time to event functions will be calculated using the standard and well known "loglog" method. If appropriate, 6, 12, and 24 month estimates for the time to event functions will also be reported.

The primary analysis will apply to the total number of evaluable subjects. Toxicity and safety information will be reported in a descriptive manner in the form of frequency tables. Toxicity will be defined through the number and frequency of treatment-emergent grade 3 and 4 toxicities as defined by National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03). Hypothesis generating exploratory analyses will be performed when appropriate sample size considerations allow. The definitions of the outcomes (or endpoints) of interest can be found in section 2.4.

9.0 STUDY MANAGEMENT

9.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

9.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent

- IRB membership list
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.
- Form FDA 1572
- Financial disclosure
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

9.3 Registration Procedures

All subjects must be registered with the LCCC CPO Multicenter Office at the University of North Carolina before enrollment to study. To register a subject call the Multicenter office at 919-966-7359 Monday-Friday 8:30 am – 5:00 pm EST. Scan and email the Multicenter Project Manager (preferred) or fax (919-966-4300) the registration form, signed informed consents, signed eligibility form and all source documents to confirm eligibility. Eligibility may be confirmed by the UNC Study Coordinator for subjects treated at UNC. When sending registration request with eligibility documentation, please allow 24 hours for source to be reviewed.

9.4 Data Management and Monitoring/Auditing

UNC LCCC will serve as the coordinating center for this trial. Data will be collected through a web based clinical research platform, OnCore®. Other study institutions will be given a password to directly enter their own data onto the web site via electronic case report forms (eCRFs). Multicenter personnel will coordinate and manage data for quality control assurance and integrity.

All data will be collected and entered into OnCore® by Clinical Research Associates (CRAs) from UNC LCCC and participating institutions. The investigators at each site will allow monitors to review all source documents supporting data entered into OnCore®. The Multicenter Data Coordinator can be reached at 919-843-2742 or 1-877-668-0683.

All data will be monitored and source data will be verified on selected subjects. Queries will be issued on an ongoing basis on all subjects. Participating sites should respond to data queries within 14 days of receipt. The LCCC compliance committee or their designee will audit trial sites every twelve months while still enrolling or subjects are still on treatment. Participating sites must send source and regulatory documents to LCCC upon request, for remote monitoring and/or audit review.

9.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

9.5.1 Emergency Modifications

UNC and Affiliate investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC or their respective institution's IRB/IEC approval/favorable opinion.

For Institutions Relying on UNC's IRB:
For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

For Institutions Relying on Their Own IRB:
For Affiliate investigators relying on their own institution's IRB, as soon as possible after the modification has been made, the implemented deviation or change and the reasons for it should be submitted to:

- To UNC Principal Investigator for agreement
- The Affiliate institution's IRB for review and approval. (Once IRB's response is received, this should be forwarded to the Multicenter Regulatory Associate).

9.5.2 Single Subject/Subject Exceptions

Eligibility single subject exceptions are not permitted for Lineberger Comprehensive Cancer Center Investigator Initiated Trials under any circumstances. Other types of single subject exceptions may be allowed if proper regulatory review has been completed in accordance with Lineberger Comprehensive Cancer Center's Single Subject Exceptions Policy.

9.5.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

For Institutions Relying on UNC's IRB:
Protocol Deviations: UNC or Affiliate personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

For Institutions Relying on Their Own IRB:
In addition to adhering to the policies regarding protocol compliance set forth by your institution's IRB, the following is also required:

Protocol Deviations: In the event a deviation from protocol procedures is identified, record the deviation in OnCore®.

Protocol Violations: Any protocol violation that occurs must be reported to your IRB per institutional policies and reported to the Multicenter Project Manager within 5 days. UNC-CH will determine if the violation affects the safety of the subject and integrity of the data. Once your institution's IRB response is received, please forward to the Multicenter Regulatory Associate.

Unanticipated Problems:
UNC
Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the Study Coordinator using the IRB's web-based reporting system.

