NYU School of Medicine
NYU LANGONE MEDICAL CENTER

Clinical Research Protocol
Perlmutter Cancer Center

A phase II multi-institutional study of nivolumab, cabiralizumab, and stereotactic body radiotherapy (SBRT) for locally advanced unresectable pancreatic cancer

Version Date: January 28, 2020

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NYULHStudy Number:	**s17-01430**
Sponsor Study Number:	*CA025-008*
Funding Sponsor:	*Bristol Myers Squibb*
IND/IDE Number:	*138964*
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Study Product:	*Nivolumab- Opdivo* *Carbiraluzumab*
ClinicalTrials.gov Number	**NCT03599362**

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training

PROTOCOL APPROVAL SIGNATURES

Protocol Title: A phase II multi-institutional study of nivolumab, cabiralizumab, and stereotactic body radiotherapy (SBRT) for locally advanced unresectable pancreatic cancer

Protocol Number: s17-01430

This study will be conducted in compliance with the clinical study protocol (and amendments), International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines for current Good Clinical Practice, and applicable regulatory requirements.

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Signature

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Date

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List of Abbreviations

AE	Adverse Event/Adverse Experience
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CRF	Case Report Form
CTO	Clinical Trials Office
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DMFS	Distant metastasis free survival rate
DSMC	Data Safety Monitoring Committee
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
LAUPC	Locally advanced unresectable pancreatic cancer
MOP	Manual of Procedures
N	Number (typically refers to participants)
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0
NIH	National Institutes of Health
NYULH	New York University Langone Health

OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
OS	Overall Survival
PCC	Perlmutter Cancer Center
PD	Progressive Disease
PFS	Progression Free Survival
PI	Principal Investigator
PK/PD	Pharmacokinetic/Pharmacodynamic
PR	Partial Response
QA	Quality Assurance
QC	Quality Control
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event/Serious Adverse Experience
US	United States
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

