Open Label Phase II Trial of Nivolumab + Cabiralizumab (BMS-986227, FPA008) + Gemcitabine in Patients with Stage IV Pancreatic Cancer Achieving Disease Control in Response to First-line Chemotherapy (Gem CaN Trial)

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SU2C Dream Team

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Study Chair (Sponsor-Investigator)

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HRPP No: 181395
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INVESTIGATOR PROTOCOL AGREEMENT

Protocol # 181395; CA025-012
SU2C Dream Team

Title: Open Label Phase II Trial of Nivolumab + Cabiralizumab (BMS-986227, FPA008) + Gemcitabine in Patients with Stage IV Pancreatic Cancer Achieving Disease Control in Response to First-line Chemotherapy (Gem CaN Trial).

I confirm that my staff and I have carefully read and understand this protocol. I/we agree to comply with the procedures and terms of the clinical trial specified herein. In particular, I/we have agreed to:

- Abide by all obligations stated on the Form FDA 1572 and on other document(s) required by local regulatory authority.
- Comply with Good Clinical Practice (GCP) and all applicable regulatory requirements.
- Maintain confidentiality and assure security of the Sponsor (UCSD), SU2C, and BMS confidential documents.
- Obtain Institutional Review Board (IRB) approval of the protocol, any amendment to the protocol, and periodic re-approval as required, and to keep the IRB informed of any adverse events and periodically report the status of the trial to the IRB.
- Not implement any deviations from or changes to the protocol without agreement from the Sponsor and prior review and written approval from the IRB, except where necessary to eliminate an immediate hazard to the patients or for administrative aspects of the trial (where permitted by all applicable regulatory requirements).
- Assure that each patient enrolled into the trial has read, understands, and has signed the informed consent.
- Ensure that I and all persons assisting me with the trial are adequately informed and trained about the trial treatment and of their trial-related duties and functions as described in the protocol.
- Make prompt reports of serious adverse events (SAEs) and deaths within 24 hours (1 business day) of becoming aware of the event to the Worldwide.Safety@BMS.com.
- Assure access by the Sponsor, BMS, and/or FDA to original source documents.
- Prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated in the investigation.
- Arrange for the transfer of appropriate data from case histories to case report forms for the collection and transmission of data to the Sponsor.
- Retain records and documents related to this trial for at least 3 years after the completion of the trial as confirmed by the sponsor.
- Cooperate fully with any trial-related GCP audit as performed by the assurance group specified by the Sponsor, BMS, or SU2C.
  Abide by the stipulations in the Confidentiality and Financial Disclosure sections and the manuscript preparation/authorship guidelines established at the outset of the trial.

Investigator's Printed Name: _____

Investigator' Signature: _____ Date: _____

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.

UCSD Principal Investigator Name:

Hitendra Patel, MD

Printed Name

Signature Date

Participating Site Principal Investigator

Printed Name Institution

Signature Date

EXPEDITED REPORTING REQUIREMENTS

The **Study Chair** and **multi-sites to include:** University of Kansas Cancer Center and University of Pennsylvania **Principal Investigator** must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.

The **UCSD Human Research Protections Program (HRPP)** and **Moores Cancer Center Data and Safety Monitoring Board (DSMB)** must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others" (UPR).

Multi-sites: 1) University of Kansas Cancer Center and 2) University of Pennsylvania. The **Institutional Review Board (IRB) of each site** must be notified by the site principal investigator according to their local policies.

The **FDA** must be notified according to the following timelines:

· within 7 calendar days of any unexpected fatal or life-threatening adverse event with possible relationship to study drug, and

· within 15 calendar days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

SAEs, whether related or not related to study drug, overdoses, and pregnancies must be reported to BMS within 24 hours \ 1 Business Day of becoming aware of the event.

SAEs must be recorded on either CIOMS, MedWatch, or approved site SAE form.

Pregnancies must be reported and submitted to BMS on any of the following form(s):

1. MedWatch or, CIOMS or
2. BMS Pregnancy Surveillance Form or,
3. Approved site SAE form

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1 609-818-3804

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours \ 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

Refer to protocol section 6.2. Adverse Events for further details.

Glossary of Abbreviations	
ADL	Activities of Daily Living
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
APC	Antigen-Presenting Cells
AST	Aspartate Aminotransferase
BMS	Bristol-Myer Squibb
BSA	Body Surface Area
CA-125	Cancer antigen 125
CA19-9	Carbohydrate antigen 19-9
CBC	Complete Blood Count
CEA	Carcinoembryonic Antigen
cHL	Classical Hodgkin's Lymphoma
CK	Creatine Kinase
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CSF1	Colony Stimulating Factor 1
CSF-1R	Colony Stimulating Factor 1 Receptor
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group (CTFG)
DCR	Disease Control Rate
DHHS	Department of Health and Human Services
DLT	Dose-Limiting Toxicities
DSMP	Data Safety Monitoring Plan
ECG	Electrocardiogram
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End of Treatment
ER	Exposure-Response
ERC	Ethical Review Committee
ESR	Expedited Safety Report
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FSH	Follicle Stimulating Hormone
FU	Follow-Up
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GSEA	Gene Set Enrichment Analysis
HBsAg	Hepatitis B Surface Antigen
HCV RNA	Hepatitis C Virus RNA
HIV	Human Immunodeficiency Virus
HRT	Hormonal Replacement Therapy

IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
iCPD	Confirmed Progression
INR	International Normalized Ratio
I-O	Immuno-Oncology
irAE	Immune-Related Adverse Event
iRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
IRB	Institutional Review Board
IUD	Intrauterine Device
iUPD	Unconfirmed Progression
IUS	Intrauterine Hormone-Releasing System
IV	Intravenous
LDH	Lactate Dehydrogenase
MRI	Magnetic Resonance Imaging
MSS	Microsatellite Stable
Nab	Nanoparticle albumin bound
NCI	National Cancer Institute
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PDA	Pancreatic Ductal Adenocarcinoma
PFS	Progression Free Survival
PK	Pharmacokinetic
PR	Partial Response
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PVNS	Pigmented Villonodular Synovitis
RA	Rheumatoid Arthritis
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SD	Stable Disease
SgRNA	Singe guide RNA
SOC	Standard of Care
SU2C	Stand Up to Cancer
SUSAR	Suspected, Unexpected Serious Adverse Reaction
TAM	Tumor-Associated Macrophages
TB	Mycobacterium tuberculosis
TGen	Translation Genomic Research Institute
TMB	Tumor Mutational Burden
TME	Tumor Microenvironment
TKI	Tyrosine Kinase Inhibitor
ULN	Upper Limit of Normal
WOCBP	Women of Childbearing Potential

TRIAL SCHEMATIC

Patients with stage IV pancreatic cancer who have achieved disease control in response to first line chemotherapy, defined as :

Must have obtained a best response of at least stable disease (SD) or partial response (PR) for a period of at least 2 months with no further shrinkage of ≥ 20% on imaging scans.

N=15

Cabira+ nivo+ gem 0 6 wks 6 mos

Optional Biop

Optional Biopsy

CA 19-9 (or CEA or CA-125 for not expressers of CA19-9) q 4 weeks
CT scan q 8 weeks

Patients continue on treatment until disease progression.

*Biopsy at C2 D15 (-3 days, +10 days) unless patient has clear progression of their disease and then biopsy to be obtained at time of progression.

Nivolumab 480 mg IV on day 1 Q4W

Cabiralizumab 4 mg/kg IV on days 1 and 15 Q4W

Gemcitabine 1000 mg/m2 IV on days 1, 8, and 15 Q4W

Treatment commences no less than 2 weeks and no more than 4 weeks after completing first line chemotherapy

TRIAL SYNOPSIS

Title and No.: SU2C Dream Team : Open Label Phase II Trial of Nivolumab + Cabiralizumab (BMS-986227, FPA008) + Gemcitabine in Patients with Stage IV Pancreatic Cancer Achieving Disease Control in Response to First-line Chemotherapy (Gem CaN Trial).

Source of Funding:
Funding Provided by Stand Up To Cancer **(**SU2C) Dream Team with drug provided by Bristol-Myer Squibb (BMS)

Consulting Investigators:

David Propper, MD
St Bartholomew's Hospital, London, UK

Lead Scientific Investigator:
Tannishtha Reya, PhD
University of California San Diego, School of Medicine

Trial Sites:

1. Hitendra Patel, MD , Andrew Lowy, MD: UCSD Moores Cancer Center, San Diego, CA
2. Peter O'Dwyer, MD University of Pennsylvania, Philadelphia, PA
3. Anup Kasi, MD University of Kansas Cancer Center, Kansas City, KS
4. St. Bartholomew's Hospital, London, UK

Clinical Phase: Phase II, open-label trial

Study Duration: Total duration of the trial will be about 18 months.

Objectives:

Primary: To estimate Progression Free Survival (PFS rates) at 6 months by RECIST1.1 in patients with stage IV pancreatic adenocarcinoma who have achieved disease control in response to first line chemotherapy when subsequently maintained on a combination regimen of cabiralizumab (FPA008)+ nivolumab + gemcitabine.

Secondary:

1. To evaluate safety and tolerability of the combination of nivolumab + cabiralizumab (FPA008) + gemcitabine

2. To evaluate PFS over the course of the study, overall survival (OS), and disease control rates at 6 months in patients administered the combination of nivolumab +cabiralizumab (FPA008) + gemcitabine. Disease control is defined as being with stable disease (SD) or partial response (PR) for a period of at least 2 months.

Exploratory:

1. To evaluate differences in disease progression outcomes according to iRECIST vs. RECIST 1.1 criteria (Appendix 5).

2. To explore potential biomarkers that may help predict response to treatment in both tumor and blood.
No. Patients: Stage 1: 8 subjects. The trial will be terminated at Stage 1 if none of the 8 subjects have a defined response; otherwise it will continue to Stage 2. Stage 2: 7 subjects. Total of 15 subjects. The recruitment period is anticipated to be 14-21 months. Total duration of study anticipated to be 20-27 months.
Name, dose of drugs: ☐ Nivolumab - 480 mg IV on day 1 Q4W ☐ Cabiralizumab (BMS-986227, FPA008) - 4 mg/kg IV on days 1 and 15 Q4W ☐ Gemcitabine - 1000 mg/m2 IV on days 1, 8, and 15 repeated Q4W
Treatment Plan: Nivolumab + cabiralizumab + gemcitabine
Patient Population: Patients with stage IV pancreatic cancer who have achieved disease control, defined as: must have obtained stable disease (SD) or partial response (PR) for a period of at least 2 months with no further shrinkage of ≥ 20% on imaging scans on prior first-line chemotherapy for their metastatic disease.
Endpoints: **Primary:** Progression free survival at 6 months since start of study treatment assessed based on RECIST 1.1 criteria. **Secondary:** Adverse events rates, according to grade and body system. The study will use the CTCAE version 5.0 (http://ctep.cancer.gov/reporting/ctc.html) for reporting of all grade 3-4 adverse events. • Overall survival and PFS over the course of the study • Disease control rate

Inclusion criteria:

1. Be willing and able to provide written informed consent for the trial. Participants must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal participant care.

2. Be ≥ 18 years of age on day of signing informed consent.

3. Histologically or cytologically confirmed pancreatic adenocarcinoma with metastasis, who have achieved disease control on prior first-line chemotherapy for their metastatic disease, defined as: Must have obtained at least stable disease (SD) or a partial response (PR) for a period of at least 2 months with no further shrinkage of ≥ 20% on imaging scans. ***Note:*** *Patients that have had prior chemotherapy as adjuvant or neoadjuvant therapy are permitted.*

4. Must have been off their prior cytotoxic regimen a minimum of two weeks but no more than four weeks from initiating trial treatment on C1/D1 (May not exceed 5 weeks).

5. Measurable disease by RECIST 1.1.

6. ECOG performance status of 0 or 1.

7. Demonstrate adequate organ function as defined in Table 1.

8. Vitamin D level ≥ 20ng/dL ***Note:*** Vitamin D supplementation is allowed. Proposed dose: 100,000 loading dose. Followed by 50,000 units 3 times a week for 2 week. Recheck level. Final dosing for supplementation is deferred to treating physician. Vitamin D supplementation throughout study treatment is allowed.

9. Able to submit an archival tumor specimen (primary or metastatic site). Patients with cytology only that do not have adequate archived tumor specimen available, will require a baseline biopsy.

10. *Optional Biopsy:* A discussion to be documented with trial investigator at screening regarding the purpose of the optional tissue collection from a newly obtained core or excisional biopsy of a tumor lesion at baseline and a second biopsy 7 weeks (C2/D15) after starting trial treatment, or at time of disease progression (refer to section 6.1.2.8), unless tumor is considered inaccessible or biopsy is otherwise considered not in the patients' best interest. *Participation in this trial is not contingent on patient consenting to optional tumor biopsies.*

11. Women of childbearing potential (WOCBP) must not be breastfeeding and must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study treatment.

12. WOCBP must agree to follow protocol specified method(s) of contraception (Section 4.3.4) for the duration of treatment with study treatment(s) and for a total of 6 months posttreatment completion. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, but still must undergo pregnancy testing as described in this section 4.3.5.

13. Males who are sexually active with WOCBP must agree to follow protocol specified method(s) of contraception (Section 4.3.4) for the duration of treatment with study treatment(s) and for a total of 7 months posttreatment completion. In addition, male participants must be willing to refrain from sperm donation during this time. Azoospermic males are exempt from contraceptive requirements.

Exclusion criteria:

1. Is currently participating and receiving trial therapy or has participated in a trial of an investigational agent and received trial therapy or used an investigational device within 3 weeks of the first dose of trial treatment.

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

3. Has a known history of active TB (*Mycobacterium tuberculosis*).

4. Microsatellite unstable patients as assessed by IHC for MMR protein

5. Hypersensitivity to cabiralizumab, nivolumab, or gemcitabine or any of its excipients.

6. Previous malignancies (except non-melanoma skin cancers, and in situ bladder, gastric, colorectal, endometrial, cervical/dysplasia, melanoma, or breast cancers) unless complete remission was achieved at least 2 years prior to study entry and no additional therapy is required during the study period.

7. Evidence of central nervous system (CNS) metastasis (negative imaging study, if clinically indicated, within 4 weeks of study treatment).

8. Participants with active, known, or suspected autoimmune disease. Participants with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, euthyroid participants with a history of Grave's disease (participants with suspected autoimmune thyroid disorders must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid stimulating immunoglobulin prior to first dose of study treatment), psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
9. Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study treatment administration except for adrenal replacement steroid doses ≤ 10 mg daily prednisone equivalent in the absence of active autoimmune disease. Note: Treatment with a short course of steroids (< 5 days) up to 7 days prior to initiating study treatment is permitted.
10. Current or history of clinically significant muscle disorders (e.g., myositis), recent unresolved muscle injury, or any condition known to elevate serum CK levels.
11. Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:
    - Myocardial infarction or stroke/transient ischemic attack within the past 6 months.
    - Uncontrolled angina within the past 3 months.
    - Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes).
    - History of other clinically significant heart disease (e.g., cardiomyopathy, congestive heart failure with New York Heart Association functional classification III to IV, pericarditis, significant pericardial effusion, or myocarditis).
    - Cardiovascular disease-related requirement for daily supplemental oxygen therapy.
12. Prior organ allograft or allogeneic bone marrow transplantation.

13. Any major surgery within 4 weeks of study treatment. Participants must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study treatment.

14. All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v5.0 or baseline before administration of study treatment. Participants with toxicities attributed to prior anti-cancer therapy that are not expected to resolve and result in long lasting sequelae are permitted to enroll. Patients with ≤ grade 2 neuropathy may qualify for this trial.

15. Evidence of uncontrolled, active infection, requiring parenteral anti-bacterial, anti-viral or anti-fungal therapy ≤ 7 days prior to administration of study medication.

16. Any uncontrolled inflammatory GI disease including Crohn's Disease and ulcerative colitis.

17. Transfusion completed within 72 hours prior to first dose of study drug administration.

18. Concomitant use of statins while on study. However, a participant using statins for over 3 months prior to study drug administration and in stable status without CK rise may be permitted to enroll.

19. Non-oncology vaccine therapies for prevention of infectious diseases (eg, human papilloma virus vaccine) within 4 weeks of study drug administration. The inactivated seasonal influenza vaccine can be given to participants before treatment and while on therapy without restriction. Influenza vaccines containing live virus or other clinically indicated vaccinations for infectious diseases (ie, pneumovax, varicella, etc) may be permitted, but must be discussed with the Sponsor and may require a study drug washout period prior to and after administration of vaccine.

20. Participants with abnormal serum chemistry values, which in the opinion of the investigator is considered to be clinically significant, will be excluded from the study. This will include participants who show clinical signs and symptoms related to their abnormal serum chemistry values, as well as participants whose serum chemistry values are asymptomatic but clinically significant (e.g, hypokalemia or hyponatremia).

21. Evidence of coagulopathy or bleeding diathesis.

22. Treatment with botanical preparations (e.g., herbal supplements, including potential drugs of abuse, or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment.

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

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

25. Has received prior therapy with a CSF-1R pathway inhibitors, anti-PD-1, anti-PD-L1, anti PD-L2, anti-CTLA-4.

26. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected). Note: Participants with positive hepatitis C antibody and negative quantitative hepatitis C by PCR are eligible.

27. Female who is pregnant or breast-feeding.

28. Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and Sponsor approval is required.

Statistical Methods: The primary endpoint for this clinical trial is progression free survival . The primary tumor assessment will be evaluated by RECIST 1.1 at 6 months. Without maintenance therapy, 96%[8] of patients are expected to progress by 6 months. A Simon's two stage optimal design is applied. Accrual will be held for interim efficacy analysis when the first 8 patients are accrued. This design will have an 80% power to reject the null hypothesis that PFS6 is ≤4% and conclude that the true PFS rate at 6 months is > 4%, if the observed PFS rate is 22%, at 10% significance level. Secondary safety and efficacy analyses will also be performed. Please refer to section 8 for more details.
Study accrual may also be held for safety reasons, please refer to section 4.6 for more details.

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TABLES

1.0 BACKGROUND AND RATIONALE

1.1 Overview

Pancreatic cancer continues to be a very lethal disease. It is estimated that in 2018, 55,440 Americans will be diagnosed with pancreatic ductal adenocarcinoma (PDA), and 44,330 will die from the disease. This makes pancreatic cancer the third leading cause of death from cancer in the US.[1]

Furthermore it is projected that by 2030, PDA will be the second leading cause of death from cancer in the US. Worldwide, PDA is the twelfth most common cancer, accounting for an estimate of > 300,000 deaths a year. [2]

Detection of pancreatic cancer has been notoriously very late in the disease and therefore the 5-year survival rate is only 8%. Right now, the only potential cure for pancreatic cancer is surgical resection (if the disease is caught early). However only about 20% of PDA patients are eligible for potentially curable resection and unfortunately most (> 80%) have reoccurrence of their cancer within 2 years of resection, and those recurrences are almost universally fatal. [3,4]

But there is some hope. Recently there are regimens that actually improve survival for patients with advanced stage IV PDA. Conroy and colleagues developed the Folfirinox regimen, which in a large randomized trial improved survival over gemcitabine as a single agent.[5] Von Hoff and colleagues developed the nanoparticle albumin (nab) associated paclitaxel plus gemcitabine regimen which improved survival over single agent gemcitabine again in a single randomized trial.[6] Even more recently Jameson and colleagues have presented a combined regimen of nab-paclitaxel + gemcitabine + cisplatin in a small 24 patient phase Ib/II trial that gave a response rate of 71% with 2 patients having complete response and a median survival of 16+ months.[7]

With the greater chance of patients with advanced pancreatic cancer achieving disease control, there is a new challenge – maintaining that control. The challenges of maintaining control include:

- Cumulative toxicities of the treatment regimens prevent continuance of the chemotherapeutic regimen.

- Patients achieve a maximum amount of tumor shrinkage but that shrinkage often stops after a partial response (PR) is reached, so the patient may no longer benefit from that regimen or resistance may develop.

- Patients get tired of the treatment regimen and want a rest

1.2 Rationale For Maintenance Regimens

In patients with stage IV pancreatic cancer, 96% of those patients who achieve disease control with first line cytotoxic chemotherapy progress within 6 months. Chemotherapy can generally not be continued because of cumulative toxicities. Many clinicians however choose to continue treatment with gemcitabine or other agents such as capecitabine after disease control and withdraw other cytotoxic agents due to cumulative toxicities. The effect of this on progression free survival is unknown.

The first randomized trial to address the role of maintenance therapy in metastatic pancreatic cancer was completed by Reni and colleagues (Reni M. et al. 2013).[8] In this phase II randomized maintenance trial, 56 patients who previously had positive optimal response to chemotherapeutic regimens (no progression after 6 months of chemotherapy) were randomized to either observation or treatment with the tyrosine kinase inhibitor (TKI) sunitinib. The results were impressive: 96% of patients had progression after 6 months in the observation arm, while only 78% progressed on sunitinib ($p = 0.01$), 2-year survival was 23% in sunitinib arm versus 7% in the observation arm ($p=0.18$). This important trial demonstrates that a maintenance approach is promising and should be further explored in patients with advanced pancreatic cancer.

Tumor-associated macrophages, TAMs, play an important role not only in tumor progression and metastasis but also in resistance to chemotherapy and radiotherapy (De Palma and Lewis, 2013; Qian and Pollard, 2010). [9, 10] Pre-clinical models have elucidated the critical role of TAMs in cancer development, progression and metastasis (Denardo et al., 2011; Mantovani et al., 2017; Nielsen et al., 2016; Xu et al., 2013)[11,12, 13, 14] Signaling through the cellular receptor for CSF-1, CSF-1R, promotes the differentiation of myeloid progenitors into populations of monocytes, macrophages, dendritic cells, and osteoclasts. Several therapeutic applications to impair recruitment or to readjust their behavior are currently being evaluated (Cannarile et al., 2017; Mantovani et al., 2017). [12, 15]

Pancreatic cancer is known to be associated with TAM infiltration and higher TAM infiltration is in turn associated with worse prognosis, suggesting that suppressed immune response contributes to tumor progression in this patient population. The preclinical studies detailed below, evaluated the impact of CSF-1R inhibition in primary KPC tumor cells.