Affiliate Sites:
Any events that meet the criteria for "Unanticipated Problems (UPs)" as defined by UNC's IRB must also be reported to the Multicenter Project Manager. The Multicenter Project Manager will report the event to the UNC IRB using the IRB's web-based reporting system. Examples of such UPs include a lost or stolen laptop computer that contains sensitive study information.

9.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the subject, a revised consent form might be required.

For Institutions Relying on UNC's IRB:
The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

For Institutions Relying on Their Own IRB:
Investigators must submit the amendment to their institution's IRB for approval. For multicenter studies, any multicenter site must submit their informed consent revisions to the Multicenter Regulatory Associate prior to submission to their IRB.

9.7 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed subject consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

9.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study subjects. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the eCRFs. Periodically, monitoring visits will be conducted, and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all eCRFs will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

10.0 REFERENCES

1. SEER Cancer Statistics Review, 1975-2011. National Cancer Institute. 2014, at http://seer.cancer.gov/csr/1975-2013/.)
2. Kopetz S, Chang GJ, Overman MJ, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol 2009;27:3677-83.
3. Vilar E, Gruber SB. Microsatellite instability in colorectal cancer-the stable evidence. Nat Rev Clin Oncol 2010;7:153-62.
4. Saridaki Z, Souglakos J, Georgoulias V. Prognostic and predictive significance of MSI in stages II/III colon cancer. World J Gastroenterol 2014;20:6809-14.
5. Sargent DJ, Marsoni S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol 2010;28:3219-26.
6. Tejpar S, Saridaki Z, Delorenzi M, Bosman F, Roth AD. Microsatellite instability, prognosis and drug sensitivity of stage II and III colorectal cancer: more complexity to the puzzle. J Natl Cancer Inst 2011;103:841-4.
7. Moriarity A, O'Sullivan J, Kennedy J, Mehigan B, McCormick P. Current targeted therapies in the treatment of advanced colorectal cancer: a review. Ther Adv Med Oncol 2016;8:276-93.
8. Strimpakos AS, Syrigos KN, Saif MW. Pharmacogenetics and biomarkers in colorectal cancer. Pharmacogenomics J 2009;9:147-60.
9. Guinney J, Dienstmann R, Wang X, et al. The consensus molecular subtypes of colorectal cancer. Nat Med 2015;21:1350-6.
10. Graham DM, Coyle VM, Kennedy RD, Wilson RH. Molecular Subtypes and Personalized Therapy in Metastatic Colorectal Cancer. Curr Colorectal Cancer Rep 2016;12:141-50.
11. Chong CR, Janne PA. The quest to overcome resistance to EGFR-targeted therapies in cancer. Nat Med 2013;19:1389-400.
12. Pylayeva-Gupta Y, Grabocka E, Bar-Sagi D. RAS oncogenes: weaving a tumorigenic web. Nat Rev Cancer 2011;11:761-74.
13. Roth AD, Tejpar S, Delorenzi M, et al. Prognostic role of KRAS and BRAF in stage II and III resected colon cancer: results of the translational study on the PETACC-3, EORTC 40993, SAKK 60-00 trial. J Clin Oncol 2010;28:466-74.
14. Comprehensive molecular characterization of human colon and rectal cancer. Nature 2012;487:330-7.
15. Allegra CJ, Rumble RB, Hamilton SR, et al. Extended RAS Gene Mutation Testing in Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal

Growth Factor Receptor Monoclonal Antibody Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update 2015. J Clin Oncol 2016;34:179-85.
16. Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol 2008;26:5705-12.
17. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in subjects with advanced cancer. N Engl J Med 2012;366:2455-65.
18. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443-54.
19. Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol 2010;28:3167-75.
20. Overman MJ KS, McDermott RS, et al. Nivolumab +/- ipilumumab in treatment of subjects with metastatic colorectal cancer with and without high microsatellite instability: CheckMate-142 interim results.: J Clin Oncol.; 2016.
21. Overman MJ, Lonardi S, Leone F, et al. Nivolumab in subjects with DNA mismatch repair deficient/microsatellite instability high metastatic colorectal cancer: Update from CheckMate 142. J Clin Oncol 2017:suppl 4S; abstract 519.
22. Tran B, Kopetz S, Tie J, et al. Impact of BRAF mutation and microsatellite instability on the pattern of metastatic spread and prognosis in metastatic colorectal cancer. Cancer 2011;117:4623-32.
23. Goldstein NI, Prewett M, Zuklys K, Rockwell P, Mendelsohn J. Biological efficacy of a chimeric antibody to the epidermal growth factor receptor in a human tumor xenograft model. Clin Cancer Res 1995;1:1311-8.
24. Vidarsson G, Dekkers G, Rispens T. IgG subclasses and allotypes: from structure to effector functions. Front Immunol 2014;5:520.
25. Schneider-Merck T, Lammerts van Bueren JJ, Berger S, et al. Human IgG2 antibodies against epidermal growth factor receptor effectively trigger antibody-dependent cellular cytotoxicity but, in contrast to IgG1, only by cells of myeloid lineage. J Immunol 2010;184:512-20.
26. Yang X, Zhang X, Mortenson ED, Radkevich-Brown O, Wang Y, Fu YX. Cetuximab-mediated tumor regression depends on innate and adaptive immune responses. Mol Ther 2013;21:91-100.
27. Botta C, Bestoso E, Apollinari S, et al. Immune-modulating effects of the newest cetuximab-based chemoimmunotherapy regimen in advanced colorectal cancer subjects. J Immunother 2012;35:440-7.
28. Srivastava RM, Lee SC, Andrade Filho PA, et al. Cetuximab-activated natural killer and dendritic cells collaborate to trigger tumor antigen-specific T-cell immunity in head and neck cancer subjects. Clin Cancer Res 2013;19:1858-72.
29. Correale P, Botta C, Cusi MG, et al. Cetuximab +/- chemotherapy enhances dendritic cell-mediated phagocytosis of colon cancer cells and ignites a highly efficient colon cancer antigen-specific cytotoxic T-cell response in vitro. Int J Cancer 2012;130:1577-89.
30. Correale P, Marra M, Remondo C, et al. Cytotoxic drugs up-regulate epidermal growth factor receptor (EGFR) expression in colon cancer cells and enhance their