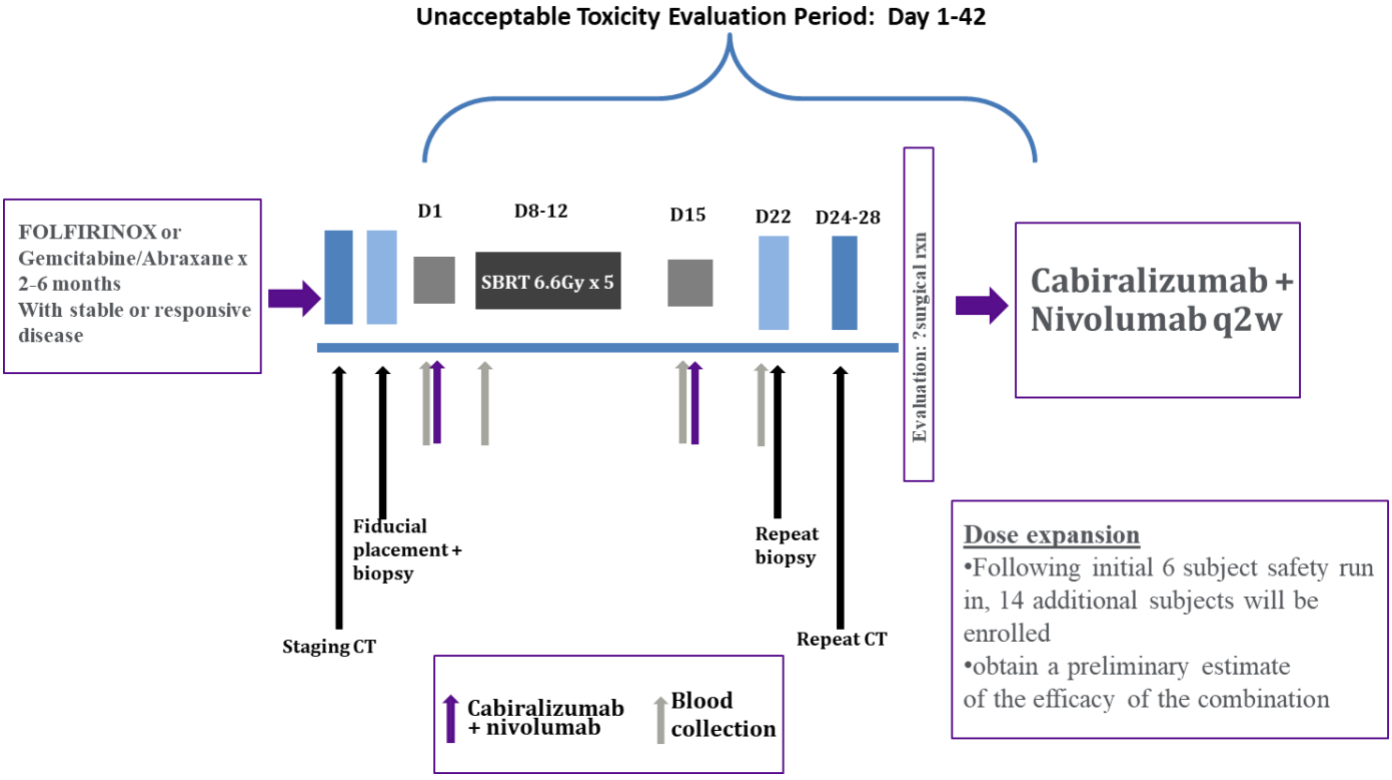
Protocol Summary

Title	*A phase II study of nivolumab, cabiralizumab, and stereotactic body radiotherapy (SBRT) for locally advanced unresectable pancreatic cancer*
Brief Summary	*A multi-institutional, single arm phase II study of nivolumab, cabiralizumab and SBRT in patients with LAUPC.*
Phase	*Phase II*
Objectives	***Primary Objectives:*** • *To determine the safety and tolerability of combined cabiralizumab, nivolumab and radiotherapy in the treatment of locally advanced pancreatic cancer.* • *To estimate the surgical resection rate following treatment with combined cabiralizumab, nivolumab and radiotherapy in subjects with locally advanced unresectable pancreatic cancer.* ***Secondary Objectives:*** • *To evaluate preliminary anti-tumor activity of combined cabiralizumab, nivolumab and radiotherapy in subjects with locally advanced unresectable pancreatic cancer.* • *To evaluate the pharmacodynamic (PD) effect of the combination regimen on biomarkers in peripheral blood samples and tumor biopsy specimens.*
Methodology	*Multi-center, open-label, single arm, phase II study*
Endpoint	***Co-Primary Endpoints*** • *Rate of unacceptable toxicity* • *R0 resection rate* ***Secondary Endpoints*** • *Overall response rate (ORR), progression free survival rate (PFS), overall survival rate (OS), and distant metastasis free survival rate (DMFSR)* ***Exploratory Endpoints*** • *Nonclassical CD16+ monocyte and CSF1 levels in peripheral blood and tissue.* • *Immune changes within blood and tissue following treatment and correlate with clinical endpoints*
Study Duration	The duration of this follow-up is up to 2 years following the last dose of study treatment, although a longer follow-up period could be considered in selected cases if an efficacy signal is apparent. Tumor assessment scans, for participants who have ongoing clinical benefit beyond the 2-year period following the first dose of study treatment, may continue to be collected as part of standard-of-care treatment. Subsequent therapies will also be recorded in this survival follow-up periodtreatment, although a longer follow-up period could be considered in selected cases if an efficacy signal is apparent. Tumor assessment scans, for participants who have ongoing clinical benefit beyond the 2-year period following the first dose of study treatment, may continue to be collected as part of standard-of-care treatment. Subsequent therapies will also be recorded in this survival follow-up period