The addition of cabiralizumab as part of a maintenance regimen is based on our preclinical data that the stem cell population within pancreatic cancer that are preferentially tumorigenic and highly drug resistant to cytotoxic therapy, are in fact, directly dependent on CSF-1R, and that its inhibition in these cells leads to significant impairment of pancreatic cancer growth. An added benefit of this regimen is that cabiralizumab also targets CSF-1R-dependent TAMs.

In this proposed trial we wish to evaluate the combination regimen of gemcitabine, CSF- 1R and PD-1 blockade on progression free survival in patients with stage IV pancreatic cancer who achieved disease control following first line chemotherapy.

1.3 Preclinical Support

Cancer stem cells are capable of unlimited self-renewal, and generate the rest of the cancer cells with more limited proliferative capacity. Importantly, pancreatic ductal adenocarcinoma (PDA) closely follows a stem cell paradigm, displaying a clear hierarchical organization, with stem cells preferentially driving tumor progression, metastasis and chemoresistance. Further, pharmacologic or genetic elimination of this population results in increased survival in mouse models, demonstrating the functional relevance of this population for pancreatic cancer growth *in vivo*. These data collectively indicate that stem cells within pancreatic cancer are critical drivers of disease progression and drug resistance, and suggest that development of effective strategies to eradicate these cells could lead to more durable treatment responses. Thus, we have focused on defining the dependencies of pancreatic cancer stem cells in order to identify their vulnerabilities and identify new targets for therapy.

Mapping stem cell dependencies in pancreatic adenocarcinoma

We have previously reported the development of a novel GFP-reporter "knock-in" mouse that visually identifies cells expressing the stem cell gene Msi2 (Msi2-GFP). Using this reporter strain, we demonstrated that Msi2 reporter+ cells possess cancer stem cell features and are responsible for tumor initiation, propagation and drug resistance in a genetically-engineered mouse model of pancreatic cancer (*Kras*$^{LSL\text{-}G12D/+}$; *p53*$^{f/f}$; *Ptf1a*$^{Cre/+}$, referred to here as "KPC") (Figs. 1 and 2). This work is consistent with that of others. This indicated that the Msi2 reporter KPC mice would be a particularly unique and powerful tool for tracking and understanding of cells that preferentially harbor capacity for drug resistance and tumor re-growth.

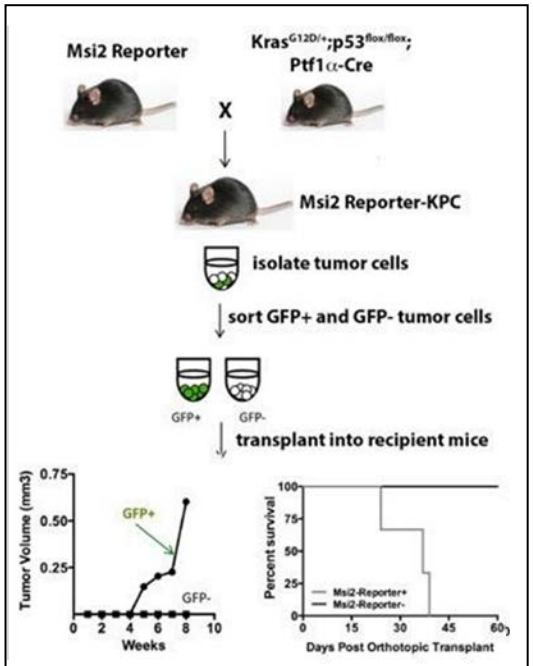

Figure 1. Msi2+ tumor cells have preferential capacity for tumor initiation. Bottom left panel: flank transplants; Bottom right panel: orthotopic transplants.

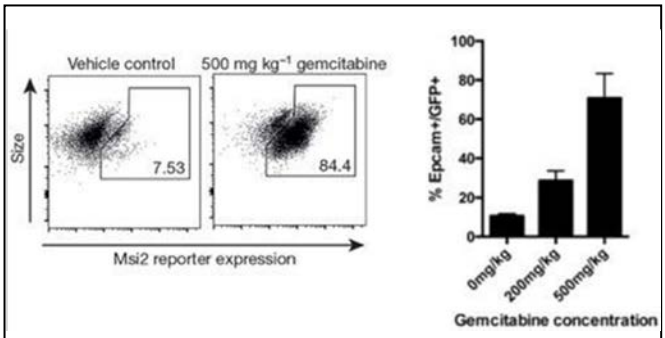

Figure 2. Cancer stem cells from KPC mice are highly resistant to gemcitabine *in vivo*.

To define the epigenetic and molecular landscape that functionally maintains the aggressive and drug-resistant stem cell state, pancreatic cancer stem cells were isolated and analyzed from primary Msi reporter KPC tumors. This showed that KPC stem cells are distinct from non-stem cells at the global transcriptional level, and driven by the differential expression of over 1000 genes.

The landscape that defined the stem cell state was markedly biased towards developmental and stem cell signals, and preferentially dormant. Consistent with their ability to survive chemotherapy and drive tumor regrowth, the stem cells also shared signatures with multiple relapsed cancers including cancer of the breast, liver, and colon. In context of immune evasion signature, it is important to note that the RNA Seq analysis also identified PDL1 expression in both stem and non-stem cells. The fact that the non- stem cell fraction had 10 fold greater expression may suggest that PDL1 blockade could be particularly useful in targeting the bulk of the tumor. In the event that stem cells are less responsive to PD1/PDL1 blockade, the work described below focused on identifying stem cell dependencies that could be exploited to reduce disease progression (Unpublished data, confidential).

To identify programs that are functionally critical for conferring the stem cell state, we complemented the transcriptomic approaches above with a genome-wide CRISPR screen. Specifically, we established independent primary cell lines from Msi2-KPC mice, and performed CRISPR screens across these replicates with mulitplexed assays to identify genes essential for pancreatic cancer stem cell growth. This unbiased approach allowed us to effectively screen the entire mouse genome using the GeCKO V2 CRISPR library, which contains 6 sgRNA for each gene in the mouse genome, 4 sgRNA targeting each of ~4000 miRNA, and >2000 control non-targeting sgRNA for a total of 130,000 guides.

An in depth integrated bioinformatics analysis on datasets from the RNA-Seq and CRISPR-based functional genomics screens unexpectedly identified a network of cytokines and other immunoregulatory signals as controlling cancer stem cells. This included the cytokine receptor CSF-1R (ligands include CSF-1 and IL-34), which has not previously been implicated as a direct regulator of cancer cell or cancer stem cell growth (Unpublished data, confidential. Given these findings, we tested whether blocking CSF-1R signaling would inhibit tumor cell growth *in vitro*. Tumor cells with shRNA against CSF-1R or IL-34 led to a significant reduction in anchorage independent growth and sphere formation in vitro. Further, inhibition of CSF-1R in the tumor cells led to a marked slowing of tumor growth in in vivo flank transplants. These data suggest a direct impact of CSF-1R signaling on cancer stem cell maintenance specifically, and tumor growth more generally (Unpublished data, confidential).

Finally, since signaling through CSF-1R also promotes the differentiation of myeloid progenitors, including tumor-associated macrophages (which play a critical role in cancer development, progression and metastasis), several therapeutic applications to impair recruitment or readjust their behavior are currently being evaluated. Work from other members of our team in GEM models indicates that macrophages play an important role in maintaining established PDAC, and inhibition of macrophage through CSF-1R blockade results in an enhanced T cell immune response. [16] Thus collectively, our findings raise the possibility that targeting this pathway could have a compound effect on cancer stem cells to improve remissions and on reducing immunosuppression, leading to reduced tumor burden and improved survival in pancreatic cancer patients.

1.4 Cabiralizumab (BMS-986227, FPA008)

For more detailed information or background on cabiralizumab, please refer to the cabiralizumab IB (BMS, 2018).[17]

Cabiralizumab is a recombinant, humanized immunoglobulin (Ig) G4 (IgG4) monoclonal antibody (mab) that binds to the human CSF-1R. Binding of cabiralizumab to CSFR1 antagonizes binding of CSF1 and IL34, thereby preventing activation of CSF-1R.

Cabiralizumab inhibits both CSF1 and IL34-induced CSF-1R phosphorylation in a cell line engineered to overexpress CSF-1R (CHO-CSF-1R), demonstrating that cabiralizumab blocks the activation of ligand-induced CSF-1R signaling pathways. Cabiralizumab also inhibits CSF1 and IL34-induced proliferation and survival of peripheral blood monocytes in vitro, demonstrating that cabiralizumab inhibits not only the initiation of CSF1 and IL34 signaling pathways but also the subsequent physiologic responses of primary human monocytes to these ligands.

CSF-1R is expressed on cells of the monocyte/macrophage lineage, and signaling through CSF-1R via its ligands, CSF1 and IL34, supports differentiation, maintenance, and function of monocytes, macrophages, and osteoclasts. TAMs are among the most abundant immune cell types in the TME. Substantial evidence suggests that TAMs are polarized toward an anti- inflammatory phenotype (M2 TAMs) and through both cell surface inhibitors and soluble factors, such as immunosuppressive cytokines, playing a major role in inhibiting anti-tumor immune responses.[12] CSF1 is a major survival factor for TAMs, and targeting CSF-1R through cabiralizumab should reduce TAM-mediated immune suppression, resulting in strengthening the anti-tumor response to immunotherapy. Therefore, a drug that inhibits CSF-1R should limit the immunosuppressive influence of TAMs on the TME and could be complementary and augment current cancer therapies.

1.4.1 Cabiralizumab Clinical Summary

The clinical summary of safety and efficacy is based on five clinical studies. Cabiralizumab was evaluated in 1 completed study (Study FPA008-001) and is currently being evaluated in 4 ongoing studies (Study FPA008-002, Study FPA008-003, Study CA025001, and Study CA025006). A summary of these studies is described below.

Overall, the combination of cabiralizumab and nivolumab appears to be well tolerated, with a safety profile similar to that of the individual components, and the frequency and types of immune-mediated AEs appear similar across multiple types of tumors. Alteration in liver enzymes (eg, AST, ALT, and CK) in the absence of changes in bilirubin and periorbital oedema have been observed across multiple trials as a consequence of the depletion of tissue-infiltrating macrophages mediated by cabiralizumab.

The combination of cabiralizumab and nivolumab with or without chemotherapy as evaluated in the preliminary safety cohort in Study CA025006 is well tolerated. Across all studies, a total of 137 subjects were treated with cabiralizumab monotherapy, and 302 subjects were treated with cabiralizumab in combination with nivolumab, with or without chemotherapy.

Study FPA008-001 evaluated the safety of cabiralizumab as single or double ascending doses in 48 healthy volunteers (36 received cabiralizumab and 12 received placebo). This study also evaluated the safety and efficacy of cabiralizumab administered as two or three doses, 14 days apart, in 18 rheumatoid arthritis (RA) subjects. This study has been completed. Thirty six healthy volunteers and 18 RA subjects received cabiralizumab with no dose-limiting toxicities (DLTs) reported and no unexpected treatment-related adverse events (AEs) reported from RA subjects treated with three doses up to 6 mg/kg.

Study FPA008-002 is evaluating the safety and efficacy of cabiralizumab monotherapy for 6 months in approximately 40 subjects with pigmented villonodular synovitis (PVNS). Study FPA008-002 is currently ongoing and is evaluating cabiralizumab as monotherapy in subjects with PVNS. Details relating to safety are included in the latest version of the cabiralizumab IB (BMS, 2018).[17]

Study FPA008-003 is evaluating the safety and efficacy of cabiralizumab as monotherapy and in combination with nivolumab in approximately 295 subjects with advanced cancers.

As of the data cutoff date of 02-Jul-2018, a total of 312 subjects have been treated in Study FPA008-003; 24 subjects have been treated in the Phase 1a dose-escalation monotherapy cohorts, 16 subjects have been treated in the Phase 1a dose-escalation combination cohorts, and 272 subjects have been treated in the Phases 1a and 1b dose-expansion combination cohorts. A total of 265 subjects across the study were treated with the recommended dose of 4 mg/kg cabiralizumab + 3 mg/kg nivolumab Q2W, and the overall safety of these subjects is reported independently.

As of 02-Jul-2018, AEs have been experienced by 264 of 265 (99.6%) subjects treated with 4 mg/kg cabiralizumab + 3 mg/kg nivolumab Q2W across multiple cohorts. Treatment-related AEs were experienced by 245 of 265 (92.5%) subjects. The most commonly reported (> 17% of subjects) treatment-related AEs included blood creatine phosphokinase increased (122 [46.0%] subjects), periorbital oedema (115 [43.4%] subjects), fatigue (102 [38.5%] subjects), AST increased (100 [37.7%] subjects), ALT increased and amylase increased (51 [19.2%] subjects each), rash (50 [18.9%] subjects), and pruritus (47 [17.7%] subjects). Grade 5 treatment-related AEs were experienced by 3 (1.1%) subjects and included acute respiratory failure (2 [0.8%] subjects) and respiratory distress (1 [0.4%] subject). Details relating to safety are included in the latest version of the cabiralizumab IB (BMS, 2018).

Cabiralizumab-related ≥ Grade 3 AEs in Phase 1b were predominantly enzyme elevations of CK (14 Grade 3 and 14 Grade 4 events), LDH (one Grade 3 and one Grade 4 event), Alkaline phosphate ([ALP] two Grade 3 events), ALT (two Grade 3 events), and AST (10 Grade 3 events). Other related AEs that were ≥ Grade 3 and reported in 2 or subjects (≥ 1%) included 13 events of amylase increased (12 Grade 3 and one Grade 4), 15 events of Grade 3 lipase increased (14 Grade 3 and one Grade 4), 11 events of Grade 3 Fatigue, and three events of Grade 3 hypertension.

Twenty-six of 195 subjects (13%) experienced a cabiralizumab-related SAE in Phase 1b. The SAEs reported in two or more subjects (≥ 1%) included: CK increased (three subjects, 3%), brain edema, pneumonitis, hyponatremia (two subjects each, 1%). Also SAEs included

one event of Grade 4 CK increased (related to cabiralizumab and nivolumab), one event of Grade 3 autoimmune colitis (related to nivolumab), and one event of Grade 3 hypopituitarism (related to cabiralizumab and nivolumab).

Two Grade 5 SAEs prior to study treatment discontinuation have occurred in Phase 1a of Study FPA008-003: one subject had a Grade 5 pulmonary embolus (not related) and a Grade 5 pneumonitis (related to both drugs; refer to Appendix 6 for management recommendations in cases of pneumonitis) and the other subject had a Grade 5 hypoxic respiratory failure secondary to pneumonia (not related). Six Grade 5 SAEs prior to study treatment discontinuation were reported in Phase 1b of this study. These included 1 sudden cardiac death (unrelated), 1 death due to tumor thrombus blocking a major blood vessel (unrelated), 2 participants with respiratory failure (unrelated), 1 participant with acute respiratory distress (related), and 1 participant with acute respiratory failure (related).

At a presentation at the Society for Immunotherapy of Cancer, Dr. Zev Wainberg presented more details on the activity of cabiralizumab plus nivoloumab. [18] A confirmed objective response was observed in 4 of 31 (13%) patients with advanced pancreatic cancer, all heavily pretreated. The responses were ongoing (range 168 + to 275+ days). This study also evaluated peripheral and tumor biomarkers in pre and post treatment paired biopsies. Of note, the four patients with confirmed responses in pancreatic cancer, were microsatellite stable (MSS) with low tumor mutation burden (TMB). The pharmacodynamics and genomic profiling of these patients treated with the combination of cabiralizumab plus nivolumab demonstrated cabira-mediated CSR-1R blockade in the periphery and tumor microenvironment, this data was presented at ASCO 2018, Abstract 3020. [19]

Study CA025-001 is evaluating the PK, safety, and efficacy of escalaing doses of boh cabiralizumab as monotherapy and in combination with nivolumab in Japanese patiets with cancer. Thirteen patients have been dosed to date. This study is ongoing

Study CA025-006 is evaluating the antitumor effects of cabiralizumab in combination with nivolumab, with or without chemotherapy in patients with advanced pancreatic cancer. This study is ongoing. As of 16-Jul-2018, 11 subjects have been treated with the study drug: 3 subjects were treated with the Investigator’s choice of chemotherapy (Arm A); 3 subjects were treated with 4 mg/kg cabiralizumab on Days 1 and 15 every 4 weeks (Q4W) in combination with 480 mg nivolumab Q4W (Arm B); 1 subject was treated with 4 mg/kg cabiralizumab on Days 1 and 15 Q4W in combination with 480 mg nivolumab Q4W and GEM/nab-paclitaxel on Days 1, 8, and 15 Q4W(Arm C); and 4 subjects were treated with 4 mg/kg cabiralizumab on Days 1 and 15 Q4W in combination with 480 mg nivolumab Q4W and oxaliplatin/5-fluorouracil/leucovorin on Days 1and 15 Q4W (Arm D).

1.5 Nivolumab (BMS-936558))

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immuno-surveillance and escape effective innate and adaptive immune responses.[20,21,22] Current immunotherapy efforts attempt to break the apparent

tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[23] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA 4, ICOS, and BTLA.[24] PD-1 signaling has been shown to inhibit CD28-mediated upregulation of IL-2, IL-10, IL-13, interferon-γ (IFN-γ) and Bcl-xL. PD-1 expression has also been noted to inhibit T-cell activation and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[25] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self- antigens.

PD-1 is a 55 kD type I transmembrane protein primarily expressed on activated T cells, B cells, myeloid cells, and antigen-presenting cells (APCs).[25] Binding of PD-1 to PD-L1 and PD-L2 has been shown to down-regulate T-cell activation in both murine and human systems.[24, 27,28,29] PD1/PD-L1 interactions may also indirectly modulate the response to tumor antigens through T-cell/APC interactions. Therefore, PD-1 engagement may represent one means by which tumors evade immuno-surveillance and clearance.[30] Blockade of the PD-1 pathway by nivolumab has been studied in a variety of preclinical in vitro assays, and anti-tumor activity using a murine analog of nivolumab has been shown in a number of immunocompetent mouse cancer models. Nivolumab has been approved for the treatment of patients with unresectable melanoma, unresectable advanced or recurrent NSCLC, and RCC in Japan. In the US, nivolumab has been approved for the treatment of melanoma, NSCLC, RCC, HCC, and classical Hodgkin lymphoma. Nivolumab is currently being evaluated extensively across a wide range of solid tumors and hematological malignancies. These findings provided the rationale for expanding the evaluation PD-1 pathway blockade in combination with novel immunotherapy agents in clinical studies.

Nivolumab is a fully human, immunoglobulin G4 (IgG4) [kappa] isotype monoclonal antibody that binds to PD-1 with nanomolar affinity (dissociation constant [Kd], 3.06 nM) with a high degree of specificity. In vitro, nivolumab binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC501± nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4, and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a cytomegalovirus (CMV) re-stimulation assay with human peripheral blood mononuclear cells (PBMC), the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and results in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02). [31]

The overall safety experience with nivolumab, as either monotherapy or in combination with

other therapeutics, is based on experience in approximately 17,700 participants. Nivolumab monotherapy is approved in multiple countries, including the US, European Union (EU), and Japan. Nivolumab has been approved by the US FDA for the treatment of patients with unresectable/metastatic melanoma (as a single agent and in combination with ipilimumab), metastatic NSCLC after disease progression on or after platinum-based chemotherapy, advanced RCC previously treated with anti-angiogenic therapy, recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after a platinum-based therapy, refractory hepatocellular carcinoma previously treated with sofarenib, classical Hodgkin lymphoma that has relapsed or progressed, locally advanced or metastatic urothelial cancer after disease progression on or after platinum-based chemotherapy, and other cancers.

For nivolumab monotherapy, the safety profile is similar across tumor types. The only exception is pulmonary inflammation AEs, which may be numerically greater in participants with NSCLC. In NSCLC patients, it can be difficult to distinguish between nivolumab-related and nivolumab-unrelated causes of pulmonary symptoms and radiographic changes. Most AEs were low-grade (Grades 1 to 2) with relatively few related high-grade (Grades 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level. These AEs have included pulmonary toxicity, renal toxicity (including acute renal failure), endocrine abnormalities, gastrointestinal (GI) toxicity, dermatologic toxicity (including rash), and hepatotoxicity. A pattern of immune-related AEs (irAEs) has been defined, for which management algorithms have been developed; these are provided in Appendix 6. Most high- grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms. There is no relationship between the incidence, severity, or causality of AEs and the nivolumab dose level.

Nivolumab, alone or in combination with chemotherapy, is currently being tested for the treatment of advanced/metastatic PDAC. Preliminary results from Study CA209032 show that nivolumab, administered as monotherapy was well tolerated in participants with advanced/metastatic PDAC. Despite the lack of objective responses in the 14 participants treated in this cohort, 1 participant experienced a prolonged stable disease (48 weeks) (Bristol-Myers Squibb) [BMS] internal data). In addition, the combination of nivolumab and gemcitabine/abraxane is currently being tested as first line treatment for participants with advanced/metastatic PDAC (NCT02309177). The combination appears to be well tolerated with a safety profile similar to the individual components. As of February 2017, 20 participants are evaluable for efficacy. The preliminary ORR is 25% (5 out of 20 participants experience PR). In addition, 12 participants experienced prolonged, stable disease (BMS internal data).

Taken together, these data suggest that while nivolumab in monotherapy may not be sufficient to improve the anti-tumor activity in advanced pancreatic cancer, the combination of nivolumab with the appropriate immunotherapy/chemotherapy may indeed improve anti-tumor activity in this setting.