susceptibility to EGFR-targeted antibody-dependent cell-mediated-cytotoxicity (ADCC). Eur J Cancer 2010;46:1703-11.
31. Pander J, Heusinkveld M, van der Straaten T, et al. Activation of tumor-promoting type 2 macrophages by EGFR-targeting antibody cetuximab. Clin Cancer Res 2011;17:5668-73.
32. Lee MS VB, McRee AJ, et al. Association between cetuximab response and differential immunolgic gene expression signatures in colorectal cancer metastases. 2016 Gastrointestinal Cancers Symposium2016.
33. Penault-IIorca F AC, Dauplat MM, et al. Response to anti-EGFR antibody panitumumab combined with standard neoadjuvant chemotherapy in triple negative breast cancer (TNBC): the immune and IGFR pathways. Cancer Research; 2013:4669.
34. Nabholtz JM, Abrial C, Mouret-Reynier MA, et al. Multicentric neoadjuvant phase II study of panitumumab combined with an anthracycline/taxane-based chemotherapy in operable triple-negative breast cancer: identification of biologically defined signatures predicting treatment impact. Ann Oncol 2014;25:1570-7.
35. Benkardino K RM, Manzoni M, et al. In vivo biological effects of panitumumab + chemotherapy in advanced colorectal cancer subjects. J Clin Oncol; 2008.
36. Larkin J, Hodi FS, Wolchok JD. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 2015;373:1270-1.
37. Hellman MD GS, Goldman JW, et al. CheckMate 012: Safety and efficacy of first-line (1L) nivolumab and ipilumumab in advanced NSCLC. J Clin Oncol; 2016.
38. Jie HB, Schuler PJ, Lee SC, et al. CTLA-4(+) Regulatory T Cells Increased in Cetuximab-Treated Head and Neck Cancer Subjects Suppress NK Cell Cytotoxicity and Correlate with Poor Prognosis. Cancer Res 2015;75:2200-10.
39. Yamaguchi T, Iwasa S, Nagashima K, et al. Comparison of Panitumumab Plus Irinotecan and Cetuximab Plus Irinotecan for KRAS Wild-type Metastatic Colorectal Cancer. Anticancer Res 2016;36:3531-6.
40. Wilke H, Glynne-Jones R, Thaler J, et al. Cetuximab plus irinotecan in heavily pretreated metastatic colorectal cancer progressing on irinotecan: MABEL Study. J Clin Oncol 2008;26:5335-43.
41. Sobrero AF, Maurel J, Fehrenbacher L, et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in subjects with metastatic colorectal cancer. J Clin Oncol 2008;26:2311-9.
42. Andre T, Blons H, Mabro M, et al. Panitumumab combined with irinotecan for subjects with KRAS wild-type metastatic colorectal cancer refractory to standard chemotherapy: a GERCOR efficacy, tolerance, and translational molecular study. Ann Oncol 2013;24:412-9.
43. Seymour MT, Brown SR, Middleton G, et al. Panitumumab and irinotecan versus irinotecan alone for subjects with KRAS wild-type, fluorouracil-resistant advanced colorectal cancer (PICCOLO): a prospectively stratified randomised trial. Lancet Oncol 2013;14:749-59.
44. Price TJ, Peeters M, Kim TW, et al. Panitumumab versus cetuximab in subjects with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. Lancet Oncol 2014;15:569-79.

45. O'Neil BH, Allen R, Spigel DR, et al. High incidence of cetuximab-related infusion reactions in Tennessee and North Carolina and the association with atopic history. J Clin Oncol 2007;25:3644-8.
46. Chung CH, Mirakhur B, Chan E, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. N Engl J Med 2008;358:1109-17.
47. Saif MW, Peccerillo J, Potter V. Successful re-challenge with panitumumab in subjects who developed hypersensitivity reactions to cetuximab: report of three cases and review of literature. Cancer Chemother Pharmacol 2009;63:1017-22.
48. Morelli MP, Overman M, Dasari A, et al. Characterizing the patterns of clonal selection in circulating tumor DNA from subjects with colorectal cancer refractory to anti-EGFR treatment. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 2014;[in press].
49. Montagut C, Dalmases A, Bellosillo B, et al. Identification of a mutation in the extracellular domain of the Epidermal Growth Factor Receptor conferring cetuximab resistance in colorectal cancer. Nature medicine 2012;18:221-3.
50. Misale S, Yaeger R, Hobor S, et al. Emergence of KRAS mutations and acquired resistance to anti-EGFR therapy in colorectal cancer. Nature 2012;486:532-6.
51. Montagut C, Bellosillo B, Gonzalez I, et al. Evolution of heterogeneous mechanisms of acquired resistance to cetuximab-based therapy in colorectal cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2014;32:suppl; abstr 3526.
52. Lee MS, Lieu CH, Overman MJ, et al. Association of prior treatment with anti-EGFR monoclonal antibodies with downregulation of circulating TRAIL and upregulation of EGFR and VEGF family ligands in metastatic colorectal cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2014;32:suppl 3; abstr 452.
53. Kjersem JB, Skovlund E, Ikdahl T, et al. FCGR2A and FCGR3A polymorphisms and clinical outcome in metastatic colorectal cancer subjects treated with first-line 5-fluorouracil/folinic acid and oxaliplatin +/- cetuximab. BMC cancer 2014;14:340.
54. Pander J, Gelderblom H, Antonini NF, et al. Correlation of FCGR3A and EGFR germline polymorphisms with the efficacy of cetuximab in KRAS wild-type metastatic colorectal cancer. Eur J Cancer 2010;46:1829-34.
55. Bibeau F, Lopez-Crapez E, Di Fiore F, et al. Impact of Fc{gamma}RIIa-Fc{gamma}RIIIa polymorphisms and KRAS mutations on the clinical outcome of subjects with metastatic colorectal cancer treated with cetuximab plus irinotecan. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2009;27:1122-9.
56. Rodriguez J, Zarate R, Bandres E, et al. Fc gamma receptor polymorphisms as predictive markers of Cetuximab efficacy in epidermal growth factor receptor downstream-mutated metastatic colorectal cancer. Eur J Cancer 2012;48:1774-80.
57. Park SJ, Hong YS, Lee JL, et al. Genetic polymorphisms of FcgammaRIIa and FcgammaRIIIa are not predictive of clinical outcomes after cetuximab plus irinotecan chemotherapy in subjects with metastatic colorectal cancer. Oncology 2012;82:83-9.
58. Zhang W, Gordon M, Schultheis AM, et al. FCGR2A and FCGR3A polymorphisms associated with clinical outcome of epidermal growth factor receptor expressing metastatic colorectal cancer subjects treated with single-agent cetuximab.

Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2007;25:3712-8.
59. Paez D, Pare L, Espinosa I, et al. Immunoglobulin G fragment C receptor polymorphisms and KRAS mutations: are they useful biomarkers of clinical outcome in advanced colorectal cancer treated with anti-EGFR-based therapy? Cancer Sci 2010;101:2048-53.
60. Geva R, Vecchione L, Kalogeras KT, et al. FCGR polymorphisms and cetuximab efficacy in chemorefractory metastatic colorectal cancer: an international consortium study. Gut 2015;64:921-8.
61. Feng Y, Roy A, Masson E, Chen TT, Humphrey R, Weber JS. Exposure-response relationships of the efficacy and safety of ipilimumab in subjects with advanced melanoma. Clin Cancer Res 2013;19:3977-86.
62. Selby MJ, Engelhardt JJ, Johnston RJ, et al. Preclinical Development of Ipilimumab and Nivolumab Combination Immunotherapy: Mouse Tumor Models, In Vitro Functional Studies, and Cynomolgus Macaque Toxicology. PLoS One 2016;11:e0161779.
63. Hellmann MD, Rizvi NA, Goldman JW, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. Lancet Oncol 2017;18:31-41.

11.0 APPENDICES

11.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol* 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

11.2 Treatment Algorithms for Nivolumab Therapy

Algorithms are presented for management of GI, renal, hepatic, pulmonary, endocrine, skin and neurological toxicities are provided. NCI-CTCAEv4.03 criteria apply as referenced in the protocol. **The algorithms are potential suggested schemes for management of potential irAEs but should only serve as a complement to investigator judgment and additional guidelines for monitoring and management of immune related toxicities.** Additionally, recommend management referring to NCCN Guidelines "Management of Immune Checkpoint Inhibitor-Related Toxicities." In cases of discrepancy between the algorithms and additional guidelines, investigator judgment should be used, and highly encourage consultation with medical monitor.

GI Adverse Event Management Algorithm

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

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

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

Renal Adverse Event Management Algorithm

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

Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	<u>If returns to baseline</u>: •Resume routine creatinine monitoring per protocol <u>If worsens:</u> •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	<u>If returns to Grade 1:</u> •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol <u>If elevations persist > 7 days or worsen:</u> •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	<u>If returns to Grade 1</u> : Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