Participant Duration	*Up to 2 years*
Enrollment Period	*4 weeks*

Duration of IP administration	*Up to 2 years*
Study Centers/Sites	*Multicenter:* *1) Perlmutter Cancer Center (PCC) at NYU Langone Health* *2) TBD* *3)TBD*
Number of participants	*20 participants with 10-12 accrued at NYU Langone Health over 2 years*
Description of Study Agent/Procedure	*Cabiralizumab 4mg/kg IV every two weeks* *Nivolumab flat dose 240mg IV every two weeks* *SBRT: 6.6 Gy for 5 days*
Key Procedures	*Tumor biopsy and blood draws*
Statistical Analysis	*Safety will be evaluated by tabulating the type and severity of all unacceptable toxicities and adverse events. If more than two of the first six patients experience an unacceptable toxicity, accrual will be temporarily halted while the study team investigates potential dose modifications. The rate of R0 resection will be calculated as the proportion of enrolled patients who achieve R0 resection. The rate of R0 resection will be estimated with its associated exact 95% confidence interval. If the lower bound of the confidence interval exceeds the null rate of 5%, the therapy will be deemed worthy of further investigation.* *Overall response will be tabulated according to RECIST criteria. PFS, OS, and DMFS will be estimated using the Kaplan-Meier method.*

Schematic of Study Design



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2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

The incidence and mortality rate from pancreatic cancer continues to rise in the United States, with an estimated 53,670 new cases expected in 2017 and 43,090 deaths.[1] Surgery remains the cornerstone of curative intent treatment; however, only 10-20% of patients present with resectable disease. The majority of the patients present with advanced disease, with 30-40% having locally advanced disease with involvement of adjacent vascular structures and the remainder of patients with distant metastases.[2]

For those patients with LAPC, treatment is not well defined, but most typically involves either chemotherapy alone or combined with radiation therapy (RT). However, the actual contribution of RT to survival in LAPC remains controversial despite five published randomized clinical trials.[3-7] Initial studies conducted in the 1980's demonstrated conflicting results. An Eastern Cooperative Oncology Group (ECOG) study randomized 91 LAPC patients to treatment with either weekly bolus 5-Fluorouracil (5FU) alone or initial concurrent chemoradiation with 5FU followed by weekly bolus 5FU.[5] There was no significant difference in outcome with median overall survival of 8.2 months in the chemotherapy arm versus 8.3 months in the chemoradiation arm. In contrast, the Gastrointestinal Tract Cancer Group (GITSG) randomized 43 patients to treatment with chemotherapy with streptozosin, mitomycin and 5FU (SMF) or initial chemoradiation with 5FU followed by SMF. While the study was terminated prematurely due to poor accrual, there was a one year survival of 41% with the addition of radiation versus 19% in the chemotherapy only arm.[3] Twenty years later, two additional studies were undertaken with the use of more modern RT methods and newer chemotherapeutics, however, once again there were inconsistent findings. The French group, FFCD/SFRO, randomized 119 patients to induction chemoradiation with 5FU and cisplatin followed by gemcitabine versus gemcitabine alone. A significantly decreased median overall survival was noted with RT compared to chemotherapy only (8.6 vs 13 months).[4] In contrast, the ECOG 4201 study demonstrated an improved median overall survival of 11.1 months with concurrent RT and gemcitabine compared to 9.2 months with gemcitabine alone.[6] Finally, the most recently reported study, LAP 07, did not show a survival benefit for the use of consolidative chemoradiation with capecitabine following 4 months of gemcitabine-based chemotherapy compared with 6 months of gemcitabine based chemotherapy alone.[7] Collectively, these data demonstrate the overall limited efficacy of standard therapies for LAPC (see table 1). While RT may provide some benefit when used at selected doses, fractionations or with certain chemotherapy combinations, its effect thus far is modest and in some cases may even be detrimental.