1.5.1 Nivolumab + Cabiralizumab

The combination of cabiralizumab and nivolumab as demonstrated in Study FPA008-003 has a manageable safety profile that is minimally overlapping with that of the chemotherapy regimen (gemcitabine) being evaluated in this study. The preliminary data suggest that the combination of cabiralizumab and nivolumab mediates favorable antitumor effects in subjects with advanced pancreatic cancer. Details relating to efficacy are included in the latest version of the cabiralizumab IB (BMS, 2018). Preclinical evidence support the potential advantages of combining immunotherapy and chemotherapy, but overall, the potential benefit of the proposed combination over standard-of-care chemotherapy is not yet known. Nevertheless, the dismal prognosis of patients with advanced pancreatic cancer who have a poor prognosis and the lack of curative options support the need of novel combinatorial approaches.

1.6 Justification for Cabiralizumab Dose

A cabiralizumab dose of 4 mg/kg has been tested in combination with nivolumab in 195 subjects across a number of tumors in Part 1b of Study FPA008-003. The safety profile of this dose is described in Section 1.4.1. The cabiralizumab dose of 4 mg/kg Q2W was selected in this trial based on the observed reduction of circulating CD16-positive peripheral blood monocytes (CD16+ monocytes) and a tolerable safety profile.

Consistent with healthy subjects, rheumatoid arthritis and PVNS trials, a dose-dependent reduction in CD16+ monocytes after cabiralizumab administration was observed in subjects with cancer in Study FPA008-003. Across trials, cabiralizumab concentrations of $\geq$ 10 µg/mL in serum maximize the reduction of non-classical CD16+ monocytes in a majority of subjects. In Study FPA008-003, the 4 mg/kg Q2W dose was associated with a Ctrough of $\geq$ 10 µg/mL and consistent suppression of circulating CD16+ monocytes after dosing. [17]

1.7 Justification for Nivolumab Dose

The nivolumab dose of 480 mg Q4W was selected for this study based on clinical data and modeling and simulation approaches using population PK (PPK) and exposure-response (ER) analyses examining relationships between nivolumab exposures and efficacy (eg, OS, OR) and safety responses, using data from studies in multiple tumor types (melanoma, NSCLC, and RCC) with body weight-normalized dosing (mg/kg). The PPK analyses have shown that exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered Q2W, and no clinically meaningful differences in PK across ethnicities and tumor types were observed. Nivolumab clearance and volume of distribution were found to increase as body weight increases but less than proportionally with increasing weight, indicating that milligram-per-kilogram dosing represents an over- adjustment for the effect of body weight on nivolumab PK.

Using the PPK and ER models, nivolumab exposures and probabilities of efficacy responses and risks of AEs were predicted following nivolumab 480 mg Q4W and compared to those following nivolumab 3 mg/kg Q2W. The overall distributions of average nivolumab steady-state exposures (Cssavg) are comparable following administration with either nivolumab 3

mg/kg Q2W or nivolumab 480 mg Q4W. While nivolumab 480 mg Q4W is predicted to result in approximately 43% greater steady-state peak concentrations (Cmaxss) compared to nivolumab 3 mg/kg Q2W, these exposures are predicted to be lower than the exposure ranges observed at doses up to nivolumab 10 mg/kg Q2W used in the nivolumab clinical program; the predicted Cmaxss following nivolumab 480 mg Q4W is well below the median Cmaxss achieved following administration of nivolumab 10 mg/kg Q2W, a safe and tolerable dose level.

Exposure-safety analysis demonstrated that the exposure margins for safety are maintained following nivolumab 480 mg Q4W. Safety analyses using available data following nivolumab 3 mg/kg Q2W and 10 mg/kg Q2W administration indicated that there were no differences in A E profiles across body weight groups.

1.8 Justification for Infusion Times for Nivolumab and Cabiralizumab

Administration of nivolumab using a 30-minute infusion time has been evaluated in subjects with cancer. Previous clinical studies of nivolumab monotherapy for the treatment of cancer have used a 60-minute infusion duration wherein nivolumab has been safely administered up to 10 mg/kg over long treatment periods. Infusion reactions including high-grade hypersensitivity reactions have been uncommon across the nivolumab clinical program. In Study CA209010, a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg, and 18.5% at 10 mg/kg). All the events were Grades 1 to 2 and were manageable. An infusion duration of 30 minutes for 3 mg/kg nivolumab (30% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60-minute duration. The safety of nivolumab 3 mg/kg administered as a 30-min infusion was assessed in Study CA209153 in patients with previously treated advanced NSCLC (see Nivolumab IB Section 5.5.1.2)[32]. Overall, there were no clinically meaningful differences in the frequency of hypersensitivity/infusion-related reactions (of any cause or treatment-related) in cancer patients administered nivolumab over a 30- minute infusion compared with that reported for patients treated with the 60-minute infusion. Thus, it was shown that nivolumab can be safely infused over 30 minutes in subjects with cancer.

Cabiralizumab has been administered safely as a 30-minute intravenous infusion at up to 10 mg/kg in a single dose. Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab and cabiralizumab clinical studies. Furthermore, a 30 minute break after the first infusion for the combination will ensure appropriate safety monitoring before the start of the second infusion. When administering nivolumab in combination with cabiralizumab, the nivolumab infusion should be administered first.

2.0 HYPOTHESIS

The combination regimen of nivolumab + cabiralizumab + gemcitabine can provide prolonged disease control in patients with advanced pancreatic cancer.

3.0 OBJECTIVES

3.1 Primary Objective

To estimate progression free survival (PFS) rates at 6 months by RECIST1.1 in patients with stage IV pancreatic adenocarcinoma who have achieved disease control in response to first line chemotherapy when subsequently maintained on a combination regimen of nivolumab + cabiralizumab (FPA008) + gemcitabine.

3.2 Secondary Objectives

1. To evaluate safety and tolerability of the combination of nivolumab + cabiralizumab (FPA008)
2. + gemcitabine. The study will use the CTCAE version 5.0 (http://ctep.cancer.gov/reporting/ctc.html) for reporting of all adverse events.

3. To evaluate PFS, overall survival (OS) and disease control rates in patients administered the combination of nivolumab + cabiralizumab (FPA008) + gemcitabine.

3.3 Exploratory Objectives

1. To evaluate the difference in disease progression outcomes according to iRECIST vs. RECIST 1.1 criteria (Appendix 5).

2. To explore potential biomarkers that may help predict response to treatment in both tumor and blood.

3.4 Primary Endpoints

The primary endpoint is Progression Free Survival (PFS) at 6 months. The primary tumor assessment will be by RECIST 1.1 criteria at 6 months. An interim analysis will be conducted at the end of Stage 1. All available data at the time the final subject has completed the primary assessment will be used in the final analysis.

3.5 Secondary Endpoints

- Adverse events rates, according to grade and body system
- Overall survival and PFS over the course of the study.

4.0 METHODS

4.1 Eligibility

Up to fifteen eligible patients who had achieved disease control, defined as: must have obtained stable disease (SD) or partial response (PR) for a period of at least 2 months with no further shrinkage of ≥ 20% on imaging scans on prior first-line chemotherapy for their metastatic disease. The best response on prior therapy will need to be evaluated and documented by the treating investigator at time of determining eligibility for this trial.

4.1.1 Inclusion Criteria

Patients must meet the following criteria in order to be eligible for participation in the trial:

1. Be willing and able to provide written informed consent for the trial. Participants must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal participant care.

2. Be ≥ 18 years of age on day of signing informed consent.

3. Histologically or cytologically confirmed pancreatic adenocarcinoma with metastasis, who have achieved disease control on prior first-line chemotherapy for their metastatic disease, defined as: Must have obtained at least stable disease (SD) or a partial response (PR) for a period of at least 2 months with no further shrinkage of ≥ 20% on imaging scan. ***Note:*** *Patients that have had prior chemotherapy as adjuvant or neoadjuvant therapy are permitted.*

4. Must have been off their prior cytotoxic regimen a minimum of two weeks but no more than five weeks from initiating trial treatment on C1/D1 (May not exceed 5 weeks unless discussed with Sponsor).

5. Measurable disease by RECIST 1.1.

6. ECOG performance status of 0 or 1.

7. Demonstrate adequate organ function as defined in Table 1.

8. Vitamin D level ≥ 20ng/dL. ***Note:*** Vitamin D supplementation is allowed. Proposed dose: 100,000 loading dose. Followed by 50,000 units 3 times a week for 2 week. Recheck level. Final dosing for supplementation is deferred to treating physician. Vitamin D supplementation throughout study treatment is allowed.

9. Able to submit an archival tumor specimen (primary or metastatic site). Patients with cytology only that do not have adequate archived tumor specimen available, will require a baseline biopsy.

Optional Biopsy: A discussion to be documented with trial investigator at screening regarding the purpose of the optional tissue collection from a newly obtained core or excisional biopsy of a tumor lesion at baseline and a second biopsy 7 weeks (C2/D15) after starting trial treatment, or at time of disease progression (refer to section 6.1.2.8), unless tumor is considered inaccessible or biopsy is otherwise considered not in the patients' best interest. *Participation in this trial is not contingent on patient consenting to optional tumor biopsies.*

10. Women of childbearing potential (WOCBP) must not be breast feeding and have a negative serum or urine pregnancy test within 24 hours prior to the start of study treatment.

11. WOCBP must agree to follow protocol specified method(s) of contraception (Section 4.3.4) for the duration of treatment with study treatment(s) and for a total of 6 months posttreatment completion. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, but still must undergo pregnancy testing as described in this section 4.3.5.

12. Males who are sexually active with WOCBP must agree to follow protocol specified method(s) of contraception (Section 4.3.4) for the duration of treatment with study treatment(s) and for a total of 7 months posttreatment completion. In addition, male participants must be willing to refrain from sperm donation during this time. Azoospermic males are exempt from contraceptive requirements.

Table 1. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) or ALT (SGPT)	≤2.0 × ULN
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Creatine Kinase	WNL
Vitamin D	≥20ng/dL
ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase) GFR=glomerular filtration rate; ULN=upper limit of normal.	
[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks. [b] Creatinine clearance (CrCl) should be calculated per institutional standard. Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.	

4.1.2 Exclusion Criteria

Patients meeting the following criteria will NOT be eligible to participate in this trial:

1. Is currently participating and receiving trial therapy or has participated in a trial of an investigational agent and received trial therapy or used an investigational device within 3 weeks of the first dose of trial treatment.

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

3. Has a known history of active TB (*Mycobacterium tuberculosis*).

4. Microsatellite unstable patients as assessed by IHC for MMR protein

5. Hypersensitivity to cabiralizumab, nivolumab, or gemcitabine or any of its excipients.

6. Previous malignancies (except non-melanoma skin cancers, and in situ bladder, gastric, colorectal, endometrial, cervical/dysplasia, melanoma, or breast cancers) unless complete remission was achieved at least 2 years prior to study entry and no additional therapy is required during the study period.

7. Evidence of central nervous system (CNS) metastasis (negative imaging study, if clinically indicated, within 4 weeks of study treatment).

8. Participants with active, known, or suspected autoimmune disease. Participants with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, euthyroid participants with a history of Grave's disease (participants with suspected autoimmune thyroid disorders must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid stimulating immunoglobulin prior to first dose of study treatment), psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

9. Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study treatment administration except for adrenal replacement steroid doses ≤ 10 mg daily prednisone equivalent in the absence of active autoimmune disease. Note: Treatment with a short course of steroids (< 5 days) up to 7 days prior to initiating study treatment is permitted.

10. Current or history of clinically significant muscle disorders (eg, myositis), recent unresolved muscle injury, or any condition known to elevate serum CK levels.

11. Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:
    i) Myocardial infarction or stroke/transient ischemic attack within the past 6 months.

    ii) Uncontrolled angina within the past 3 months.

    iii) Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes).

    iv) History of other clinically significant heart disease (e.g., cardiomyopathy, congestive heart failure with New York Heart Association functional classification III to IV, pericarditis, significant pericardial effusion, or myocarditis).

    v) Cardiovascular disease-related requirement for daily supplemental oxygen therapy.

12. Prior organ allograft or allogeneic bone marrow transplantation.

13. Any major surgery within 4 weeks of study treatment. Participants must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study treatment.

14. All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v5.0) or baseline before administration of study treatment. Participants with toxicities attributed to prior anti-cancer therapy that are not expected to resolve and result in long lasting sequelae after platinum- based therapy, are permitted to enroll. Patients with ≤ grade 2 neuropathy may qualify for this trial.

15. Evidence of uncontrolled, active infection, requiring parenteral anti-bacterial, anti-viral or anti-fungal therapy ≤ 7 days prior to administration of study medication.

16. Any uncontrolled inflammatory GI disease including Crohn’s Disease and ulcerative colitis.

17. Transfusion completed within 72 hours prior to first dose of study drug administration.

18. Concomitant use of statins while on study. However, a participant using statins for over 3 months prior to study drug administration and in stable status without CK rise may be permitted to enroll.

19. Non-oncology vaccine therapies for prevention of infectious diseases (eg, human papilloma virus vaccine) within 4 weeks of study drug administration. The inactivated seasonal influenza vaccine can be given to participants before treatment and while on therapy without restriction. Influenza vaccines containing live virus or other clinically indicated vaccinations for infectious diseases (ie, pneumovax, varicella, etc) may be permitted, but must be discussed with the Sponsor and may require a study drug washout period prior to and after administration of vaccine.

20. Participants with abnormal serum chemistry values, which in the opinion of the investigator is considered to be clinically significant, will be excluded from the study. This will include participants who show clinical signs and symptoms related to their abnormal serum chemistry values, as well as participants whose serum chemistry values are asymptomatic but clinically significant (e.g, hypokalemia or hyponatremia).

21. Evidence of coagulopathy or bleeding diathesis.

22. Treatment with botanical preparations (e.g., herbal supplements, including potential drugs of abuse, or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment.

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

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

25. Has received prior therapy with a CSF-1R pathway inhibitors, anti-PD-1, anti-PD-L1, anti PD-L2, anti-CTLA-4.

26. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected). Note: Participants with positive hepatitis C antibody and negative quantitative hepatitis C by PCR are eligible.

27. Female who is pregnant or breast-feeding

28. Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and Sponsor approval is required.

4.2 Trial Treatments

The treatments to be used in this trial are outlined below in Table 2.

Table 2. Trial Treatments

Study Treatment	Potency	Dose/ Route	Dose Frequency	Route	IP/Non-IP
Nivolumab	100 mg/vial and/or 40 mg/vial (10 mg/mL)	480 mg IV	Day 1 Q4W	IV Infusion over 30 minutes	IP
Cabiralizumab Solution for Injection	Per available vial from manufacturer (20 mg/mL)	4 mg/Kg IV	Days 1 and Day 15 Q4W	IV infusion over 30 minutes	IP
Gemcitabine	1000 mg/vial and various strengths	1000 mg/m2 IV	Days 1, 8, and 15 Q4W	IV Infusion over 30 minutes	Non-IP

Nivolumab + cabiralizumab + gemcitabine will be given on Day 1 of each 28-day treatment cycle until the progression of disease, discontinuation due to toxicity, withdrawal of consent, or study closure.

Day 1:

Nivolumab will be administered as a 480 mg IV infusion over 30 minutes and then, after a 30 minute rest period, cabiralizumab will be administered as a 4mg/kg IV infusion over 30 minutes. **Note:** Nivolumab must always be administered first in this combination regimen.

Pre-medication for gemcitabine (based on standard-of-care and local institutional standards) will then be administered after a further 30 minute rest period. Efforts should be made to avoid use of steroids if at all possible.

Gemcitabine will be then administered as 1000 mg/m2 over 30 to 40 minutes.

Day 8:

Pre-medication for gemcitabine (based on standard-of-care and local institutional standards) will then be administered after a further 30 minute rest period. Efforts should be made to avoid use of steroids if at all possible.

Gemcitabine will be administered as 1000 mg/m2 over 30 to 40 minutes.

Day 15:

Cabiralizumab will be administered as an IV infusion over 30 minutes.

Pre-medication for gemcitabine (based on standard-of-care and local institutional standards) will then be administered after a further 30 minute rest period. Efforts should be made to avoid use of steroids if at all possible.

Gemcitabine will be then administered as 1000 mg/m2 over 30 to 40 minutes.

4.2.1 Dose Selection/Modification

The rationale for selection of doses to be used in this trial is provided in Sections 1.6-1.8.

Details on preparation and administration of trial treatments are provided in the Investigator Brochure (cabrilizumab) and Package Inserts (nivolumab and gemcitabine).

4.2.2 Dosing of Cabiralizumab and Nivolumab

For the combination regimen, nivolumab should always be administered first as a 30-minute IV infusion followed by a 30-minute IV infusion of cabiralizumab. The time in between infusions is expected to be approximately 30 minutes but can be more or less depending on the situation. Cabiralizumab will be administered every 2 weeks (± 2days) and nivolumab will be administered every 4 weeks (± 2 days). Participants may be dosed with cabiralizumab no less than 12 days from the previous dose and with nivolumab no less than 24 days from the previous dose.

Dosing calculations should be based on the body weight assessed at Cycle 1 Day 1 prior to the first dose of cabiralizumab. If the participant's weight on the day of dosing differs by > 10% from the weight used to calculate the prior dose, the dose must be recalculated. All doses should be rounded to the nearest milligram and chemotherapy should be rounded as per SOC (usually 10 mg).

Doses of study drugs may be interrupted, delayed, or discontinued depending on how the participant tolerates the treatment.

4.2.3 Dose Delay for Cabiralizumab and Nivolumab

Administration of cabiralizumab and/or nivolumab in combination therapy should be delayed for the following:

- Any Grade 3 fatigue which does not resolve to Grade 1 or baseline before the next treatment visit;
- Any drug-related laboratory abnormalities would not require a dose delay unless clinically indicated or specified in the protocol or abnormal laboratory management table (Appendix 7). Please discuss with the Sponsor or designee as needed;
- For dose delays or modifications for all other AEs, please refer to the AE management table in Appendix 6.

Participants who require a dose delay of cabiralizumab or nivolumab should be re- evaluated weekly or more frequently if clinically indicated and resume study drug dosing when re-treatment criteria are met. If a participant experiences an infusion reaction to cabiralizumab or

nivolumab, or both study drugs, the infusion reaction should be treated following the infusion reaction treatment guidelines in Appendix 6.

4.2.4 Guidelines for Subject Monitoring After Infusions

Obtain baseline vitals, then every 30 minutes during the infusion and continue to monitor the pt for at least 30 minutes after completion.

Notify PI for infusion-related events; blood pressure < 90/60 or > 170/110 mmHg; heart rate > 100, or < 60 beats per minute or irregular; shortness of breath.

4.2.5 Management Algorithms for Immuno-oncology Agents

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

- GI
- Renal
- Pulmonary
- Hepatic
- Endocrinopathies
- Skin
- Neurological

Specific algorithms for the management of irAEs are provided in Appendix 6 and are applicable to immune-related AEs for all immuno-oncology study treatment combinations.

4.2.6 Dose Reductions for Cabiralizumab and Nivolumab

Dose reduction for cabiralizumab and nivolumab are not permitted.

4.2.7 Dose Discontinuation Criteria for Cabiralizumab and Nivolumab

For comprehensive discontinuation rules, refer to Appendix 6 (AE management) and Appendix 7 (Laboratory Abnormalities Management Table).

Treatment of cabiralizumab in combination with nivolumab should be discontinued in the following cases unless otherwise specified:

- Any Grade 3 or higher uveitis or any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 within the second re-treatment period or that requires systemic treatment.

- Any Grade 3 or higher infusion-related reactions and hypersensitivity requiring discontinuation. Any re-initiation of therapy in this circumstance would require consultation with the Sponsor or designee.

- Any Grade 3 non-skin, drug-related AE lasting > 7 days, or recurrences including drug-related uveitis, pneumonitis, hypoxia, bronchospasm, and endocrinopathies with the following exceptions:

    - Grade 3 drug-related diarrhea, colitis, neurologic toxicity, 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. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:

        - Grade 3 drug-related thrombocytopenia > 7 days or associated with Grade ≥ 2 bleeding requires discontinuation.

- Any drug-related liver function test abnormality that meets any one of the following criteria requires discontinuation:

    - ALT or AST > 3 x ULN and total bilirubin > 2 x ULN or INR > 1.5 x ULN (in the absence of anticoagulation). If bilirubin raised and Gilberts syndrome suspected discuss conjugated bilirubin levels with Sponsor.

        - See Appendix 6 and Appendix 7 for guidelines and possibility of restarting therapy

    - ALT or AST > 20 x ULN (with or without concurrent liver metastases)

    - Total bilirubin > 3 x ULN (> 5 x ULN with concurrent liver metastases)

- Any Grade 4 drug-related AE or laboratory abnormality, except for the following events which do not require discontinuation:

    - Grade 4 neutropenia < 7 days

    - Grade 4 lymphopenia or leukopenia < 7 days

- Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. The Sponsor or designee should be consulted for Grade 4 amylase or lipase abnormalities.

- 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 drug-related endocrinopathy AEs, such as adrenal insufficiency, adrenocorticotropic hormone 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 Sponsor or designee.

- Grade 4 CK up to 20 x ULN (in the absence of clinical sequelae)

- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:

  - Dosing delays to manage drug-related AEs are allowed. Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks from the previous dose, the Sponsor or designee must be consulted. Tumor assessments should continue as per-protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue per protocol, or more frequently if clinically indicated during such dosing delays or per the Investigator's discretion.

  - Dosing delays lasting > 6 weeks from the previous dose that occur for non- drug-related reasons may be allowed if approved by the Sponsor or designee. Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks, the Sponsor must be consulted. Tumor assessments should continue per-protocol every 8 weeks (± 7 days) even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue per-protocol or more frequently if clinically indicated during such dosing delays or per the investigator's discretion.

- Any AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, presents a substantial clinical risk to the participant with continued cabiralizumab and/or nivolumab dosing

- Any drug-related Grade 3 or higher neurological toxicity

- Any Grade 3 or higher periorbital edema and persistent Grade 2 periorbital edema requiring 2 missed doses unless approved by Sponsor.

- Any Grade 3 or higher drug-related diarrhea or colitis, which does not resolve to Grade 1 or baseline within 28 days

- Any Grade 4 skin toxicity
- Any Grade 4 renal toxicity
- Any drug-related Grade 3 or higher pulmonary toxicity

If the causality of the AE requiring discontinuation is confirmed to be due to 1 of the study drugs in the combination therapy, the other drug(s) may be continued per-protocol schedule under the following scenarios:

· Timely resolution of the AE based on the treatment modification table

· Clinical benefit is shown by the participant based on investigator assessment.