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

Pulmonary Adverse Event Management Algorithm

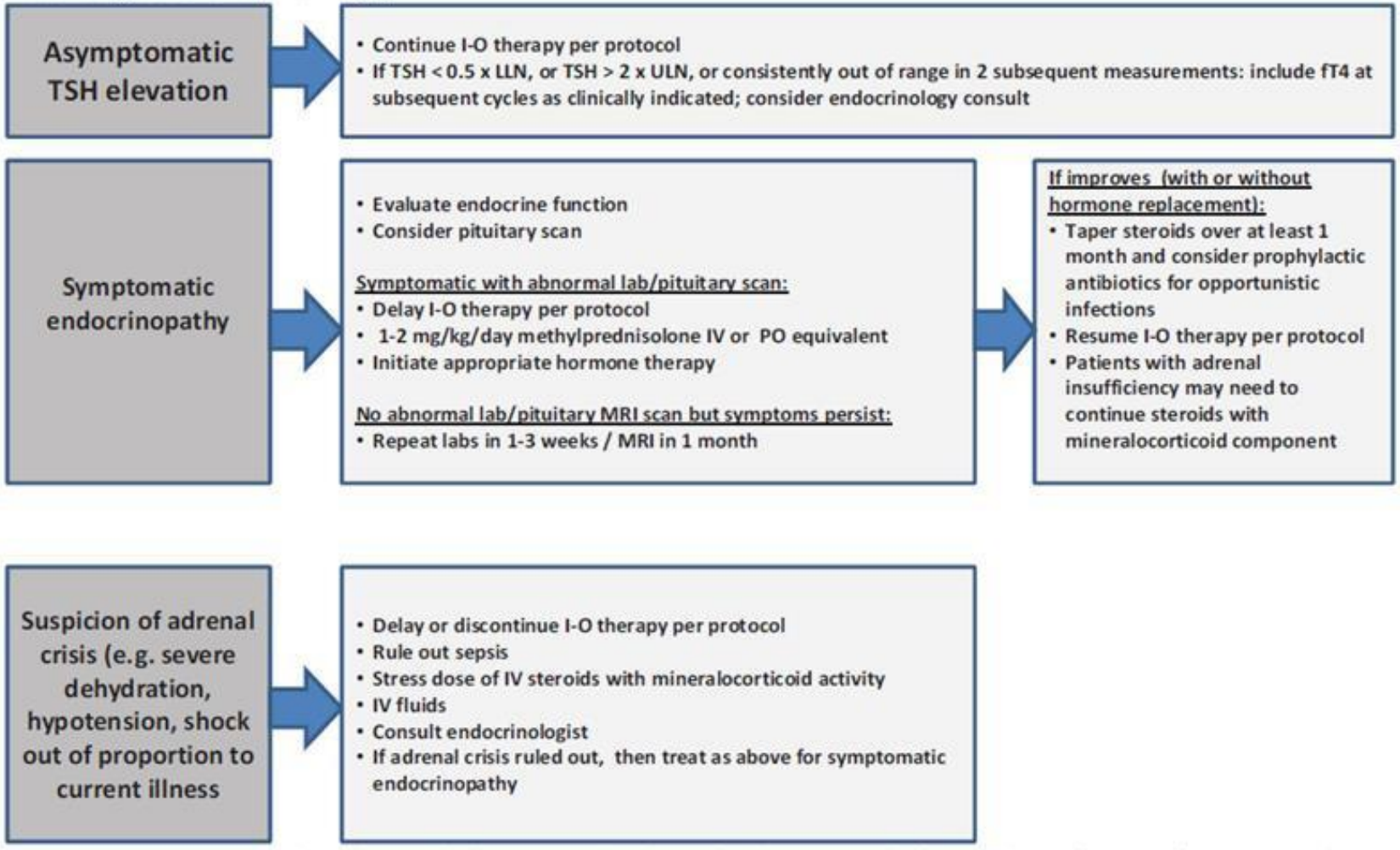
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression

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

Endocrinopathy Management Algorithm

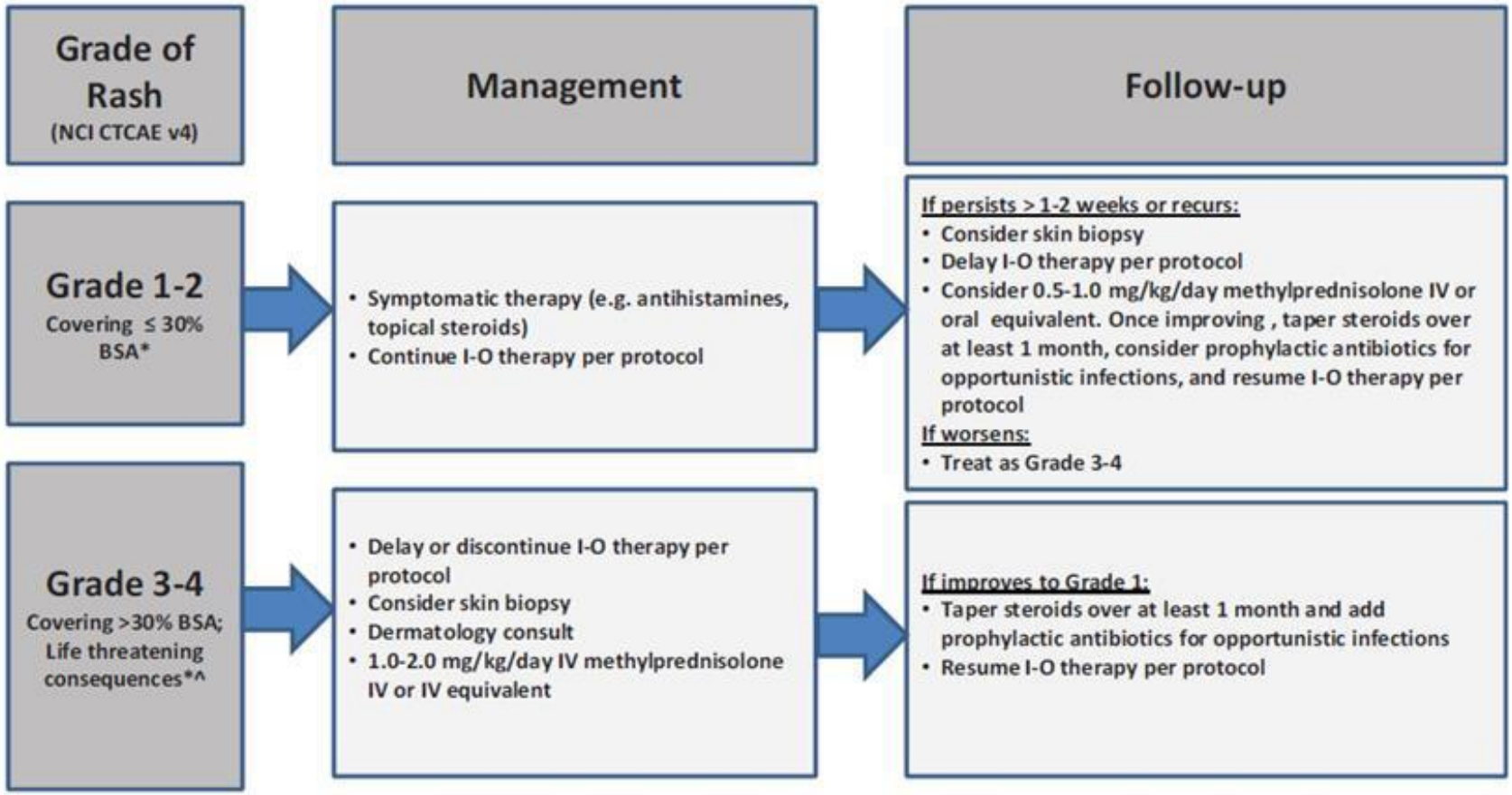
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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.