Table 1: Results from randomized studies of radiation therapy in LAPC

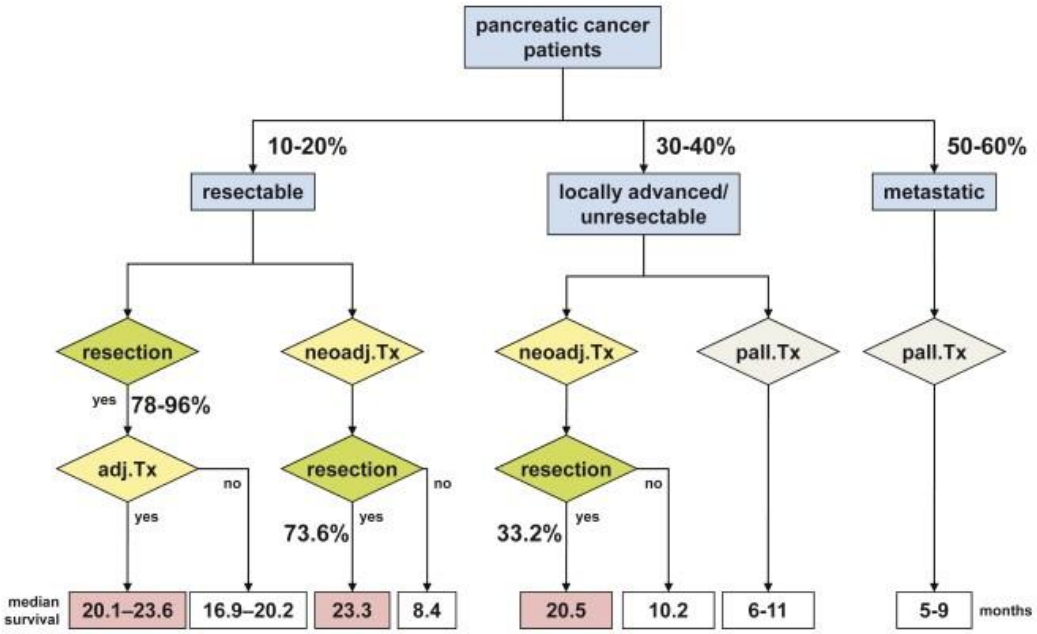
Study	N	Treatment	Outcome
ECOG	91	5FU vs 5FU/RT	Med OS 8.2 vs 8.3m
GITSG	43	SMF vs 5FU/RT->SMF	1 year OS 19% vs 41%
FFCD/SFRO	119	Gem vs 5FU/cis/RT->gem	Med OS 13 vs 8.6m
ECOG 4201	74	Gem vs gem/RT	Med OS 9.2 vs 11.1m
LAP 07	449	Gem vs gem->5FU/RT	Med OS 16.5 vs 15.2m

At this time, NCCN recommendations for LAPC include either chemotherapy or chemoradiotherapy, with emphasis on enrollment in clinical trial as the preferred treatment option.

Survival rates for patients with LAPC remain low with the most recently completed randomized phase III LAP07 study demonstrating a median overall survival with combined modality therapy of 15-16.5 months[7]. In this study, single agent gemcitabine was compared to gemcitabine followed by chemoradiotherapy with capecitabine. Only 4% of patients underwent curative-intent resection. Since this study was conducted, both FOLFIRINOX and gemcitabine plus nab-paclitaxel have demonstrated superiority compared to single agent gemcitabine in patients with metastatic disease.[8, 9] As a result, there have been several subsequent retrospective and single arm prospective reports suggesting such combination regimens are appropriate neoadjuvant treatment in patients with locally advanced pancreatic cancer who have good functional status[10-14] However, to date, no randomized clinical trial has been published.