4.2.8 Criteria to Resume Treatment with Cabiralizumab and Nivolumab

Participants may resume treatment with cabiralizumab and/or nivolumab when the drug-related AE resolves as noted in the AE management tables in Appendix 6 or the abnormal laboratory management table in Appendix 7. The Sponsor or designee can be contacted at any time if further clarification is needed.

4.2.9 Dose Modification for Gemcitabine

Since gemcitabine is standard therapy for pancreatic cancers, sites use the suggested dosing. Any laboratory-only abnormalities without clinical manifestations or electrolyte abnormalities that may be managed with supplementation also do not automatically need dose modification.

Suggested dose modification will be performed according to the Gemcitabine package insert (Refer to Table 3).

Table 3. Dose Modification for Gemcitabine

Absolute granulocyte count (x 10^6/l)		Platelet count (x 10^6/l)	Percentage of standard dose of gemcitabine (%)
≥ 1,000	and	≥ 100,000	100
500- < 1,000	or	50,000 - < 100,000	75
< 500	or	< 50,000	Omit dose

If the causality of the AE requiring drug hold is confirmed to be gemcitabine, the other drugs, nivolumab and cabiralizumab may be continued per protocol schedule.

4.2.11.1 Dose Modification on Day 1 of Cycle

In the event dose modifications are required at the beginning of a cycle or within a cycle due to hematologic toxicities, the dose of gemcitabine may be adjusted as detailed in Table 3.

Please note that all study drugs will be held at the start of a new cycle if Table 3 criteria are not met.

4.2.12 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial treatment or vaccination may be required. The investigator should discuss any questions regarding this with the Investigator Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary physician.

4.2.13 Acceptable Concomitant Medications

All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), multivitamins, nutritional and/or herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 30 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be reported for SAEs and ECIs as defined in Section 6.2.

4.2.14 Prohibited Concomitant Medications

Patients are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial. For specific therapies there is a washout window prior to cycle1/day1, indicated below and per eligibility criteria in Section 4.1.

- Immunosuppressive agents;
- Immunosuppressive doses of systemic corticosteroids;
- Vaccines except as noted in Sections 4.1.2 and 4.3.2;
- Statins for treatment of hypercholesterolemia. Statins will be allowed only if the participant is on a stable dose for over 3 months prior to the study and is in a stable status without any creatine kinase (CK) elevations;
- Other anti-neoplastic therapies including biologic, immunotherapy, extensive non palliative radiation therapy, standard treatments, or investigational agents or devices.

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Patients may receive other medications (not listed here as prohibited) that the investigator deems to be medically necessary.

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

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

4.3 Other Restrictions and Precautions

4.3.1 Corticosteroids

Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of treatment assignment are excluded. Inhaled or topical steroids, and adrenal replacement steroid doses $\leq$ 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease.

Participants are permitted to use topical, ocular, intra-articular, intranasal, and inhaled corticosteroids (with minimal systemic absorption) in the absence of active autoimmune disease. Adrenal replacement steroid doses $\leq$ 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g. contrast dye allergy) or for treatment of non-autoimmune conditions (e.g. delayed-type hypersensitivity reaction caused by a contact allergen) and also for the treatment of tumor-related AEs is permitted.

4.3.2 Vaccines

The inactivated seasonal influenza vaccine can be given to participants while on therapy without restriction. Influenza vaccines containing live virus or other clinically indicated vaccinations for infectious diseases (i.e., pneumovax, varicella, etc.) may be permitted, but must be discussed with the Sponsor and may require a study drug washout period prior to and after administration of the vaccine.

4.3.3 Diet

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

4.3.4 Contraception

The trial treatments (cabiralizumab, nivolumab, and gemcitabine) may have adverse effects on a fetus in utero. Furthermore, it is not known if the trial treatments may have transient adverse effects on the composition of sperm.

4.3.4.1 Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP:

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

      Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

4.3.4.2 Contraception Requirements

Male Participants:
Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol - defined timeframe in section 5.0:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 4 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
    - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception that has a low user dependency consistently and correctly as described in Table 4 during the protocol-defined time frame in Section 5.0.

Table 4. Highly Effective Contraceptive Methods That Have Low User Dependency

Highly Effective Methods That Have Low User Dependency Failure rate of <1% per year when used consistently and correctly.
• Progestogen- only contraceptive implant [a, b] • Intrauterine hormone-releasing system (IUS) [b] • Intrauterine device (IUD) • Bilateral tubal occlusion
• **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 6 months after the last dose of study treatment.

4.3.5 Pregnancy Testing

WOCBP should only be included after a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24-hours before the first dose of trial treatment.

Following initiation of treatment additional pregnancy testing will be performed prior to day 1 of each cycle during the treatment period, at the end of treatment (EOT) and at 30 days after the last dose of study treatment and as required locally.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

4.3.6 Use in Pregnancy

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

The trial investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male patient impregnates his female partner, the trial personnel at the site must be informed immediately and the pregnancy reported to the Sponsor. The Sponsor will report to BMS and follow the pregnancy as described above and in Section 6.2.

4.3.7 Use in Nursing Women

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

4.4 Patient Withdrawal/Discontinuation Criteria

Patients may withdraw consent at any time for any reason or be withdrawn from the trial at the discretion of the investigator should any untoward effect occur. In addition, a patient may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details

regarding assessments to be done at an End of Treatment (EOT) visit at time of discontinuation or withdrawal are provided in Section 6.1.5.3.

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

- The patient or legal representative (such as a parent or legal guardian) withdraws consent
- Confirmed disease progression
- Unacceptable adverse experiences
- Inter-current illness that prevents further administration of treatment
- Investigator's decision to withdraw the patient
- The patient has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The patient is lost to follow-up
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 5 (Trial Schedule) and Section 6.1.5 (Visit Requirements). After the end of treatment, each patient will be followed for at least 90 days for adverse event monitoring (serious adverse events will be collected for 100 days after the end of treatment as described in Section 6.2.3.1). Patients who discontinue for reasons other than progressive disease will have post-treatment follow- up every 100 days for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up, or the end of the trial, whichever occurs first.

4.5 Clinical Criteria for Early Trial Termination by the Sponsor

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

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

4.6 Safety Stopping Rule

For the purposes of the safety stopping rule, a safety event of interest will be defined as any drug discontinuation which arises from the adverse event/ laboratory abnormalities management algorithms in section 4.2.7 and Appendices 6 and 7, or, as any grade 3 or higher adverse event which is not covered by these management algorithms and which is related to GI, pulmonary, hepatic, or neurological toxicity, and is at least possibly related to study drug.

For other toxicity and dose modifications please see attached schema/table.

If a subject experiences a safety event of interest, no additional doses of the investigational product will be given to that subject. The subject will be counted in the ITT population for the efficacy analysis.

As reported in the most recent IB, 43 of 265 (16.2%) subjects experienced discontinuation due to a treatment related AE after treatment with cabiralizumab +nivolumab. Based on this experience, we reasonably expect to see an event rate of 16% in this trial. The safety stopping rule will be designed to continue with probability approximately 80% in case the event rate is 16% or less:

If at any time 4 subjects experience a safety event of interest, further accrual will be held pending safety review, and the study will be restarted only with Principal Investigator approval. The safety review will take the form of review of a formal Safety Report, prepared following the SOP's for a DSMC report, by a Safety Review Team which includes the Investigators who enrolled subjects in the study, the Principal Investigator, and the UCSD DSMC.

This rule has probability 21% of being invoked if the event rate is 16%, and thus 80% probability to continue through 15 subjects in this case. Alternatively, if the event rate is as high as 30%, the safety rule has 70% chance of stopping the study for review.

If one or more grade 4 or 5 AE's are observed (with the exception of a grade 4 AE's covered by the management algorithms of Appendices 6 and 7, which does not lead to drug discontinuation) which are at least possibly attributable to study drug, further accrual will be held pending safety review as described above, and the study will be restarted only with Principal Investigator approval.

FDA will be notified if one of the thresholds to hold a safety review is met.

5.0 Trial Schedule

The trial will consist of the following three periods:

Screening (SCN) Period: The screening period will take place only after informed consent is obtained and within the 30 days prior to C1/D1. The screening visit may be counted as the baseline visit if completed within 7 days of initial dosing on C1/D1.

Treatment Period: Patients will be treated at 28 ± 2 day intervals. Patient must begin cycle 1 within 30 days of signing the IRB approved informed consent document and after the screening assessments have been performed and reports have been reviewed to confirm eligibility. The patient will continue on maintenance therapy until there is evidence of clear- cut tumor progression, has treatment ending toxicities, or withdraws from treatment. Table 5 below summarizes the Screen-Treatment Period Schedule of Assessments.

Post Treatment Period: All participants should complete the 3 clinical safety follow-up visits (at 30, 60, and 100 days from EOT) regardless of whether new anti-cancer therapy is started, except those participants who will withdraw consent for study participation or are unable to come to clinic due to disease progression". Table 6 below summarizes the Post- Treatment Period Schedule of Assessments. (6.1.5.4).

Table 5. Table of Assessments (Screen – Treatment Period)

	SCN	CYCLE 1			CYCLE 2				CYCLE 3 and subsequent cycles		
Trial week		**1**	**2**	**3**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Cycle day	-	**1**	**8**	**15**	**1**	**8**	**15**	**21**	**1**	**8**	**15**
Window (Days):	--30 to -1	± 2	± 2	± 2	± 2	± 2	± 2		± 2	± 2	± 2
Informed Consent	X [a, c]										
Inclusion/ Exclusion Criteria	X	x									
Medical History	X [b]										
Prior and Concomitant Medication Review	X	x			x				x		
Assess & Report Adverse Events [c]		x	x	x	x	x	X		x	x	X
Complete Physical Examination including height and Weight	X										
Weight and BSA calculation		x			x				x		
Symptom Directed Physical Examination		x			x				x		
Vital Signs [d]	X	x	x	x	x	x	X		x	x	X
12- lead ECG	X										
ECOG (see appendix 4)	x[e]	x			x				x		
Serum β HCG Pregnancy Test (if applicable) [f]	X	x [f]			x				x		
PT/INR and aPTT	X										
TSH, T4, T3	X	x[k]			x				x		
CBC with Differential, Platelets	X	x	x	x	x	x	X		x	x	X
Comprehensive Serum Chemistry Panel [g]	X	x	x	x	x	x	X		x	x	X
Serum Vitamin D	X										
Creatinine Kinase	X	x	x	x	x	x	X		x	x	X
Urinalysis	X	x			x				x		
HBsAg HCV RNA (qualitative)	X										
IHC for MMR protein	X										
Tumor Imaging (CT/MRI) & Response Assessment [h]	x[h]						|------	X[h]	------|		
CA19-9 (or CA 125, or CEA if not expressers of CA19-9)	X	x			x				x		
Archival Tumor Biopsy (refer to 6.1.2.8)	X										
Optional -Fresh Tumor Biopsy [i] (refer to 6.1.2.8)	X						x[h]				
Central Lab Blood Sample [j] (refer to 6.1.2.7)	X	x			x		X				X
Cabiralizumab		**x**		**x**	**x**		**X**		**x**		**X**
Nivolumab		**x**			**x**				**x**		

Gemcitabine		x	x	x	x	x	X		x	x	X

Footnotes:

a. Written IRB-approved informed consent must be obtained prior to any screening assessments being performed.

b. Documented medical history to include, demographics, concurrent baseline conditions (using NCI-CTCAE V5.0. Appendix 3), prior cancer treatment and surgeries.

c. For the time that the consent form is signed until treatment allocation/randomization, any events of clinical interest (ECI, refer to 6.2.3.2), serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any patient must be reported within 24 hours to the Sponsor. AEs will continue to be assessed and reported throughout the trial treatment period, for at least 90 days following the EOT and again at 100 days for serious adverse events (refer to Section 6.2 for complete details).

d. Vital signs to include: Blood pressure, pulse, and temperature.

e. ECOG Performance Status must be 0 or 1 to be eligible for entry to the trial.

f. Negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) is required for women of child-bearing potential (WOCBP) within 24 hours of start of trial medication. Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected. Participants must agree to use a contraception as detailed in Section 4.3.4

g. Refer to Table 7 for details of required labs to be included. Adequate organ function must be demonstrated in accordance with protocol criteria within 10 days of start of trial medication as defined in Table 1.

h. CT/MRI scan to document disease status at baseline to include chest abdomen and pelvis and other regions as clinically indicated Brain scan is not required unless to rule out brain metastases if clinically indicated (per PI discretion). The same radiographic procedures used to document disease status at baseline must be used throughout the trial. Tumor assessments will be conducted using CT or MRI, approximately every 8 ± 1 weeks until trial discontinuation or disease progression, whichever is later. All sites of disease must be followed using the same baseline assessment method. The investigator will complete tumor measurements and response evaluation per RECIST 1,1 and iRECIST (for nivolumab + cabiralizumab + gemcitabine arm only) .

i. For patients consenting to the optional tumor biopsy, a baseline tumor biopsy and paired blood sample will be taken from each patient and used for profiling (collected within the 4 weeks prior to cycle 1/day1). If possible (patient condition permitting) this will be repeated at C2/D15 (-3 days, + 10 days) or at the time of disease progression. If a biopsy is proposed outside these times, it should be discussed with trial monitor, If the biopsy cannot be collected within this timeframe this is to be discussed with the sponsor.

j. Each patient will have 30 ml of blood collected at the following timepoints: Pre-treatment (0-14 days prior to C1/D1), and during the trial prior to treatment on days 1 of cycles 1, 2, 4, 6, and every 2 cycles thereafter. For those patient consenting to the optional tumor biopsy, an additional 30 ml blood sample will also be collected at the time of biopsy refer to section 6.1.2.8.

k.Thyroid panel: TSH, T4, T3 test if screening labs is done within two weeks of cycle 1 day1 then no need to repeat.

Table 6. Table of Assessments (EOT– Follow-Up)

Post-Treatment Period	EOT	Safety Follow-Up	Survival Follow-up
Scheduling Window (Days)	At time of discontinuation (+7 days of last dose or date of discontinuation)	30, 60, 100 days(± 7 days) from EOT	Every 100 days post Safety FU
Post-trial anticancer treatment status	X	X	X
Disease/Survival Status [a]	X	X	X
Concomitant Medication Review	X	X	
Assess & Report Adverse Events [b]	X	X	
Symptom Directed Physical Examination	X		
Vital Signs and Weight [c]	X		
ECG	X		
ECOG (see appendix 4)	X		
Serum β HCG Pregnancy Test for WOCBP	X	X	
CBC with Differential	X		
Comprehensive Serum Chemistry Panel	X		
Urinalysis	X		
Tumor Imaging & Response Assessments [d]	X		
CA19-9 [e]	X		
Central Lab Blood Samples	X	X[f]	
Review contraception use as required by protocol Section 4.3.4 (where applicable)	X	X	
Contact Information Review [f]	X	X	X

Footnotes for Table 6. Post –Treatment Period

[a.] Post-treatment follow-up for disease status until documented disease progression, initiating a non-trial cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each pt will be followed by telephone for survival status.

[b]. Assess and record any new or ongoing AEs at time of EOT. Following the EOT, each patient will be followed for 30 days, for adverse event monitoring. Serious adverse events and Events of Clinical Interest (ECI) will be collected for 100 days after the end of treatment as described in Section 6.2

[c.] Vital signs to include: Blood pressure, pulse, respiratory rate, and temperature.

[d.] Tumor assessments will be conducted using CT or MRI at trial discontinuation or disease progression, whichever is later. All sites of disease must be followed using the same baseline assessment method.

[e.] CA19-9 assessments will be taken at baseline and approximately every 4 weeks during the trial treatment period and at the end of treatment visit. All CA19-9 assessments are to be assayed by the same laboratory for each patient. The Investigator is encouraged to obtain radiological assessments and CA19-9 values earlier if there is a strong clinical suspicion of disease progression, in order to confirm or refute the clinical impression.

[f.] Site to confirm contact information for patient and a designated family member and remind patient of FU telephone contact that will be conducted every 90 days for survival status

6.0 TRIAL PROCEDURES

6.1 Trial Procedures

Individual trial procedures (Administrative, Clinical, and Laboratory) are described in detail below. The specific visit requirements are detailed in Section 6.1.5. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

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

6.1.1 Administrative Procedures

6.1.1.1 Informed Consent

The Investigator or qualified designee must obtain documented consent from each potential patient prior to participating in a clinical trial.

Consent must be documented by the patient's dated signature. A copy of the signed and dated consent form should be given to the patient before participation in the trial.

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

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

6.1.1.2 Inclusion/Exclusion Criteria

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

6.1.1.3 Medical History

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

6.1.1.4 Prior and Concomitant Medications Review

6.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the patient within the 30 days before starting the trial. Treatment for the disease for which the patient has enrolled in this trial will be recorded separately and not listed as a prior medication.

6.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medications including prescription, over- the-counter (OTC), multivitamins, nutritional and/or herbal supplements, IV medications and fluids, if any, taken by the patient during the trial. All medications related to reportable SAEs and Events of Clinical Interest (ECIs) should be recorded as defined in Section 6.2.

6.1.1.5 Disease Details and Treatments

6.1.1.5.1 Disease Details

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

6.1.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries. The investigator will assess and provide as part of the baseline eCRF data, the Best Response on the last treatment prior to enrollment in this trial. Patients must have been off their prior cytotoxic regimen a minimum of two weeks but no more than five weeks from initiating trial treatment on C1/D1.

6.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a patient initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the EOT visit must occur before the first dose of the new therapy. -

6.1.2 Clinical Procedures/Assessments

6.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each patient to evaluate for potential new or worsening AEs as specified in the Trial Schedule Section 5.0 (during the trial treatment period, for 100 ((±7 days) following last dose of trial treatment, or date of discontinuation. This will be contingent on patients clinical status. Adverse experiences will be graded and recorded throughout the trial and during the 30 day follow-up period according to NCI CTCAE Version 5.0 Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 6.2 for detailed information regarding the assessment and recording of AEs.

6.1.2.2 Full Physical Exam

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

6.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration on day 1, 8, and 15 of each cycle.

6.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Schedule (Section 5.0). Vital signs should include temperature, pulse, respiratory rate, and blood pressure. Weight will be measured at the start of each treatment cycle. Height will be measured at screening only.

6.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (Appendix 4) at screening, prior to the administration of trial treatment on day 1 of each cycle and at discontinuation of trial treatment as specified in the Trial Schedule.

6.1.2.6 Tumor Imaging and Assessment of Disease (Refer to Appendix 5)

The patient's pancreatic cancer will be evaluated by the investigator based on tumor assessments using RECIST 1.1 criteria. In additional, iRECIST criteria will be assessed.

Tumor assessments for evaluation of response will be conducted using CT or MRI, with IV contrast if not medically contraindicated, approximately every 8 ± 1 weeks until trial discontinuation or disease progression, whichever is later. All sites of disease must be followed using the same baseline assessment method.

All target lesions will be measured by consistent imaging techniques for each patient throughout the trial. Suitable imaging techniques include CT-scan, or MRI. The same technique should be used for each evaluation in an individual patient. Copies of the scans must be available for review.

In the event that PD by RECIST 1.1 or iUPD is determined for a patient, a repeat scan must be performed within 4 - 6 weeks to confirm PD. Trial treatment may be continued during this time (past the initial PD assessment) but only if patient is clinically stable as defined by:

- No worsening of performance status

- No clinically relevant increase in disease related symptoms

- No requirement for intensified management of disease related symptoms (analgesics, radiation, palliative care)

CA19-9 assessments (or CEA or CA-125 for not expressers of CA19-9) will be taken at baseline and approximately every 28 days during the trial treatment period. All CA19-9 assessments must be assayed by the same laboratory for each patient. Disease progression will not be determined by CA19-9, however increases in CA19-9 may warrant the investigator to obtain radiographic assessments.

Note: In order to more precisely determine time to progression, the investigator is encouraged to obtain radiological assessments and CA19-9 values earlier if there is a strong clinical suspicion of disease progression. In order to either confirm or refute the clinical impression.

Note: Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)

6.1.2.7 Blood Collection

Each patient will have 30 ml of blood collected at the following timepoints: Pre-treatment (0-14 days prior to cycle1/day1), and during the trial prior to treatment on days 1 of cycles 1, 2, 4, 6, and every 2 cycles thereafter.

For those patient consenting to the optional tumor biopsy, an additional 30 ml blood sample will also be collected at the time of biopsy refer to section 6.1.2.8.

Blood samples will be sent and analyzed by Dr. Reya's Laboratory at University of California San Diego.

Specific details for blood sample collection and processing will be provided to the investigative sites in the Trial Laboratory Manual.

6.1.2.8 Tumor Tissue Collection

All patients will be required to provide an archival tissue block from either primary or metastatic site.

Patients with cytology only that do not have adequate archived tumor specimen available, will require a baseline biopsy.

For patients consenting to the optional tumor biopsy, a baseline tumor biopsy will be taken from each patient and used for profiling (collected within the 4 weeks prior to cycle 1/day1). If possible (patient condition permitting) this will be repeated on Week 7, C2 Day 15 (-3 days, + 10 days) or at the time of clear disease progression. If the biopsy cannot be collected within this timeframe this is to be discussed with the sponsor. Tissue samples will be sent and analyzed by Dr. Reya's Laboratory at University of California San Diego.

Specific details for tumor tissue collection and handling will be provided to the investigative sites in the Trial Laboratory Manual.

6.1.3 Laboratory Procedures/Assessments

Safety laboratory tests for hematology, chemistry, and urinalysis (as detailed in Table 7) will be performed by the local laboratory for each investigational site at screening, baseline and throughout the trial treatment period. HBsAg and HCV RNA (qualitative) will be performed at screening if not performed within the last 3 months.