Skin Adverse Event Management Algorithm

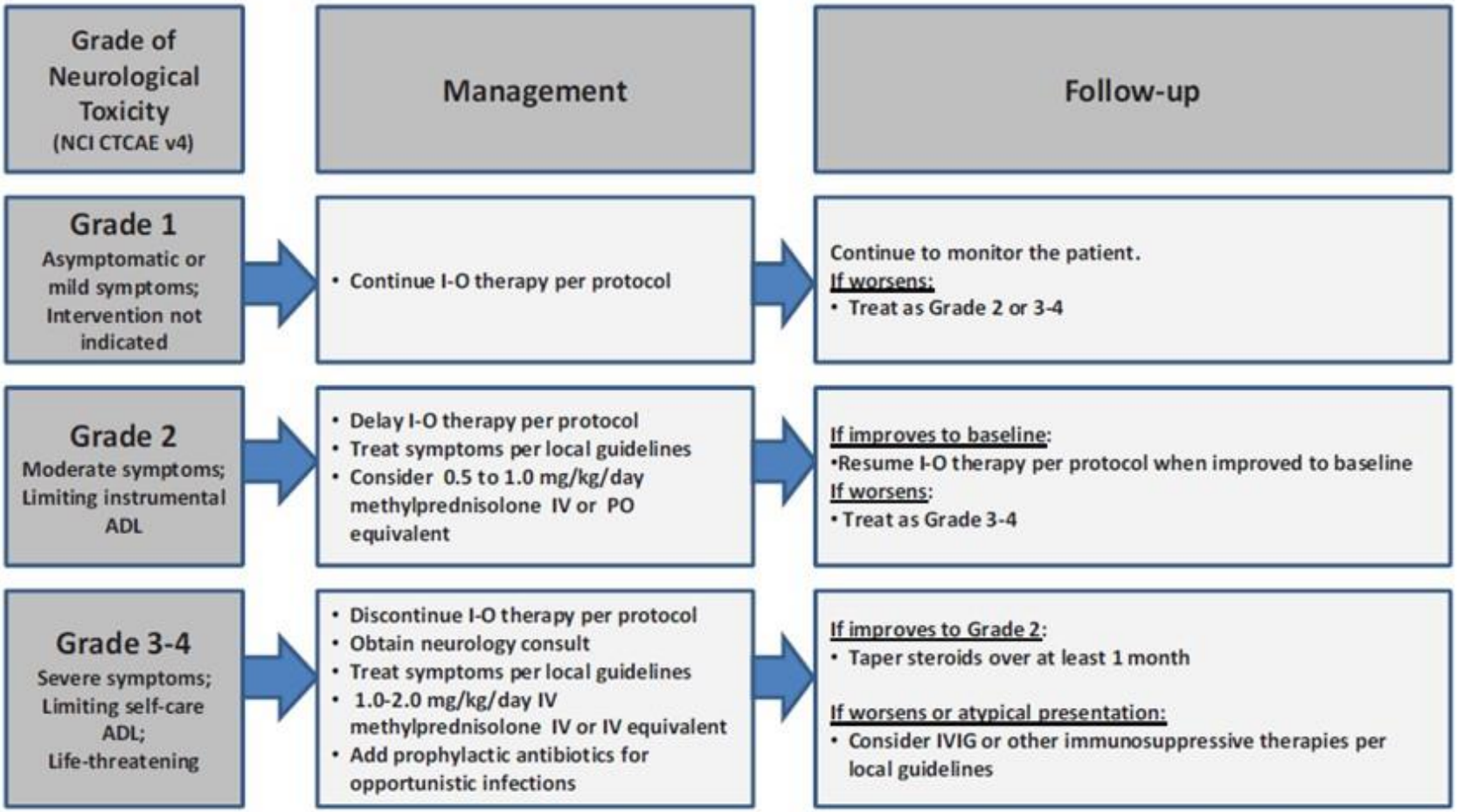
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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.

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.

11.3 Cockcroft-Gault Formula

Males:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}.$$

Females:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$