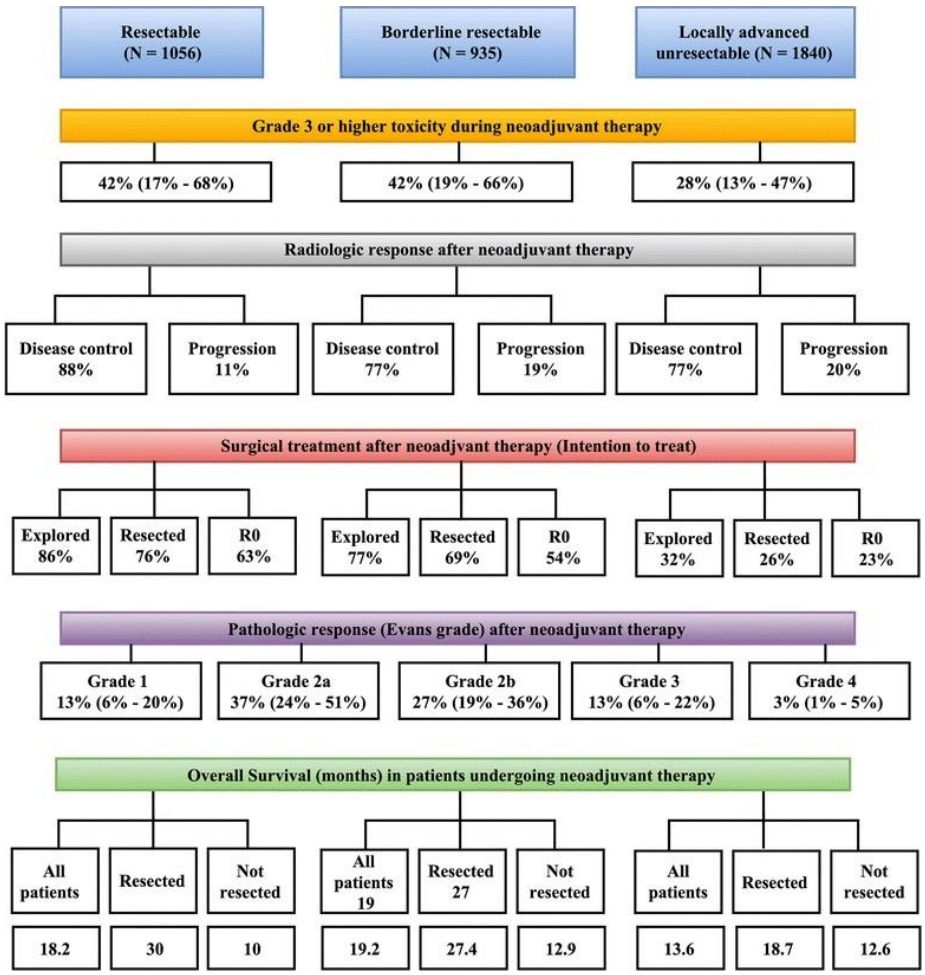
A meta-analysis including over 4000 pancreatic cancer patients, found that survival rates for LAPC patients receiving neoadjuvant therapy (of whom 93.7% received neoadjuvant radiotherapy) and subsequent surgical resection had median survival of 20.5 months, which is within the range of pancreatic cancer patients with primary resection and adjuvant therapy[15] (see figure 1).

Figure 1: Summary overview of survival and resection percentages of different groups of patients with pancreatic cancer



In another meta-analysis which included over 5000 non-metastatic pancreatic cancer patients, the role and outcomes of neoadjuvant therapy (in which radiotherapy was given in 79.2% of patients) were examined(see figure 2)[16].In this review, a similar survival rate was noted for LAPC patients receiving neoadjuvant therapy followed by resection (18.7 months) compared to the survival rate for all initially resectable patients who underwent neoadjuvant therapy +/- surgical resection (18.2 months). This again demonstrates the value of upfront therapy for this challenging patient population. While survival is the main intent of neoadjuvant therapy, R0 resection rate is a secondary goal as positive resection margins have repeatedly been shown to be associated with worse survival.[17-19] Typically R0 resection rate for patients with LAPC is very low. In the most recently reported randomized trial looking at neoadjuvant chemoradiotherapy compared to chemotherapy alone, the overall R0 resection rate was 2.5%.[7] In this study, chemotherapy administered was with single agent gemcitabine. Higher R0 rates have been reported when combination chemotherapy is administered. In a systematic review and patient-level meta-analysis of FOLFIRINOX with or without radiation therapy for LAPC, the R0 resection rate was reported to be 18%. Similarly, in another meta-analysis, R0 rate was found to be 23% following chemotherapy +/- radiation.[16]

Figure 2: Summary of outcomes after neoadjuvant therapy among non-metastatic pancreatic patients.



While the optimal treatment paradigm for LAPC has yet to be defined, there is good rationale for the further study of RT. First, local tumor progression contributes to significant morbidity and mortality in this disease. As more effective systemic treatments evolve and are incorporated into practice, the complications related to local disease progression are predicted to increase and more commonly limit long-term survival. Currently, it is estimated based on clinical and autopsy data that approximately 30% or more of patients die from complications related to local disease progression.[20] Second, because complete surgical resection continues to be a necessary component to cure pancreatic cancer, the focus on improving local treatment modalities is essential. If a LAPC patient can be "downstaged" and converted to a resectable state, then higher cure rates may be possible

Given the poor outcomes in patients with LAPC, there is a clear need for improved therapy. Current clinical trials focused on RT in LAPC investigate the effects of intensifying radiation regimens (RTOG 1201), optimizing combinations with systemic agents(SCALOP-2 and CONKO-007), and improving patient selection(RTOG 1201). However, none of these strategies takes into account the fact that despite the direct and well known tumoricidal effects of radiation on malignant epithelial cells, its clinical efficacy in pancreatic cancer may be limited by its promotion of innate and adaptive immune suppression.