Table 7. Laboratory Tests – performed locally

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin- WOCBP only
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR)
Platelet count	Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST)	Protein	aPTT
WBC (total and differential)		Microscopic exam *(If abnormal results are noted)*	HBsAG
Red Blood Cell Count	Lactate dehydrogenase (LDH)		HCV RNA qualitative
Absolute Neutrophil Count	Calcium		Creatine Kinase
Absolute Lymphocyte Count	Potassium		Vitamin D
	Sodium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		
	Creatinine		
	TSH with T3, free T4		

6.1.4 Patient Discontinuation

When a patient discontinues prior to trial completion, all applicable activities scheduled for the EOT visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 6.2 - Adverse Events.

6.1.5 Visit Requirements

Visit requirements are outlined in Section 5.0 - Trial Schedule. Specific procedure-related details are provided above in Section 6.1 - Trial Procedures.

6.1.5.1 Screening Period

Screening of potential patients will be performed only after informed consent is obtained and within 30 days prior to first dose of trial medication (unless otherwise noted below). All necessary laboratory values and assessment reports must be available and reviewed prior to cycle1/ day 1.

The following will be completed as part of the screening visit:

1. Written informed consent
2. Medical history including concurrent baseline conditions (using NCI CTCAE version 5.0; Appendix 3), prior cancer therapy (including documentation of prior surgery, adjuvant or neoadjuvant chemotherapy and radiotherapy)
3. Complete physical examination including height (cm) and weight (kg)
4. ECOG Performance Status (see Appendix 4)
5. Vital signs (blood pressure, pulse, and temperature)
6. Computed tomography (CT) / magnetic resonance imaging (MRI) scan to document disease status (including chest, abdomen, pelvis, and other regions as clinically indicated. In addition, brain scan is not required but will be done to exclude brain metastases if clinically indicated only. This decision will at PI discretion. If a CT scan was taken within 28 days prior to first dose, a new scan is not necessary. However, if a new scan is to be done, it should be performed within 10 ± 2 days prior to starting trial medication.
7. Electrocardiogram (ECG)
8. PT/INR and aPTT
9. Complete blood count (CBC) with differential and platelet count
10. Comprehensive serum chemistries (refer to Table 7)
11. Serum Vitamin D
12. Creatine kinase (CK)
13. TSH with T3, free T4
14. IHC for MMR protein

15. CA19-9 (or CEA or CA-125 if not expressers of CA19-9)
16. HBsAg and HCV RNA (qualitative) if not performed in the last 3 months
17. Urinalysis (refer to Table 7)
18. Serum or urine β-HCG pregnancy test for women of child-bearing potential (refer to Section 4.3.4 for more details)
19. Concomitant medication notation (to include all medications taken within 30 days prior to enrollment)
20. Optional baseline biopsy is to be obtained up to 4 weeks (28 days) prior to first dose of trial medication (C1/D1). Refer to Section 6.1.2.8
21. Central Lab Blood Sample 3 X 10 mL vials

6.1.5.2 Treatment Period

Patients will be treated at 28 ± 2 day intervals. Patient must begin cycle 1 within 30 days of signing the IRB approved informed consent document and after the screening assessments have been performed and reports have been reviewed to confirm eligibility. Screening clinical evaluations and laboratory assessments may be used as the Cycle 1/ Day 1 evaluations if they are completed within 7 days prior to trial treatment administration.

Treatment will be administered by qualified and trained site personnel in a hospital, clinic, or other outpatient setting appropriate for chemotherapeutic infusions.

For subsequent cycles, all assessments must be conducted prior to treatment administration and within 72 hours (except those noted), or if medical or scheduling conditions require a delay.

<u>Day 1 of each cycle</u>

- Inclusion/exclusion review (Cycle 1 only)
- Directed physical exam
- Vital signs
- BSA only needs to be changed if there has been a change > 10% in body weight from Cycle 1 /Day 1
- ECOG Performance Status (Appendix 4)
- Hematology: CBC with differential and platelet count. Results must be reviewed prior to treatment initiation to ensure patient still meets inclusion criteria.
- Serum chemistries (refer to Table 7). Results must be reviewed prior to treatment

initiation to ensure patient still meets inclusion criteria.

- Creatinine kinase (CK)
- TSH, T3 and T4 free
- CA19-9 (C1/D1) (or CEA or CA-125 for non-expressers of CA19-9)
- Urinalysis
- Serum or urine β-HCG pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG). Results must be reviewed prior to treatment initiation confirming a negative serum β-HCG for women of child-bearing potential and documentation of the patients confirmation of preferred acceptable method of contraception per Section 4.3.4 starting from the day of trial treatment initiation (refer to Section 4.3.4 for more details).
- AEs using the NCI CTCAE V5.0 (Appendix 3)
- Concomitant medication notation of all medications taken within the 30 days prior to C1/D1
- Nivolumab + cabiralizumab + gemcitabine administration
- Day 8, and 15 (± 2 day) of each cycle
- Vital signs
- AEs using the NCI CTCAE 5.0 (Appendix 3)
- Concomitant medication notation
- Hematology: CBC with differential and platelet count - results must be reviewed prior to trial treatment administration
- Serum chemistries (refer to Table 7) - results must be reviewed prior to trial treatment administration
- Gemcitabine administration - Days 8 and 15
- Cabiralizumab administration - Day 15 only Week 7 C2/D15 (-3 days, +10 days)
- Optional repeat biopsy refer to Section 6.1.2.8
- Central Lab Blood Sample to be collected at time of biopsy, 3 X 10 mL vials

End of 2 treatment cycles (every 8 ± 7 days) until disease progression or end of trial, whichever comes first

Note: In order to more precisely determine time to progression, the investigator is encouraged to obtain radiological assessments and CA19-9 values earlier if there is a strong clinical suspicion of disease progression. In order to either confirm or refute the clinical impression.

Duration of Treatment Period: The patient will continue on study and have the assessments performed as detailed above and per Table 5 beyond 3 cycles until there is evidence of clear-cut tumor progression, has treatment ending toxicities, or withdraws from treatment. At which time the patient will be scheduled for the End of Treatment (EOT) visit.

6.1.5.3 End of Treatment (EOT)

The patient will return to the clinic for the EOT visit and have the following performed within 7 days after completing the last dose of study treatment or date of discontinuation.

- Directed physical exam
- ECOG Performance Status (see Appendix 4)
- Vital signs
- ECG
- Hematology: CBC with differential and platelet count
- Serum chemistries
- CA19-9 (or CEA or CA-125 if not expressers of CA19-9)
- Urinalysis
- Serum β-HCG pregnancy test (for WOCBP)
- Central lab blood sample, 3 X10 mL vials
- Concomitant medication
- CT/MRI scan to evaluate disease status (using same imaging method as Baseline, 14 day window) .
- AEs using the NCI CTCAE Version 5.0 (see Appendix 3)
- Review contraception use as required by protocol Section 4.3.4 (where applicable)
- Confirm contact information for patient and a designated family member and remind patient of FU telephone contact that will be conducted every 100 days for survival status after the last safety follow-up visit.

6.1.5.4 Follow-up Period

Three Safety Follow-up visits should be conducted approximately 30, 60, and 100 (±7 days) after the last dose of trial treatment, or date of discontinuation. All participants should complete the three clinical safety follow-up visits regardless of whether new anti-cancer therapy is started, except those participants who will withdraw consent for study participation or are unable to come to clinic due to disease progression. The following assessments will be performed:

- Serum β-HCG pregnancy test (for WOCBP)
- AEs using the NCI CTCAE Version 5.0 (see Appendix 3)
- Review contraception use as required by protocol Section 4.3.4 (where applicable)
- Confirm contact information for patient and a designated family member and remind patient of FU telephone contact that will be conducted every 100 days for survival status.

All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Patients with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first.

SAEs that occur within 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug.

6.1.5.5 Survival Follow-up Phase

Following the 100 days safety follow up, the patients are to be contacted via telephone every 100 days for survival information until death, withdrawal of consent, or the end of the trial, whichever occurs first.

6.2 Adverse Events

6.2.1 Adverse Event Definition

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

Progression of the cancer under study or events which are unequivocally due to disease progression should not be reported as an AE during the study (unless it is considered to be drug related by the investigator).

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

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

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

Although pregnancy and potential drug-induced liver injury (DILI), are not always serious by regulatory definition, however, these events must be reported within the SAEs timeline.

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

NOTE: The following hospitalizations are not considered SAEs:

- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Elective surgery, planned prior to signing consent
- Admissions as per protocol for a planned medical/surgical procedure

- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)

- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.

- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

- Admission for administration of anticancer therapy in the absence of any other SAEs.

6.2.2 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

As far as possible, each adverse event should be evaluated to determine:
- duration (start and end dates)
- severity (grade)
- seriousness
- relationship to study agent
- action taken (i.e., none, study agent modification, medical intervention)
- outcome (i.e., resolved without sequelae, resolved with sequelae, ongoing)

Adverse events monitoring begins after initiation of study treatment and ends 3 days following the last administration of study treatment or start of new anti-cancer therapy, whichever is earlier.

All patients experiencing an adverse event, regardless of its relationship to study drug [or at least possibly related to the drug], will be monitored until:
- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any clinically significant abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

6.23 Laboratory Test Abnormalities

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

The following laboratory abnormalities should be documented and reported appropriately:

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

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

6.24 Reporting Requirements of Adverse Events

6.24.1.1 Expedited Reporting

The **Study Chair** and **multi-sites:** University of Kansas Cancer Center and University of Pennsylvania **Principal Investigator** must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.

SAEs, whether related or not related to study drug, overdoses and pregnancies must be reported to BMS within 24 hours \ 1 Business Day of becoming aware of the event. SAEs must be recorded on either CIOMS, MedWatch, or approved site SAE form.

Pregnancies must be reported and submitted to BMS on any of the following form(s):

1. MedWatch or, CIOMS or
2. BMS Pregnancy Surveillance Form or,
3. Approved site SAE form

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1 609-818-3804

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours \ 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

The **UCSD Human Research Protections Program (HRPP)** and **Moores Cancer Center Data and Safety Monitoring Board (DSMB)** must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others" (UPR).

The following events meet the definition of UPR:

Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.

Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.

Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.

Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.

Any breach in confidentiality that may involve risk to the subject or others.

Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

Multi-sites: The **Institutional Review Board (IRB) of each site** must be notified by the site principal investigator according to their local policies.

The **FDA** must be notified according to the following timelines:

- within 7 calendar days of any unexpected fatal or life-threatening adverse event with possible relationship to study drug, and
- within 15 calendar days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

6.24.1.2 Routine Reporting Requirements

The UCSD HRPP must be notified of any adverse events that are not unanticipated problems involving risk to subjects or others (non-UPRs) at the time of the annual Continuing Review.
The IRB of each site must be notified by the site principal investigator according to their local policies.
The FDA must be notified of all non-serious adverse events annually at the time of the annual report.

6.24.1.3 Serious Adverse Events

All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

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

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

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

An appropriate SAE form (e.g. ex-US = CIOMS form or USA = Medwatch form) should be used to report SAEs to BMS. If you prefer to use your own Institutional form, it must be reviewed by BMS prior to study initiation. Note: Please include the BMS Protocol number on the SAE form or on the cover sheet with the SAE form transmission.

- The CIOMS form is available at: http://www.cioms.ch/index.php/cioms-form-i
- The MedWatch form is available at: MedWatch 3500 Form

The Sponsor will reconcile the clinical database AE cases (**case level only**) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com).

- The Investigator will request from BMS GPV&E, aepbusinessprocess@bms.com the SAE reconciliation report and include the BMS protocol number every 3 months and prior to data base lock or final data summary
- GPV&E will send the investigator the report to verify and confirm all SAEs have been transmitted to BMS GPV&E.
- The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS (Worldwide.Safety@bms.com).

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

In accordance with local regulations, BMS will notify sponsor investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Sponsor investigator notification of these events will be in the form of either a SUSAR Report or a Semi-Annual SUSAR Report.

- Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (e.g., animal) study, important safety

recommendations from a study data monitoring committee, or Sponsor Investigator, or BMS decision to end or temporarily halt a clinical study for safety reasons.

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

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours \ 1 Business Day of becoming aware of the event. SAEs must be recorded on either CIOMS, MedWatch, or approved site SAE form.

Pregnancies must be reported and submitted to BMS. BMS will perform due diligence follow-up using the BMS Pregnancy Form which the investigator must complete.

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SAE Facsimile Number: +1 609-818-3804

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours \ 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

Non-Serious Adverse Event

Non-serious Adverse Events (AE) are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [eg, IND US trial] as part of an annual reporting requirement.

Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Non-serious Adverse Event Collection and Reporting

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

Adverse Events that are routinely collected according to GCP shall be submitted to BMS every three (3) months by the last working day of the third month.

The Adverse Event information required to be sent to BMS is noted in the 'Bristol-Myers Squibb Early Asset Investigator Sponsored Research (ISR) Import Plan' which describes the method of collection and submission to BMS via the mailbox:

MG-RD-GPVE-PHARMACOVIGILANCE@bms.com

When the file is submitted to BMS, it must be noted the file contains All Non Serious Adverse Events (only adverse events not previously submitted to BMS within the 3 months) should be reported.

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

6.24.1.4 Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor Investigator and the Sponsor Investigator will report within 24 hours (working days) to BMS Worldwide Safety.

Events of clinical interest for this trial include:

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.

Potential drug-induced liver injury (DILI) is defined as:

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

AND

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

AND

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

Whenever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs meeting the defined criteria above must be reported as serious adverse events (SAEs). See Section 6.24.1.3 and Appendix 3 for reporting details.

Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product

exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant).

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

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

*Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the CIOMS, MedWatch, BMS Pregnancy Surveillance Form, **or** approved site SAE form. A BMS Pregnancy Surveillance Form may be provided upon request.

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

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any patient must be reported within 24 hours to the Sponsor Investigator and the Sponsor Investigator will report within 24 hours (working days) to BMS Global Safety if it causes the patient to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 100 days following cessation of treatment, or 30 days following cessation of treatment if the patient initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to study drug, must be reported within 24 hours to the BMS Global Safety.

6.25 Evaluating Adverse Events

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

AE Severity Grade

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP website at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Any adverse event which changes CTCAE grade over the course of a given episode will have

each change of grade recorded on the adverse event case report forms/worksheets.

When specific adverse events are not listed in the CTCAE they will be graded by the investigator according to the following grades and definitions, consistent with the CTCAE Version 5.0.

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

Duration

The investigator will record the start and stop dates of the adverse event. If less than1 day, this will be indicated in the appropriate length of time in units.

Action Taken

Did the adverse event cause the trial treatment to be discontinued?

Relationship

All adverse events regardless of CTCAE grade must also be evaluated for causal relationship to trial treatment/ trial interventions.

The determination of the likelihood that trial treatment caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame.

The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the trial treatment and the adverse event based upon the available information.

The following components are to be used to assess the relationship between trial treatment and the AE; the greater the correlation with the components and their respective elements (in

number and/or intensity), the more likely the trial treatment caused the adverse event (AE):

Exposure: Is there evidence that the patient was actually exposed to trial treatment such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

Time Course: Did the AE follow in a reasonable temporal sequence from administration of trial treatment? Is the time of onset of the AE compatible with a drug-induced effect?

Likely Cause: Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors?

Dechallenge: Was trial treatment discontinued or dose/exposure/frequency reduced?

If yes, did the AE resolve or improve? If yes, this is a positive dechallenge.

If no, this is a negative dechallenge.

Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the trial treatment; or (3) the trial is a single-dose drug trial); or (4) trial treatment is/are only used one time.

Rechallenge: Was the patient re-exposed to trial treatment in this trial?

If yes, did the AE recur or worsen?

If yes, this is a positive rechallenge.

If no, this is a negative rechallenge.

Note: If a rechallenge is planned for an adverse event which was serious and which may have been caused by either of the trial treatments, or if re-exposure to trial treatment poses additional potential significant risk to the patient, then the rechallenge must be approved in advance by the Sponsor Investigator as per dose modification guidelines in the protocol.

Consistency with Trial Treatment Profile: Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding trial treatment or drug class pharmacology or toxicology?

Relationship	**Attribution**	**Description**
Unrelated to the trial treatment/intervention	Unrelated	The AE is clearly NOT related to the trial treatment/intervention
	Unlikely	The AE is *doubtfully related* to the trial treatment/intervention
Related to the trial treatment/intervention	Possible	The AE *may be related* to trial treatment/intervention
	Probable	The AE *is clearly related* to trial treatment/intervention

6.26 Investigator Responsibility for Reporting Adverse Events

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

7.0 PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

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

For the purposes of this trial the term *Investigational Products* refer to both nivolumab and cabiralizumab.

Gemcitabine will not be provided to the site as part of this trial but will be obtained directly from the treating investigator's designated pharmacy supply. Therefore the packaging, storage, and handling of gemcitabine will follow the dispensing pharmacy's own standard operation procedures.

7.1 Packaging and Labeling Information

Investigational Product will be provided by BMS. For further instructions regarding the investigation product for this trial please refer to the current version of the Investigator's Brochures for complete storage, handling, dispensing, and infusion information.

7.2 Storage and Handling Requirements

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

The investigator or authorized person at the trial site must maintain records of receipt and ongoing inventory of clinical trial supply of Investigational Products at the site including the dispensing and administration of the Investigational product vials used for each patient.

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

7.2.1 Nivolumab

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) or 40 mg/4 mL (10 mg/mL), is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 80 (Tween™ 80), at pH 6.0 and includes an overfill to account for vial, needle, and syringe holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals. The only difference between the two drug product presentations is the vial fill volume.

Vials of nivolumab injection must be stored at 2°C to 8°C (36°F to 46°F) and protected from light and freezing.

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

7.2.2 Cabiralizumab

Cabiralizumab drug product is supplied for IV administration as a sterile, aqueous, colorless to pale yellow, clear to slightly opalescent, pyrogen-free solution in glass vials stoppered with coated stoppers, and equipped with aluminum seals. Light (few) particulates may be present. Cabiralizumab drug product is shipped refrigerated at 2 - 8°C and stored refrigerated 2- 8°C until time of use. Vials are for single-use only. Drug product should be protected from light and freezing.

7.3 Returns and Reconciliation

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

8.0 STATISTICAL CONSIDERATIONS

8.1 Trial Design

This is an open label single arm clinical trial compared against historical response rates.

A Simon's optimal two-stage design will be used for this study. Up to 15 subjects will be accrued and treated with Nivolumab + cabiralizumab + gemcitabine. The primary endpoint is the proportion who are progression free at 6 months (PFS6) according to RECIST 1.1 criteria. [33] Based on no maintenance after best response to prior chemotherapy [8], historical controls treated with gemcitabine alone had only 4% of patients with no progression at 6 months. If the PFS6 rate in this study is ≤4%, we will consider the treatment as not meeting the threshold of further consideration. We will test the null hypothesis H_0: p≤ 4% against the alternative hypothesis H_1: p>22%, where p is the progression free response rate after six months of study treatment. The two-stage design proposed below will have 80% power to reject the null hypothesis at 10% significance level and conclude that the true PFS rate at 6 months is above 4%, if the observed PFS6 rate is ≥22%. The study design is described in detail is as follows:

Stage 1: 8 subjects will be treated; if needed, accrual will be held until the progression results for these subjects are known for the first six months. The trial will be terminated at Stage 1 if none of the 8 subjects are progression free at 6 months; otherwise it will continue to Stage 2.

Stage 2: 7 more patients will be accrued. We will reject the therapy if, among all the 15 (8+7) subjects, the number of patients who have a PFS6 response is ≤1; if ≥2 patients are progression free at 6 months by RECIST 1.1, the treatment will be claimed to be successful. We will conclude that the study treatment is associated with a progression free response in more than 4% of patients at 6 months.

Note that if a patient is not evaluable at 6 months (e.g., if there is an early dropout), as specified in section 8.2.5, it will be treated as disease progression for the primary efficacy outcome.

Early stopping probability: Under this design, if the null hypothesis is true, the probability of stopping the trial early will be 72.1%. The sample size calculation was done using PASS version 14.0.3 (released September 22, 2015). Sample size calculation did not incorporate the safety endpoint. Statistics for safety outcomes will be presented descriptively.

We expect to accrue 1-2 patients every month. All patients will be accrued within 14-21 months. Patients will be followed for 6 months. The total duration of this study will be about 20-27 months.

8.2 Statistical Analysis Plan

8.2.1 Analysis of primary endpoint

Primary efficacy analysis includes interim efficacy analysis and final efficacy analysis for the primary endpoint.

The interim efficacy analysis will be conducted at the end of Stage 1. The study enrollment will be put on hold for interim analysis until tumor response results for Stage 1 patients are known.

The final efficacy analysis will calculate the UMVUE estimate of PFS at 6 months, p-value and 95% CI for progression free response rates.[39, 40] The calculation will be performed using R *clinfun* package (www.r-project.org).

8.2.2 Analysis of the Conduct of the Trial

Enrollment, major protocol violations, and discontinuations for the trial will be summarized using a CONSORT diagram.

8.2.3 Analysis of Patient Characteristics

Demographic and baseline characteristics, such as age, race, BSA, duration of pancreatic cancer, site(s) of metastatic disease, prior cancer treatment, and baseline ECOG performance status will be summarized using medians (range) for continuous variables and proportions for categorical variables.

8.2.4 Analysis of Study Treatment Administration

Study treatments dose administration will be listed and dose modifications will be flagged.

8.2.5 Definition of study population for primary efficacy analysis

All subjects who undergo at least one dose of the study treatment will be included in the analysis. For the primary endpoint, “Intention-to-treat” analyses will be performed for an endpoint. To be specific, if the endpoints for a subject cannot be assessed (for example, a subject drops out early prior to the 6 months assessments due to any reason), it will be considered to be an event that does not favour the study therapy (e.g., disease progression for the primary outcome).

8.2.6 Analysis of Secondary Endpoints

8.2.6.1 Safety Analyses

This study can also be stopped early due to safety reasons, please refer to section 4.6 for more details.

Safety analyses will be performed for all patients having received at least one dose of study treatment. The proportion of subjects experiencing adverse events, serious adverse events, and treatment delays will be summarized. Tolerability will be assessed based on dosage delays and discontinuation due to adverse events.

All AEs will be listed, documenting the course, outcome, severity, and relationship to the study treatment. Incidence rates of AEs and the proportion of subjects prematurely withdrawn from the study due to AEs will be shown**.**

8.2.6.2 Secondary Efficacy Analyses

Secondary efficacy analysis will be performed for outcomes including progression free survival over the course of the study, duration of response, disease control rate and overall survival. For survival outcomes including overall survival, median survival times together with their 95% confidence intervals will be estimated with the Kaplan-Meier method, and report number of events. For proportions, a 95% confidence interval will be calculated using the exact method.

8.2.7 Analysis of Exploratory Endpoints

8.2.7.1 Comparison of RECIST 1.1 and iRECIST criteria

Given that both nivolumab and cabiralizumab are immunotherapy agents, disease progression will be defined by RECIST and iRECIST criteria (Appendix 5). Proportion of progression-free patients at 6 months using iRECIST will be performed using the same method as for the primary endpoint of RECIST 1.1. Cross tables of response categories from the two criteria will be presented. Number and proportion of patients who are considered to be PFS based on RECIST but a non-response based on iRECIST (and vice versa) will be described.

Tumour and blood samples will be collected pre-treatment and during treatment. These biomarker assessments will potentially aid in understanding treatment efficacy. All samples will be linked anonymised and only identified by the trial ID and unique sample number

allocated by the trial coordinating team. The results of any exploratory analysis will not be included in the clinical study report and may be reported separately from the main study results. Association between a biomarker and a response outcome will be assessed using Cox models. The stage (1 vs 2) variable will be included as a covariate.

9.0 ADMINISTRATIVE AND REGULATORY DETAILS

9.1 Institutional Review Board/Ethics Committee Approval

Before trial initiation, this protocol and informed consent form will be submitted for review and approval to the IRBs charged with oversight for the clinical sites. In addition, any form of proposed advertising and advertising text for patient recruitment must be reviewed and approved by the IRB. The Investigator will forward to the Sponsor Investigator a copy of the IRB's approval of this protocol, any amendments, informed consent form, and any modifications to the informed consent, based on the FDA regulations set forth in 21 CRF 56 of the *Code of Federal Regulations.*

In addition, the Investigator will be responsible for forwarding to the Sponsor Investigator a description of the IRB members (including profession and affiliation) or a United States (US) Department of Health and Human Services (DHHS) General Assurance number and expiration date. If neither of these is available, the chairperson must submit a statement indicating that the members of the board responsible for the review meet the FDA and other appropriate regulatory requirements. In addition, the labeling for all approved trial medications should be submitted to the IRB for information purposes.

Clinical supplies will not be shipped to the clinical site until IRB approval is obtained for the protocol. Any existing amendments, informed consent, and photocopies of the approved documents must be received by the Sponsor Investigator prior to drug shipment.

9.2 Investigators protocol agreement

The Investigator must sign the Investigator's Protocol Agreement. The original must be kept on file by the Sponsor Investigator and the Investigator must retain a copy. The completed Investigator's Protocol Agreement signifies agreement to comply with all procedures outlined by this protocol by the Investigator. An Investigator's Protocol Agreement must be signed if and when a protocol amendment is issued.

9.3 Remaining Samples

Any samples remaining after the trial specified analyses is completed will be stored by the Sponsor Investigator at UCSD if the patient consented for use of their remaining samples for future research purposes. This includes the original specimen collected from the patient [blood, tumor tissue]) as well as derivatives created from the original specimen (DNA, RNA, blocks or slides).

If a patient has not consented for their remaining samples to be used for future research purposes, remaining samples and derivatives will be destroyed and documented on the Sample Destruction/Return Request Form- refer to Trial Laboratory Manual.

9.4 Confidentiality

The Investigator and any other personnel involved in this trial shall not disclose, or use for any purposes (other than for the performance of this trial any data, records, or other information (hereinafter collectively “information”) disclosed to the Investigator or other trial personnel. Such information shall remain the confidential and proprietary property of the Sponsor Investigator, BMS and SU2C, and shall be disclosed only to the Investigator or other designated trial personnel.

Patient confidentiality will be ensured by using assigned site-specific Screening and Randomization numbers (refer to Section 6.1) throughout the trial.

9.5 Publication

As a general rule, no trial results should be published without prior approval of the Sponsor Investigator. The rights of the investigator and the Sponsor Investigator with regard to publication of the results of this trial are described in the investigator contract.

9.6 Compliance with Financial Disclosure Requirements

All Investigators will be required to submit written financial disclosures to the Sponsor Investigator prior to participating in this clinical trial and any changes in disclosures during the course of the trial as per 21 CFR part 54.

9.7 Compliance with Trial Registration and Results Posting Requirements

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

9.8 Required Site Documentation

Before the study can be initiated at any site, the following documentation must be provided to the UCSD Moores Cancer Center Clinical Trials Office.

- A copy of the official IRB approval letter for the protocol and informed consent.
- A copy of the IRB-approved consent form.
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation.
- CAP and CLIA Laboratory certification numbers and institution lab normal values.
- Executed clinical research contract.

9.8.1 Site Registration Procedures

All patients must be registered with the UCSD Moores Cancer Center Clinical Trials Office

before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the UCSD Study Coordinator. To register a patient, call Monday through Friday, 8:00AM-4:30PM. Study sites other than UCSD must fax informed consent documentation, completed eligibility checklist, and all source documentation for eligibility confirmation to the UCSD Clinical Trials Office (Fax: 858-822-5360). Once eligibility is confirmed, patient will be given a unique sequential study number.

Patients will be given a unique sequential study number and will be randomized at the time of enrollment. UCSD will fax the outside study site for confirmation of patient registration and ability to start study treatment, the patient's study number, and the Arm the patient is randomized to.

9.8.2 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), subjects who have provided written informed consent must also sign a subject authorization to release medical information to the study Sponsor and allow a regulatory authority, or Institutional Review Board access to subject's medical information relevant to the study.

9.9 Quality Management System

All aspects of the study will be carefully monitored by the Sponsor Investigator and/or its authorized representative for compliance with applicable government regulations with respect to current ICH GCP guidelines as well as other applicable regulations and guidelines.

9.9.1 Data Monitoring Plan

Data monitoring procedures will be carried out by the Sponsor Investigator for all participating sites, and will be performed on a regular basis to comply with Good Clinical Practice guidelines.

Review of the case report forms, cross-reference with source documents (including radiology review), review of trial related regulatory documents and logs (e.g. enrollment, trial site staff), would be monitored on an ongoing basis during monitoring sessions. The monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements.

The monitor will complete a written monitoring report and provide to the Sponsor Investigator. The report will include a summary of what the site monitor reviewed and the site monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to ensure compliance. The site Principal Investigator will be expected to submit any Corrective Action Plans, in writing, to the Sponsor Investigator. A copy of the monitoring forms, final monitoring reports, and Corrective Action Plan will be kept in the site monitor's trial file follow up at the next monitoring session.

9.9.2 Data Safety Monitoring

Data and Safety Monitoring/Auditing

Data and Safety reporting will be supported by the study statisticians according to the monitoring plan. Briefly, comprehensive safety and data monitoring reports will be generated

every six months for review by the study team before being sent to the UCSD DSMC, described below. The study will used the VELOS electronic data capture system at UCSD.

In addition to adverse event monitoring and clinical oversight by the principal investigator and co-investigators, this study will also use the UCSD Moores Cancer Center Data Safety and Monitoring Committee (DSMC) to provide oversight in the event that this treatment approach leads to unforeseen toxicities. Data from this study will be reported semi-annually and will include:

1) the protocol title, IRB protocol number, and the activation date of the study.
2) the number of patients enrolled to date
3) the dates of patient enrollment
4) demographic summary of patients
5) a summary of safety including all death, and adverse events regardless of grade and attribution
6) a response evaluation for evaluable patients when available
7) a summary of any recent literature that may affect the ethics of the study.

9.10 Data Management

9.10.1 Case Report Forms

All the clinical data will be captured by the site on electronic case report forms (eCRFs). The eCRFs will be used for all consented patients. The investigator and trained trial personnel will enter and edit the data via a secure network, with secure identification and password requirement. A complete electronic audit trial will be maintained. The investigator will be required to provide approval of all data to confirm accuracy. Copies of the eCRFs will be provided to the investigator at the conclusion of the trial.

9.10.2 Source Documents

Source documents serve as the evidence of the existence of the patient and the data collected for this trial. Source documents will be the responsibility of the Investigator and will be filed at the site and available as needed by the Sponsor Investigator or assigned clinical monitor.

Data captured on the eCRF is to be transcribed from source document and must be consistent with any discrepancies explained and documented.

REFERENCES

1. Cancer Facts and Figures 2018, in American Cancer Society.2018: Atlanta.

2. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014 Jun 1;74(11):2913-21. doi: 10.1158/0008-5472.

3. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, Niedergethmann M, Zülke C, Fahlke J, Arning MB, Sinn M, Hinke A, Riess H. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA. 2013 Oct 9;310(14):1473-81. doi: 10.1001/jama.2013.279201.

4. Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, Padbury R, Moore MJ, Gallinger S, Mariette C, Wente MN, Izbicki JR, Friess H, Lerch MM, Dervenis C, Oláh A, Butturini G, Doi R, Lind PA, Smith D, Valle JW, Palmer DH, Buckels JA, Thompson J, McKay CJ, Rawcliffe CL, Büchler MW; European Study Group for Pancreatic Cancer.. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA. 2010 Sep 8;304(10):1073-81. doi: 10.1001/jama.2010.1275.

5. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M; Groupe Tumeurs Digestives of Unicancer.; PRODIGE Intergroup.. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011 May 12;364(19):1817-25. doi: 10.1056/NEJMoa1011923.

6. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013 Oct 31;369(18):1691-703. doi: 10.1056/NEJMoa1304369.

7. Jameson G, Borazanci E, Babiker H, Poplin E, Niewiarowska A,. Gordon M, Barrett M, Ansaldo K, Lebron L, Stoll A, Rosenthal A, Shemanski L, Korn R, Ramanathan R.K, Von Hoff D.D. A phase Ib/II pilot trial with nab-paclitaxel plus gemcitabine plus cisplatin in patients (pts) with stage IV pancreatic cancer. J Clin Oncol 35, 2017 (suppl 4S; abstract 341).

8. Reni, Michele et al. Maintenance sunitinib or observation in metastatic pancreatic adenocarcinoma: A phase II randomised trial European Journal of Cancer, Volume 49 Issue 17, 3609 – 3615.

9. De Palma M, Lewis CE. Macrophage regulation of tumor responses to anticancer therapies. Cancer Cell. 2013 Mar 18;23(3):277-86. doi: 10.1016/j.ccr.2013.02.013.Review. PubMed PMID: 23518347.

10. Qian BZ, Pollard JW. Macrophage diversity enhances tumor progression and metastasis. Cell. 2010 Apr 2;141(1):39-51. doi: 10.1016/j.cell.2010.03.014. Review. PubMed PMID: 20371344; PubMed Central PMCID: PMC4994190.

11. DeNardo DG, Brennan DJ, Rexhepaj E, Ruffell B, Shiao SL, Madden SF, Gallagher WM, Wadhwani N, Keil SD, Junaid SA, Rugo HS, Hwang ES, Jirström K, West BL,Coussens LM. Leukocyte complexity predicts breast cancer survival and functionally regulates response to chemotherapy. Cancer Discov. 2011 Jun;1(1):54- 67. doi: 10.1158/2159-8274.CD-10-0028. Epub 2011 Jun 1. PubMed PMID: 22039576; PubMed Central PMCID: PMC3203524.

12. Mantovani A, Marchesi F, Malesci A, Laghi L, Allavena P. Tumour-associated macrophages as treatment targets in oncology. Nat Rev Clin Oncol. 2017 Jul;14(7):399-416. doi: 10.1038/nrclinonc.2016.217. Epub 2017 Jan 24. Review. PubMed PMID: 28117416; PubMed Central PMCID: PMC5480600.

13. Nielsen SR, Schmid MC. Macrophages as Key Drivers of Cancer Progression and Metastasis. Mediators Inflamm. 2017;2017:9624760. doi: 10.1155/2017/9624760. Epub 2017 Jan 22. Review. PubMed PMID: 28210073; PubMed Central PMCID: PMC5292164.

14. Xu H, Lai W, Zhang Y, Liu L, Luo X, Zeng Y, Wu H, Lan Q, Chu Z. Tumor-associated macrophage-derived IL-6 and IL-8 enhance invasive activity of LoVo cells induced by PRL-3 in a KCNN4 channel-dependent manner. BMC Cancer. 2014 May 10;14:330. doi: 10.1186/1471-2407-14-330. PubMed PMID: 24885636; PubMed Central PMCID: PMC4024187.

15. Cannarile MA, Weisser M, Jacob W, Jegg AM, Ries CH, Rüttinger D. Colony-stimulating factor 1 receptor (CSF-1R) inhibitors in cancer therapy. J Immunother Cancer. 2017 Jul 18;5(1):53. doi: 10.1186/s40425-017-0257-y. Review. PubMed PMID: 28716061; PubMed Central PMCID: PMC5514481.

16. Candido JB, Morton JP, Bailey P, Campbell AD, Karim SA, Jamieson T, Lapienyte L, Gopinathan A, Clark W, McGhee EJ, Wang J, Escorcio-Correia M, Zollinger R, Roshani R, Drew L, Rishi L, Arkell R, Evans TRJ, Nixon C, Jodrell DI, Wilkinson RW, Biankin AV, Barry ST, Balkwill FR, Sansom OJ. CSF-1R+ Macrophages Sustain Pancreatic Tumor Growth through T Cell Suppression and Maintenance of Key Gene Programs that Define the Squamous Subtype. Cell Rep. 2018 May 1;23(5):1448- 1460. doi: 10.1016/j.celrep.2018.03.131

17. Cabiralizumab (FPA008) Anti-CSF-1R Humanized IgG4 Monoclonal Antibody Investigator's Brochure v4. May 2017.

18. Wainberg ZA, Piha-Paul SA, Luke JJ, et al. First-in-Human Phase 1 Dose Escalation and Expansion of a Novel Combination, Anti–CSF-1 Receptor (cabiralizumab) Plus Anti–PD-1 (nivolumab), in Patients With Advanced Solid Tumors. Presented at: 32nd SITC Annual Meeting; November 8-12, 2017; National Harbor, MD. Abstract O4

19. Carleton M, Powers J, Philips P, Beg M, et al. Pharmacodynamics and genomic profiling of patients treated with cabiralizumab plus nivolumab provide evidence of on- target tumorimmune modulations and support future clinical applications . ASCO Annual Meeting 2018; June 1-5, 2018; Chicago IL, Abstract #3020.

20. Pardoll D. Does the immune system see tumors as foreign or self? Annu Rev Immunol. 2003;21:807-39.

21. Zitvogel L, Tesniere A, Kroemer G. Cancer despite immunosurveillance: immunoselection and immunosubversion. Nat Rev Immunol. 2006;6:715-27.

22. Dunn GP, Bruce AT, Ikeda H, et al. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol. 2002;3:991-8.

23. Greenwald RJ, Freeman GH, Sharpe AH. The B7 family revisited. Annu Rev Immunol. 2004;23:515-48.

24. Freeman FJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunohibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 2000; 192(7): 1027-34.

25. Sharpe AH, Wherry EJ, Ahmed R, et al. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. Nature Immunol. 2007;8:237-45.

26. Keir M E, Butte M J, Freeman G J, Sharpe A H. PD-1 and Its Ligands in Tolerance and Immunity. Ann. Rev. Immunol. 2008;26:677–704.

27. Latchman Y, Wood CR, Chernova T, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. Nat Immunol. 2001;2:261-8.

28. Carter LL, Fouser LA, Jussif J, et al. PD-1: PD-L1 inhibitory pathway affects both CD4+ and CD8+ T cells and is overcome by IL-1. Eur J Immunol. 2002;32:634-43.

29. Barber DL, Wherry EJ, Masopust D et al. Restoring function in exhausted CD8 T cells during chronic viral infection. Nature 2006;439:682-7.

30. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nature 2012;12:252-64.

31. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009;15:7412- 20.

32. BMS-936558 Investigator Brochure v16. 23-June-2017. Document Control No. 930038243.

33. Eisenhauer EA, Therasse P, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).Eur J Cancer. 2009 Jan;45(2):228-47.

34. PASS 15 Power Analysis and Sample Size Software (2017). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.

35. Miettinen, O.S. and Nurminen, M. 1985. 'Comparative analysis of two rates.' Statistics in Medicine 4: 213-226.

36. StatXact® 11, Cytel Corporation

37. Lakatos, Edward. 1988. 'Sample Sizes Based on the Log-Rank Statistic in Complex Clinical Trials', Biometrics, Volume 44, March, pages 229-241.
38. Lakatos, Edward. 2002. 'Designing Complex Group Sequential Survival Trials', Statistics in Medicine, Volume 21, pages 1969-1989
39. Jung SH, Kim KM. On the estimation of the binomial probability in multistage clinical trials. Statistics in Med. 2004; 23: 881-96.
40. Koyama T, Chen H. Proper inference from Simon’s two-stage designs. Statistics in Med. 2008; 27: 3145-54.

APPENDICES

Appendix 1 – Nivolumab Package Insert

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125554s058lbl.pdf

Appendix 2 – Gemcitabine Package Insert

https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/020509s033lbl.pdf

Appendix 3 – NCI CTCAE version 5.0

The CTCAE Version 5.0 can be accessed and downloaded from the CTEP website at:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

Appendix 4 – ECOG Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group.*Am J Clin Oncol.* 1982;5:649-655.

Appendix 5 – Protocol Criteria for Measurement of Trial Endpoint RECIST 1.1 and iRECIST

1. Definitions

1.1. Evaluable for adverse events. All patients will be evaluable for adverse event evaluation from the time of their first treatment.

1.2. Evaluable for response. All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below.

Response and progression will be evaluated in this study using the revised international criteria (1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumours) committee as well as the modified iRECIST guidelines. Investigators should note the different requirements for confirmatory scans as well as follow up for the two criteria.

See section 6.1.2.6 for criteria for continuing treatment past RECIST 1.1 disease progression.

2. RECIST 1.1 Response and Evaluation Endpoints

2.1. Measurable Disease. Measurable tumour lesions (nodal, subcutaneous, lung parenchyma, solid organ metastases) are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with chest x-ray and as ≥10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥10 mm by CT scan). Malignant lymph nodes must be ≥15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumour measurements must be recorded in millimetres (or decimal fractions of centimetres). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

2.2. Non-measurable Disease. All other lesions (or sites of disease), including small lesions are considered non- measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non- measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

2.3. Target Lesions. When more than one measurable tumour lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 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 longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Note that pathological nodes must meet the criterion of a short axis of ≥15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed (see 8.2.4). At baseline, the sum of the target lesions (longest diameter of tumour lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

2.4. Non-target Lesions. All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered non- target lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as “present” or “absent”.

2.5. Response.

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of target and non-target lesions and normalization of tumour markers. Pathological lymph nodes must have short axis measures <10 mm (Note: continue to record the measurement even if <10 mm and considered CR). Residual lesions (other than nodes <10 mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases[4] before CR can be accepted. Confirmation of response is only required in non-randomised studies.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumour lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD. Confirmation of response is only required in non-randomised studies.

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

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥5 mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-

target disease may be accepted as evidence of disease progression, where the overall tumour burden has increased sufficiently to merit discontinuation of treatment or where the tumour burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Table S1: Integration of target, non-target and new lesions into response assessment

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category also Requires
Target lesions ± non target lesions				
CR	CR	No	CR	Normalization of tumour markers, tumour nodes <10 mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	Documented at least once ≥4 wks. from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Non target lesions ONLY				
No Target	CR	No	CR	Normalization of tumour markers, tumour nodes <10 mm
No Target	Non-CR/non-PD	No	Non-CR/non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes*	PD	

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

*Investigators should record all new lesions; if the new lesion is felt to be equivocal, treatment may be continued pending further assessments – see table S2.

3. iRECIST Response Assessment

Overall response will also be assessed using iRECIST. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumour burden, or the appearance of new lesions, does not reflect true

tumour progression.

Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix. iRECIST time-point and best overall responses will be recorded separately.

3.1. Confirming Progression

Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD.

iCPD is confirmed if further increase in tumour burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumour burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions
    - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
    - Continued unequivocal progression in non-target disease with an increase in tumour burden
    - Increase in size of previously identified new lesion (s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST 1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline). As can be seen in table 2, the prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented at the next assessment after iUPD.

3.2. New lesions

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions), and recorded as New Lesions-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case record form.

PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions.

Table S2: Time-point (TP) iResponse

Target Lesions*	Non-Target Lesions*	New Lesions*	Time Point Response	
			No prior iUPD**	Prior iUPD**; ***
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD)
iUPD	Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on: o further increase in SOM of at least 5 mm, otherwise remains iUPD
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: o previously identified T lesion iUPD SOM ≥5 mm and / or o NT lesion iUPD (prior assessment - need not be unequivocal PD)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: o previously identified T lesion iUPD ≥5 mm and / or o previously identified NT lesion iUPD (need not be unequivocal) and /or o size or number of new lesions previously identified

Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on o increase in size or number of new lesions previously identified
* Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same. ** in any lesion category. *** previously identified in assessment immediately prior to this TP.				

All patients will have their iBOR from the start of study treatment until the end of treatment classified as outlined below.

Table S3: iRECIST Best Overall Response (iBOR)

TPR1	TPR2	TPR3	TPR4	TPR5	iBOR
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR, iPR, iSD, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	PR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, ICPD, NE	iSD
iUPD	iCPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD

1. Table assumes a randomised study where confirmation of CR or PR is not required.
2. NE = not evaluable that cycle.
3. Designation "I" for BOR can be used to indicate prior iUPD to aid in data interpretation.
4. For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation.

5. Response and Stable Disease Duration (RECIST 1.1 and iRECIST)

Response duration will be measured from the time measurement criteria for CR/PR or iCR/iPR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

Stable disease duration will be measured from the time of start of treatment until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

6. Methods of Measurement

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. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small

(e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

6.1. Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

6.2. Chest X-ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

6.3. CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Other specialized imaging or other techniques may also be appropriate for individual case.[4] For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast). PET scans per PI discretion.

6.4. Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

6.5. Endoscopy, Laparoscopy. The utilization of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

6.6. Tumour Markers. Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response.

6.7. Cytology, Histology. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the

measurable tumour has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

Appendix 6 – Adverse Event Management for Cabiralizumab and Nivolumab Combination Therapy Cohorts

Gastrointestinal Adverse Event Management		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab 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 v5.0)	**Management**	**Treatment and Follow-Up**
Grade 1: Diarrhea:<4 stools/day over baseline; Colitis: asymptomatic	– Continue cabiralizumab andnivolumab 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/day over baseline; IV fluids indicated <24 hours; not interfering with ADL; Colitis: abdominal pain; blood in stool	– Delay cabiralizumab and nivolumab per protocol – Symptomatic treatment	**If improves to Grade 1 in ≤4 days:** – Resume cabiralizumab and nivolumab therapy per protocol **If persists in 5–7 days or recurs:** – 0.5–1 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 cabiralizumab and nivolumab therapy per protocol **If worsens or persists after >3-5 days with oral steroids:** – Treat as Grade 3 or 4
Grade 3–4: Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hours; interfering with ADL; Colitis (G3): Severe abdominal pain, medical intervention indicated, and peritoneal signs **Grade 4:** Life-threatening perforation	– Delay or discontinue cabiralizumab and nivolumab therapy per protocol – 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent[a] – Add prophylactic antibiotics for opportunistic infections – Consider lower endoscopy if clinically indicated	**If Grade 3 AE improves to Grade 1 or baseline within 28 days:** – Taper steroids over at least 1 month – Resume dosing of cabiralizumab and nivolumab **If Grade 4:** – Permanently discontinue cabiralizumab and nivolumab – Continue steroids until Grade 1, then taper steroids over at least 1 month **If persists for >3-5 days or recurs after improvement:** – Add infliximab 5 mg/kg (if no contraindications) – Follow up until resolution – Note: Infliximab should not be used in cases of perforation or sepsis

[a] Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, 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		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab therapy.		
Grade of Creatinine Elevation (NCI CTCAE v 5.0)	**Management**	**Follow-Up**
Grade 1: Creatinine >1.0x to 1.5x baseline; >1 x ULN to 1.5x ULN	– Continue cabiralizumab and nivolumab therapy at the same dose level per protocol – Monitor creatinine weekly	**If returns to baseline :** – Resume routine creatinine monitoring per protocol **If worsens:** – Follow as stated below
Grade 2: Creatinine >1.5x to 3.0x baseline; >1.5 x ULN to 3.0x ULN	– Delay cabiralizumab and nivolumab therapy per protocol – Monitor creatinine every 2 to 3 days – 0.5 to 1 mg/kg/day methylprednisolone IV or oral equivalent[a] – Consider renal biopsy if clinicallyindicated	**If returns to Grade 1 or baseline before the next dosing visit:** – Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume cabiralizumab and nivolumab therapy at the same dose level – Routine creatinine monitoring per protocol **If elevations persist for >14 days or worsen:** – Treat as Grade 4
Grade 3: Creatinine >3.0 x baseline; >3.0x ULN to 6.0x ULN	– Delay cabiralizumab and nivolumab therapy per protocol – Monitor creatinine every 2 to 3 days – 0.5 to 1 mg/kg/day methylprednisolone IV or oral equivalent[a] – Consider renal biopsy if clinicallyindicated	**If returns to Grade 1 or baseline before the next dosing visit:** – Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume cabiralizumab and nivolumab therapy at the same dose level – Routine creatinine monitoring per protocol **If elevations persist for >14 days or worsens:** – Treat as Grade 4
Grade 4: Creatinine >6.0x ULN	– Discontinue cabiralizumab andnivolumab therapy per protocol – 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent[a] – Consult nephrologist – Consider renal biopsy if clinicallyindicated	**If returns to baseline or Grade 1:** – Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections **If worsens:** – Follow up until resolution – Clinical referrals as needed

[a] Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, 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		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab therapy. Evaluate with imaging and pulmonary consultation.		
Grade of Pneumonitis (NCI CTCAE v 5.0)	**Management**	**Follow-Up**
Grade 1: Radiographic changes only	– Consider delay of cabiralizumab and nivolumab therapy – Monitor for symptoms every 2 to 3 days – Consider pulmonary and infectious disease 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 cabiralizumab and nivolumab therapy per protocol – Pulmonary and infectious disease consults – Monitor symptoms daily, consider hospitalization – 1 mg/kg/day methylprednisolone IV or oral equivalent – Consider bronchoscopy and lung biopsy, if clinically indicated	– Re-image every 1–3 days **If improves <14 days:** – When symptoms return to near baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections and resume cabiralizumab and nivolumab therapy per protocol **If does not improve after 2 weeks or worsens:** – Treat as Grade 3–4
Grade 3–4: Severe new symptoms; New/worsening hypoxia; Life-threatening	– Discontinue cabiralizumab and nivolumab therapy per protocol – Hospitalization – Pulmonary and infectious disease consults – 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent[b] – Add prophylactic antibiotics for opportunistic infections – Consider bronchoscopy, lung biopsy if clinically indicated	**If improves to baseline:** – Taper steroids over at least 6 weeks **If does not improve after 48 hours or worsens:** – Add additional immunosuppression (eg, cyclophosphamide, IVIG, or mycophenolate mofetil) – Follow up until resolution

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

Hepatic Adverse Event Management Without Liver Metastasis		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab therapy. Consider imaging for obstruction.		
Grade of Liver Test Elevation	**Management**	**Follow-Up**
AST or ALT >3.0x ULN ***and*** Total bilirubin >2x ULN **or** INR > 1.5	– Discontinue cabiralizumab and nivolumab per protocol – Start steroids	– Continue LFT monitoring per protocol until resolution. – Continue monitoring for and other associated clinical signs or symptoms – Contact the Sponsor – Evaluate for non-drug related causes of the laboratoryabnormalities (eg, obstruction, viral infection, Gilbert's disease, etc.) – Under selected circumstances (eg, alternative etiology is identified), patient may receive additional therapy only after consultation and agreement between the Sponsor/MM and the investigator if receiving additional treatment with cabiralizumab and nivolumab is in the best interest of the patient (eg, if the subject has demonstrated a response to therapy)
AST or ALT >5 to ≤12 xULN ***and*** Total bilirubin ≤2x ULN	– Continue cabiralizumab and nivolumab therapy if there are no clinical signs of significant muscle or hepatic damage – Increase frequency of monitoring of AST, ALT, bilirubin, alkaline phosphatase, and INR (every 48-72 hours or more frequently, as clinically indicated) – Monitor for other clinical symptoms (fatigue, nausea, vomiting, abdominal pain, fever, rash, and/or eosinophilia)	– Contact the Sponsor if there are clinical signs of muscle or hepatic injury or other clinical symptoms – Contact the Sponsor if there is a concurrent increase of bilirubin, AST, ALT, or alkaline phosphatase – Notify the Sponsor if there is an AST or ALT increase >5x ULN – Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic – Consider gastroenterology or hepatology referral
AST or ALT > 12 to ≤ 20 xULN ***and*** Total bilirubin ≤ 2 xULN ***or*** Isolated total bilirubin > 2 to ≤ 3 xULN	– Delay cabiralizumab and nivolumab therapy per protocol – Increase frequency of monitoring of (including but not limited to) AST, ALT, bilirubin, alkaline phosphatase, and INR (every 48-72 hours or more frequently, as clinically indicated) – If there is a 2-fold ALT increase compared to the previous measurement, start steroids immediately – Consider steroid treatment on any total bilirubin increase of over 2.0x ULN – If there is a concurrent increase of alkaline phosphatase along with ALT, start steroids immediately	**If AST/ALT return to ≤12x ULN within ≤7 days:** – Resume routine monitoring – Resume cabiralizumab and nivolumab therapy at same dose level per protocol **If elevations persist and remain at the same level >7 days but ≤28 days:** – Start steroids immediately and discontinue further dosing – Continue monitoring and consider dosing the subject with nivolumab therapy at the same dose level – Consider tapering steroids over at least 1 month **If elevations persist at the same level >28 days or worsen:** – Discontinue cabiralizumab and nivolumab therapyper protocol – 0.5-1 mg/kg/day methylprednisolone or oral equivalent, and when LFT returns to Grade 1 or baseline, taper steroids over at least 1 month – Consider prophylactic antibiotics for opportunistic infections – Discuss with Sponsor

Hepatic Adverse Event Management Without Liver Metastasis		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab therapy. Consider imaging for obstruction.		
Grade of Liver Test Elevation	**Management**	**Follow-Up**
	– Monitor for other clinical symptoms (fatigue, nausea, vomiting, abdominal pain, fever, rash, and/or eosinophilia)	
AST or ALT > 20 xULN ***or*** Total bilirubin >3 xULN	– Discontinue cabiralizumab and nivolumab therapy – Increase frequency of monitoring to every 1 to 2 days – Consider 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent[a] – Consider adding prophylactic antibiotics for opportunistic infections – Consult gastroenterologist and hepatologist, if clinically indicated	**If returns to Grade 2:** – Consider steroid taper over at least 1 month if they have been started **If does not improve in >3–5 days, worsens, or rebounds:** – Consider adding mycophenolate mofetil 1 g BID – If no response within an additional 3–5 days, consider other immunosuppressants per local guidelines – Follow up until resolution

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

Hepatic Adverse Event Management with Liver Metastasis		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab therapy. Consider imaging for obstruction.		
Grade of Liver Test Elevation	**Management**	**Follow-Up**
AST or ALT >3.0x ULN ***and*** Total bilirubin >2x ULN **or** INR > 1.5	– Discontinue cabiralizumab and nivolumab therapy per protocol –	– Continue LFT monitoring per protocol until resolution. – Continue monitoring for and other associated clinical signs or symptoms – Contact the Sponsor – Evaluate for non-drug-related causes of the laboratory abnormalities (e.g. obstruction, viral infection, Gilbert's disease, etc) – Under selected circumstances (e.g alternative etiology is identified), the patient may receive additional therapyonly after consultation and agreement between the Sponsor/MM and the investigator if receiving additional treatment with cabiralizumab and nivolumab is in the best interest of the patient (e.g if the subject has demonstrated a response to therapy)
AST or ALT > 5 to ≤ 12 xULN ***and*** Total bilirubin ≤ 2 xULN	– Continue cabiralizumab and nivolumab therapy if there are no clinical signs of significant muscle or hepatic damage – Increase frequency of monitoring of AST, ALT, bilirubin, alkaline phosphatase and INR (every 48-72 hours or more frequently, as clinically indicated) – Monitor for other clinical symptoms (fatigue, nausea, vomiting, abdominal pain, fever, rash, and/or eosinophilia)	– Contact the Sponsor if there are clinical signs of muscle or hepatic injury or other clinical symptoms – Contact the Sponsorif there is a concurrent increase of bilirubin, AST, ALT, or alkaline phosphatase – Notify the Spnsor if there is an AST or ALT increase > 5 xULN – Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic. – Consider gastroenterology or hepatology referral
AST or ALT > 12 to ≤ 20xULN ***and*** Total bilirubin ≤ 2 xULN ***or*** Isolated total bilirubin > 3.0 to ≤ 5 xULN	– Delay cabiralizumab and nivolumab therapy perprotocol – Increase frequency of monitoring of (including but not limited to) AST, ALT, bilirubin, alkaline phosphatase, and INR (every 48-72 hours or more frequently, as clinically indicated) – If there is a 2-fold ALT increase compared to the previous measurement, start steroids immediately – Consider steroid treatment on any total bilirubin increase of over 2.0x ULN	**If AST/ALT return to ≤ 12 xULN within ≤ 7 days:** – Resume routine monitoring, resume cabiralizumab and nivolumab therapy at same dose level per protocol **If elevations persist and remain at the same level > 7 days but ≤ 28 days:** – Start steroids immediately and discontinue further dosing – Continue monitoring and consider dosing the subject with nivolumab therapy at the same dose level – Consider tapering steroids over at least 1 month **If elevations persist at the same level >28 days or worsen:**

Hepatic Adverse Event Management with Liver Metastasis		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab therapy. Consider imaging for obstruction.		
Grade of Liver Test Elevation	**Management**	**Follow-Up**
	– If there is a concurrent increase of alkaline phosphatase along with ALT, start steroids immediately – Monitor for other clinical symptoms (fatigue, nausea, vomiting, abdominal pain, fever, rash, and/or eosinophilia)	– Discontinue cabiralizumab and nivolumab therapy per protocol – 0.5–1 mg/kg/daymethylprednisolone or oral equivalent and when LFT returns to Grade 1 or baseline, taper steroids over at least 1 month – Consider prophylactic antibiotics for opportunistic infections – Discuss with Sponsor
AST or ALT > 20 xULN ***or*** Total Bilirubin > 5 xULN	– Discontinue cabiralizumab and nivolumab therapy – Increase frequency of monitoring to every 1–2 days – Consider 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent[a] – Consider adding prophylactic antibiotics for opportunistic infections – Consult gastroenterologist and hepatologist, if clinically indicated	**If returns to Grade 2 or baseline:** – Consider steroid taper over at least 1 month if they have been started **If does not improve in >3–5 days, worsens, or rebounds:** – Consider adding mycophenolate mofetil 1 g BID – If no response within an additional 3–5 days, consider other immunosuppressants per local guidelines – Follow up until resolution

[a] Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, 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 Adverse Event Management		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab therapy. Consider visual field testing, endocrinology consultation, and imaging.		
Description	**Management**	**Follow-Up**
Asymptomatic TSH elevation	– Continue cabiralizumab and nivolumab therapy per protocol	**If TSH <0.5x LLN or TSH >2x ULN, or consistently out of range in 2 subsequent measurements:** – Include free T4 at subsequent cycles as clinically indicated; consider endocrinology consult
Symptomatic endocrinopathy	– Evaluate endocrine function – Consider pituitary scan **Symptomatic with abnormal lab/pituitary scan:** – Delay cabiralizumab and nivolumab therapy per protocol – 1 to 2 mg/kg/day methylprednisolone IV or PO equivalent[a] – Initiate appropriate hormone therapy **No abnormal lab/pituitary MRI scan but symptoms persist:** – Repeat labs in 1–3 weeks and MRI in 1 month	**If improves within 28 days (with or without hormone replacement):** – Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections – Resume cabiralizumab and nivolumab therapyper protocol – Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component **If persists for over 28 days:** – Delay cabiralizumab and nivolumab therapy – Continue steroids as needed – Upon resolution, discuss with Sponsor if patients are clinically stable on further dose delay and discontinuation – Follow up until resolution or return to baseline
Suspicion of adrenal crisis (e.g. severe dehydration, hypotension, shock out of proportion to current illness)	– Delay or discontinue cabiralizumab and nivolumab therapy per protocol[a,c] – Rule out sepsis – Stress dose of IV steroids with mineralocorticoid activity – IV fluids – Consult endocrinologist – If crisis is ruled out, treat as above for symptomatic endocrinopathy	

[a] Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, 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		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab therapy.		
Grade of Rash (NCI CTCAE v 5.0)	**Management**	**Follow-Up**
Grade 1–2: Covering ≤ 30% BSA[a]	– Symptomatic therapy (e.g. antihistamines, topicalsteroids) – Continue cabiralizumab andnivolumab therapy per protocol	**If persists >1-2 weeks or recurs:** – Consider skin biopsy – Delay cabiralizumab and nivolumab therapyper protocol – Consider 0.5–1 mg/kg/day methylprednisolone IV or oral equivalent. – Once improving ,taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, andresume cabiralizumab and nivolumab therapy per protocol **If worsens:** – Treat as Grade 3–4
Grade 3–4: Covering > 30% BSA; life-threatening consequences[d]	– Delay or discontinue cabiralizumab and nivolumab therapy per protocol – Consider skin biopsy anddermatology consult – 1 to 2 mg/kg/day IV[b] methylprednisolone IV or IV equivalent	**If improves to Grade 1 within 28 days:** – Taper steroids over at least 1 month and addprophylactic antibiotics for opportunistic infections – Resume cabiralizumab and nivolumab therapy per protocol **If persists > 28 days or worsens:** –Consider to discontinue cabiralizumab and nivolumab therapy per protocol

[a] Refer to NCI CTCAE v 5.0 for term-specific grading criteria.

[b] Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, 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.

Neurological Adverse Event Management		
Grade of Neurological Toxicity (NCI CTCAE v 5.0)	**Management**	**Follow-Up**
Grade 1: Asymptomatic or mild symptoms; Intervention not indicated	– Continue cabiralizumab and nivolumab therapy per protocol	**If worsens:** – Treat as Grade 2, 3, or 4
Grade 2: Moderate symptoms; limiting instrumental ADL	– Delay cabiralizumab and nivolumab therapy per protocol – Treat symptoms per local guidelines – Consider 0.5 to 1 mg/kg/day[a] methylprednisolone IV or PO	**If improves to baseline within 28 days:** – Resume cabiralizumab and nivolumab therapy at same dose level per protocol when improved to baseline **If worsens or persists after 28 days:** – Treat as Grade 3-4
Grade 3–4: Severe symptoms; limiting self-care ADL; life-threatening	– Discontinue cabiralizumab and nivolumab therapy – Obtain neurology consult – Treat symptoms per local guidelines 1 to 2 mg/kg/dayIV methylprednisolone or PO[a] – Add prophylactic antibiotics for opportunistic infections	**If improves to Grade 2:** – Taper steroids over at least 1 month **If worsens or atypical presentation:** – Consider IVIG or other immunosuppressive therapies per local guidelines – Continue follow-up until resolution

[a] Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, 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.

Periorbital Edema Adverse Event Management		
Grade of Periorbital Edema (NCI CTCAE v 5.0)	**Management**	**Follow-Up**
Periorbital Edema > baseline but **< Grade 2** **Grade 2**	– Continue cabiralizumab and nivolumab therapy per protocol – Monitor edema weekly – Delay cabiralizumab and nivolumab therapy per protocol – Start systemic treatment including steroids, eye drops, or analgesics as needed[a]	**If worsens:** – Follow as stated below **If returns to Grade 1 or baseline before the next dosing visit:** – Continue systemic treatment – Resume cabiralizumab and nivolumab therapy at same dose level without delay – Routine eye monitoring per protocol, if clinically stable **If swelling persists >14 days but returns back to baseline or normal within 28 days:** – Continue nivolumab and cabiralizumab dosing at same level – If recurs at Grade 2 or above, discontinue cabiralizumab and nivolumab therapy
Grade ≥3	– Discontinue cabiralizumab andnivolumab therapy per protocol – Systemic treatment including steroids, eye drops, or analgesics as needed[a] – Consult an ophthalmologist if needed	**If returns to Grade 1 after discontinuation:** – Systemic treatment including tapering steroids as needed – Any follow-up and ophthalmology consults, if clinically indicated – Monitor and follow up until resolution

[a] Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, 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.

Infusion Reaction Adverse Event Management		
Grade of Infusion Reactions (NCI CTCAE v 5.0)	**Management**	**Follow-Up**
Grade 1	– Decrease infusion rate of cabiralizumab and nivolumab therapy per protocol and restart at normal infusion rate once symptoms subside – Monitor patient and use symptomatic treatment as clinically indicated (which includes antihistamines and NSAIDs)	**If infusion reaction symptoms subside within 3 hours of nivolumab** – cabiralizumab therapy can be given without any prophylactic medications if the reaction is nivolumab related – Subsequent dosing should include prophylactic pre-infusion medications for nivolumab – If the infusion reaction is related to cabiralizumab therapy, prophylactic medication should be given prior to dosing of cabiralizumab and nivolumab – Continue cabiralizumab and nivolumab dosing at same level
Grade 2	– Interrupt cabiralizumab and/or nivolumab infusion per protocol – Systemic treatment including NSAIDs, corticosteroids and antihistamines[a] – Normal saline infusion and constant monitoring of vitals and other parameters – If symptoms resolve within 3 hours, continue infusion at 50% rate for 30 minutes and then increase to 100% if clinically stable	– Resume cabiralizumab and nivolumab therapy at same dose level and monitor per protocol – Pre-infusion prophylactic medications are recommended for future dosing, including antihistamines, NSAID, and corticosteroids up to 25 mg as needed. **If symptoms recur:** – Discontinuetreatment at the visit – Discuss with Sponsor as needed
Grade ≥3	– Discontinue cabiralizumab and nivolumab therapy per protocol – Systemic treatment including NSAID , corticosteroids, and antihistamines[a] – Normal saline infusion and constant monitoring of vitals and other parameters – Follow institutional guidelines for anaphylaxis – Bronchodilators as clinically indicated with or without hospitalization	**If returns to Grade 1 after discontinuation:** – Systemic treatment including tapering steroids, NSAIDs, and antihistamines until resolution, as needed – Follow up until resolution – Any other clinical referrals, ifindicated

[a] Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, 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.

Uveitis Adverse Event Management		
Grade of Uveitis (NCI CTCAE 5.0)	**Management**	**Follow-Up**

Grade 1	– Observe symptoms – Continue cabiralizumab andnivolumab therapy –	– Watch for worsening of symptoms including visual disturbances, light sensitivity, decrease vision – Monitor weekly **If worsens:** – Follow as stated below
Grade 2	– Delay or discontinue cabiralizumab and nivolumab therapy per protocol – Start antibiotics and inflammatory medications including steroids[a] – Ophthalmologicconsult, if clinically indicated – Immunosuppressive agents(e.g, anti-TNF agents such as Infliximab)	**If symptoms resolve within 14 days:** – Continue cabiralizumab and nivolumab therapy at same dose level andstart tapering of steroid doses **If symptoms resolve between 14 -28 days:** – Consider continuing dosing at same dose level for nivolumab and a dose level lower for cabiralizumab on resolution to baseline or Grade 1 and start tapering of steroid doses. – If it is Grade 2 drug-related uveitis that does not resolve within 14 days, consider to discontinue study drug(s) **If symptoms persist or worsen in 28 days regardless of systemic treatment:** – Discontinue both cabiralizumab and nivolumab therapy – Continue monitoring of symptoms including visual disturbances, eye pain, and dimness of vision and follow up until resolution or return to baseline – Continue steroids, antibiotics, and other medications such asinfliximab, as clinically indicated
Grade ≥3	– Discontinue cabiralizumab and – nivolumab therapy per protocol Start antibiotics and inflammatory medications including steroids[a] – Ophthalmologicconsult, if clinically indicated – Immunosuppressive agents (e.g, anti-TNF agents such as Infliximab)	– Discontinue both cabiralizumab and nivolumab therapy – Continue monitoring of symptoms including visual disturbances, eye pain, and dimness of vision, and follow up until resolution or return to baseline – Continue steroids, antibiotics, and other medications such asinfliximab, as clinically indicated – Follow up until resolution

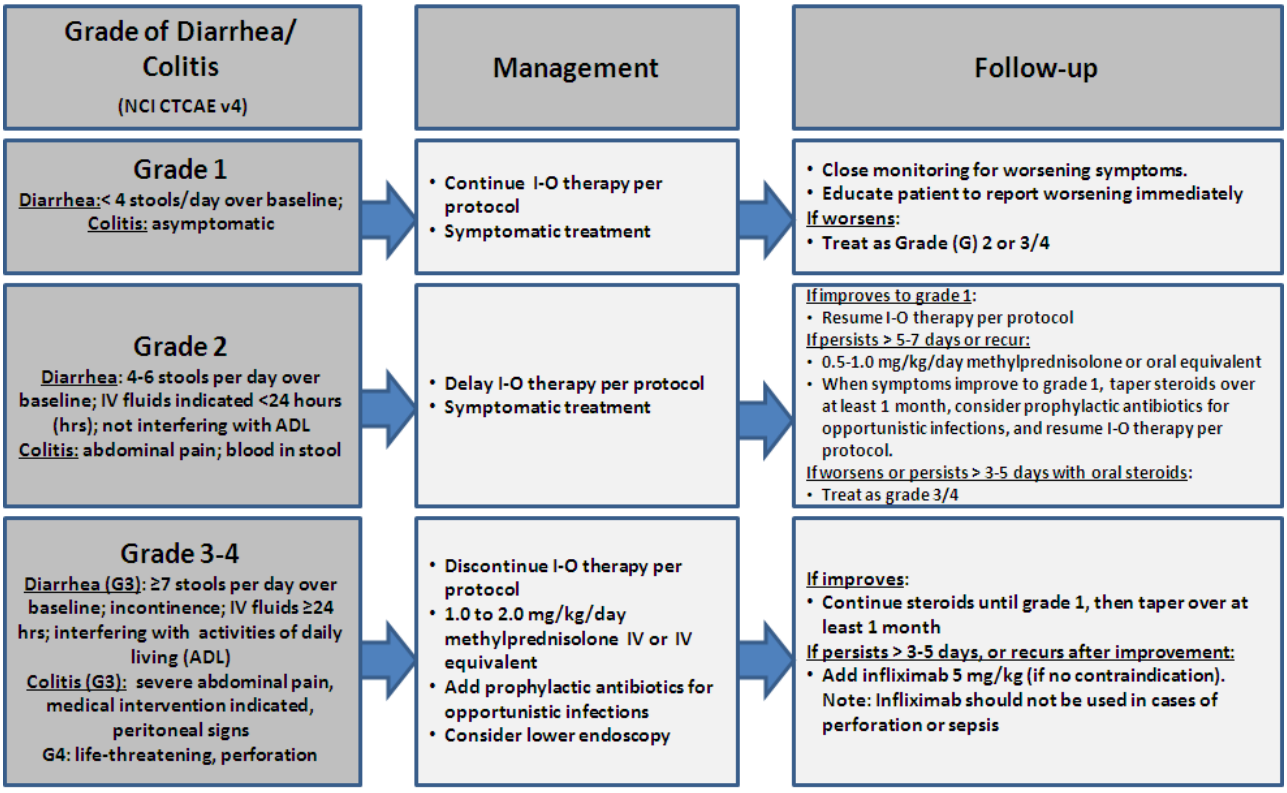
[a] Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose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

Appendix 7 – Laboratory Abnormalities Management Table

Laboratory Abnormalities Management (CK and LDH)		
Grade of Liver Test Elevation	**Management**	**Follow-Up**
CK > 10x ULN	Consider measuring CK isoenzymes as clinically indicated	**If CK isoenzymes are abnormal** Consider checking troponin levels Consider other assessments (including uromyoglobin) as clinically indicated **If CK isoenzymes are normal** Continue dosing, per protocol Monitor CK level as clinically indicated
CK or LDH > 15 to ≤ 20x ULN	Delay cabiralizumab and nivolumab therapy per protocol Measure CK isoenzyme panel to identify source of elevation Increase frequency of monitoring (every 48-72 hours or more, as clinically indicated) Notify the Sponsor	**If CK or LDH returns to ≤ 15 xULN within ≤ 28 days:** Resume routine monitoring, resume cabiralizumab and nivolumab therapy at same dose level as per protocol If CK isoenzyme panel is normal continue monitoring the subject. If CK isoenzyme panel is abnormal then consider measuring troponins. If troponins are abnormal, contact Sponsor to determine if the subject can be retreated. **If CK or LDH elevations persist at the same level > 28 days or worsen:** Discontinue further dosing Discuss with Sponsor
CK or LDH > 20 xULN	Discontinue cabiralizumab and nivolumab therapy per protocol	Follow up until resolution

GI Adverse Event Management Algorithm

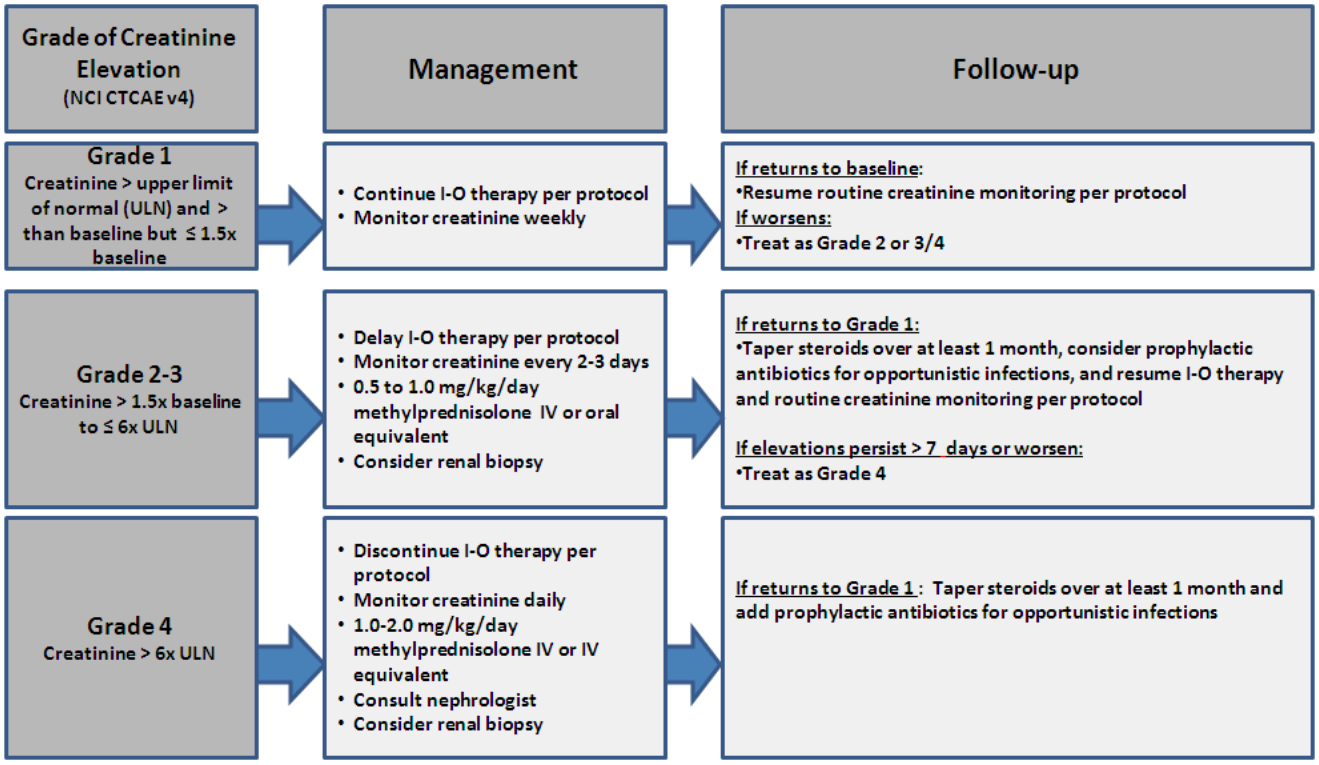
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

Renal Adverse Event Management Algorithm

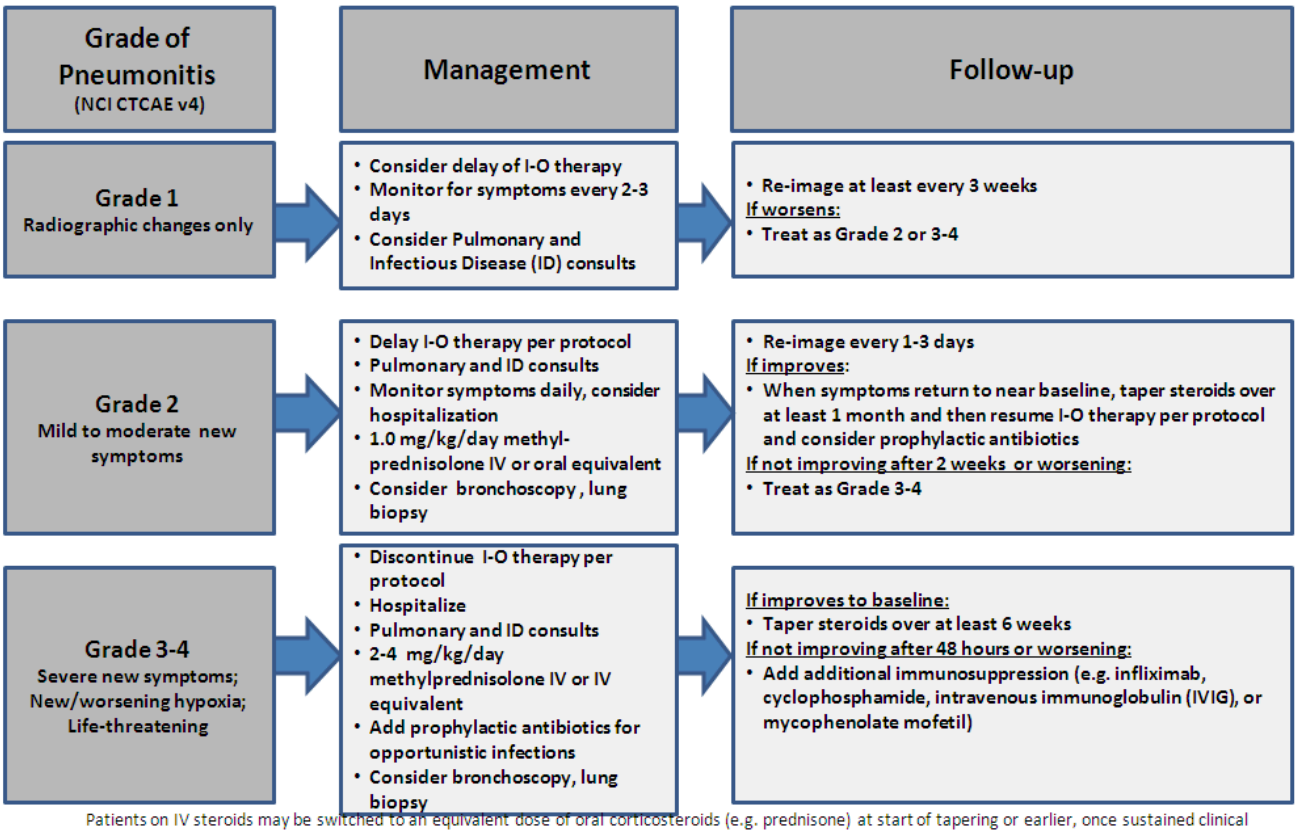
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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

Pulmonary Adverse Event Management Algorithm

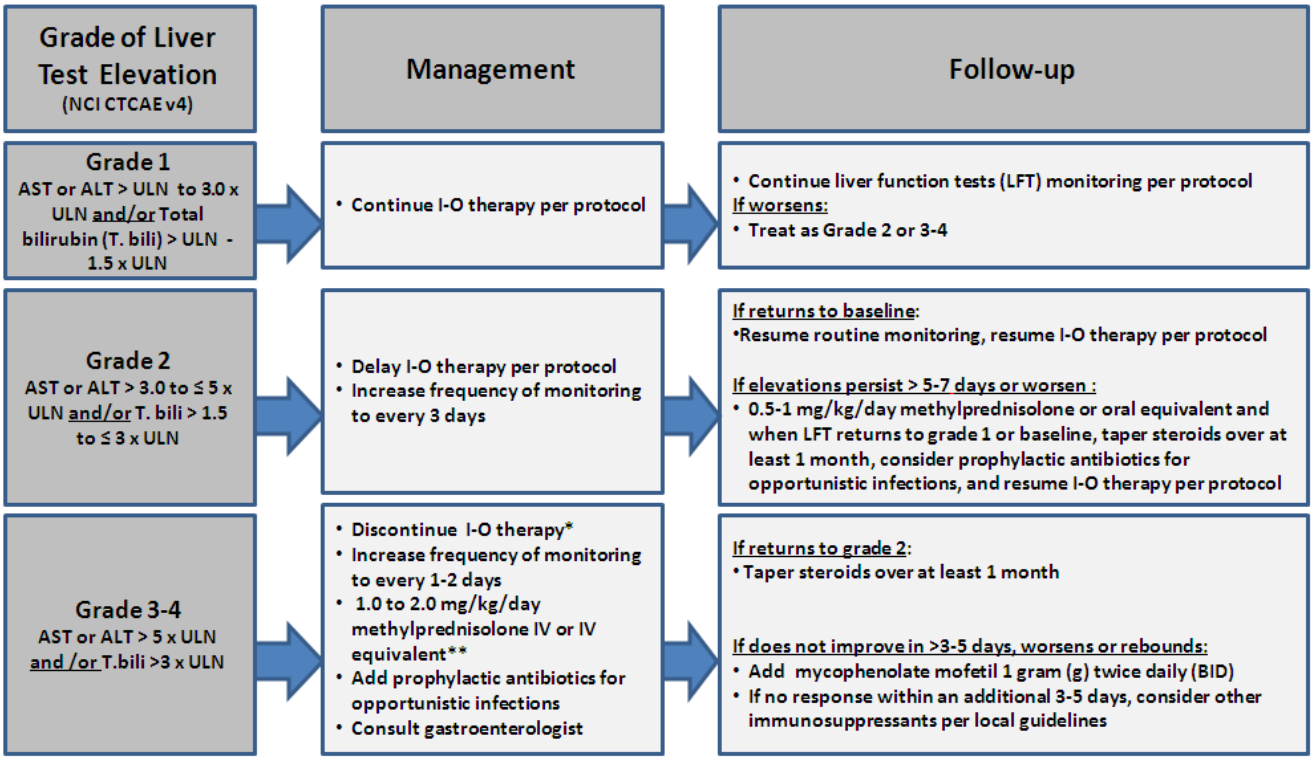
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

Hepatic Adverse Event Management Algorithm

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



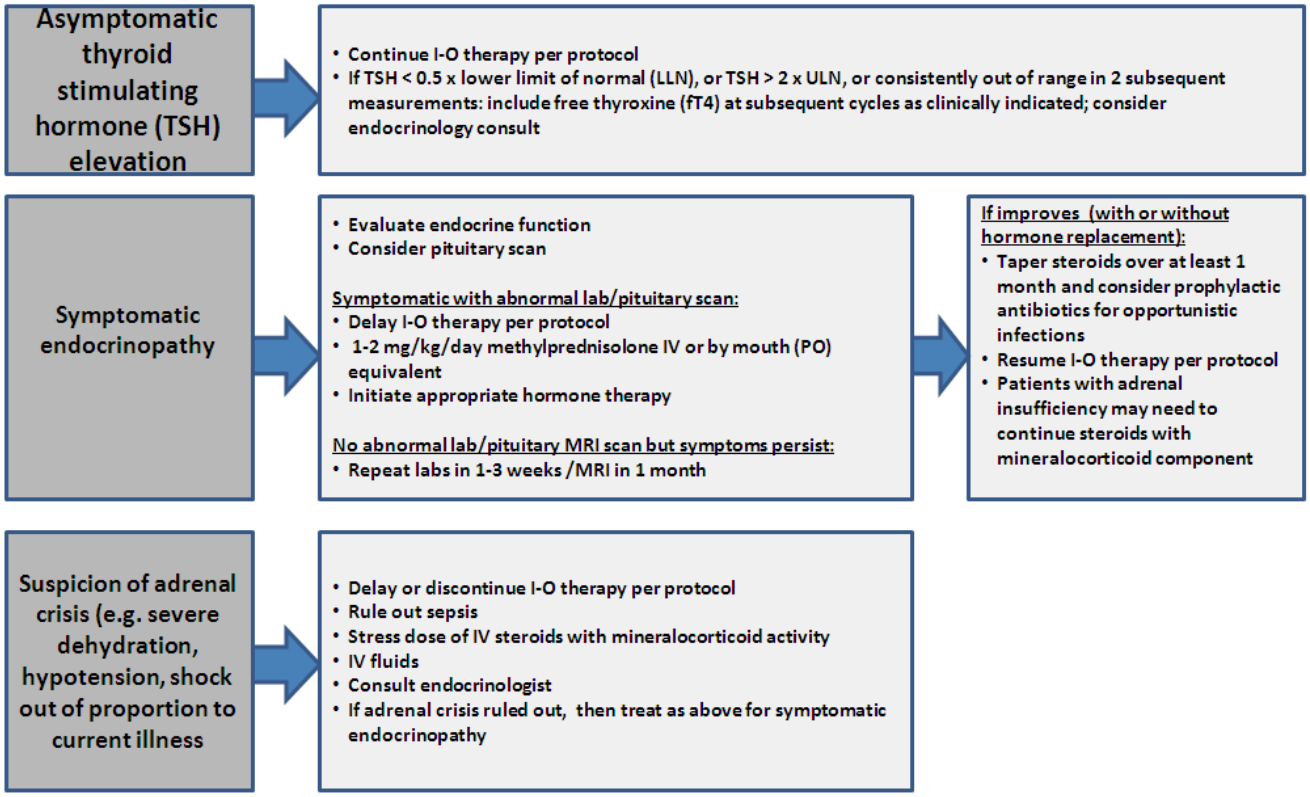
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

Endocrinopathy Management Algorithm

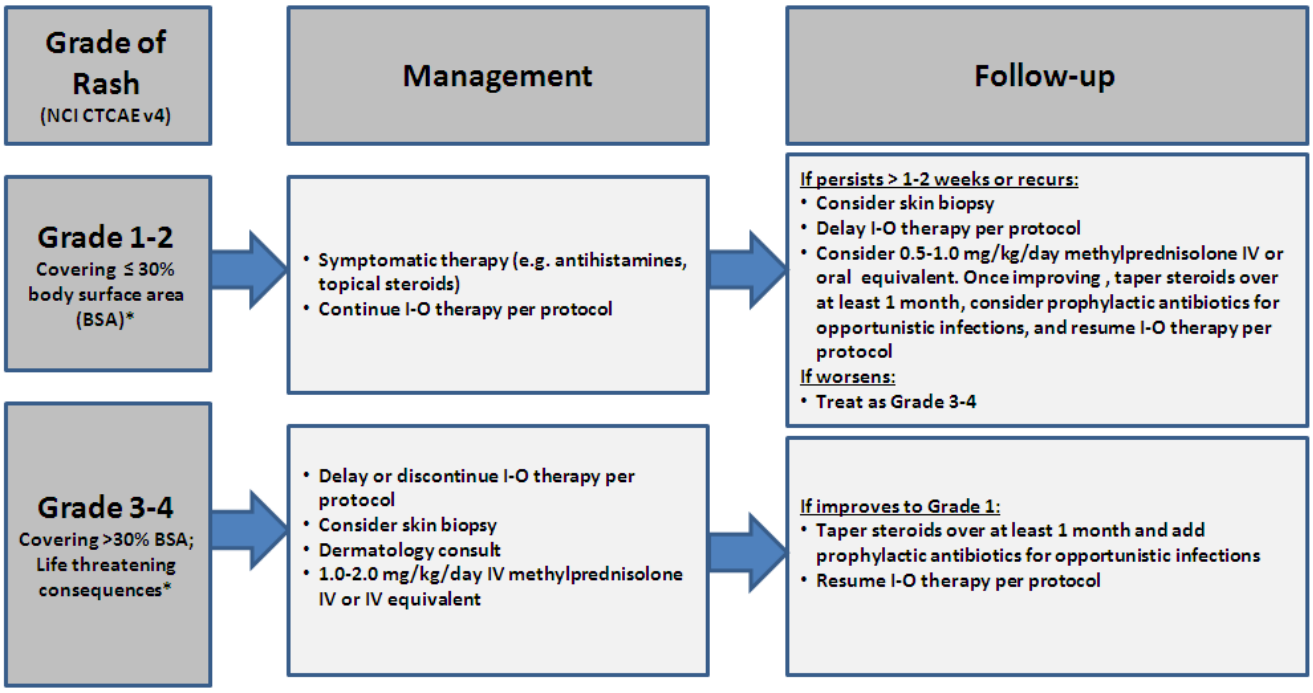
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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.

Neurological Adverse Event Management Algorithm

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

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

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.