2.2 Cabiralizumab

Cabiralizumab is a recombinant, humanized Immunoglobulin G4 (IgG4) monoclonal antibody that binds to human colony stimulating factor 1 receptor (CSF1R; c-fms). Binding of cabiralizumab to CSF1R antagonizes binding of CSF1 and IL34, the two ligands to CSF1R, thereby preventing activation of CSF1R. Cabiralizumab contains a single amino acid substitution in the hinge region to prevent hemi-dimer exchange.

CSF1R signaling plays a fundamental role in the differentiation, maintenance, trafficking, and function of monocytic lineage cells including monocytes, macrophages, and osteoclasts.[21] Two ligands have been identified for CSF1R: CSF1 and IL34 (reviewed in ([22]). Cabiralizumab blocks the binding of these ligands to CSF1R, thus inhibiting downstream functions such as development and survival of monocytic lineage cells.

The tumor microenvironment, composed of non-cancer cells and stroma, is recognized as a major factor influencing the growth of tumor cells. Tumor-associated macrophages (TAMs) are particularly abundant in the tumor microenvironment and are thought to play a key role in promoting tumor growth. TAMs can promote angiogenesis (blood vessel formation in tumors), tumor survival, and metastasis, and may confer resistance to current therapies. TAMs are also immunosuppressive and through the release of soluble factors and cell surface T cell checkpoint inhibitors can suppress anti-tumor T cell responses. In the majority of tumors increased numbers of TAMs correlate with poor clinical outcome,[23] supporting TAMs as an attractive therapeutic target. Immunosuppressive TAMs are dependent on CSF1 for survival; a drug that inhibits CSF1R could limit the influence of TAMs on the tumor microenvironment and could be complementary and augment current cancer therapies (e.g., checkpoint-based immunotherapies such as antibodies that target the PD1 or CTLA4 pathways).

2.2.1 Preclinical Data

2.2.1.1 Pharmacokinetics

Cabiralizumab binds to CSF1 in cynomolgus monkeys and humans with similar affinity. Therefore, pharmacokinetics (PK) and toxicokinetics (TK) of cabiralizumab were characterized in cynomolgus monkeys following single IV bolus administration or weekly repeat IV infusion administration, respectively. The duration of the IV infusion was 30 minutes.

Four PK/TK studies were conducted in cynomolgus monkeys to support clinical development of cabiralizumab (Table 2). A ligand binding enzyme-linked immunosorbent assay (LBA) was used to measure cabiralizumab plasma concentration. Antibodies against cabiralizumab were measured in cynomolgus monkey plasma using an electrochemiluminescent bridging immunoassay (ECLA) method.

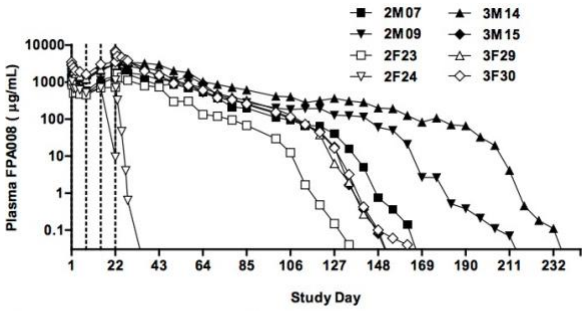
Table 2: Nonclinical Pharmacokinetic and Toxicokinetic Studies

Study Number	GLP	Study Type	Species and Number of Subjects per Group	Dose (mg/kg)	Route	Dose Regimen
0787-11180	No	PK	Cynomolgus monkey n=1/sex/group	3, 10, 30, 150	IV	Single
0787-11287	No	TK	Cynomolgus monkey n=1/sex/group	3, 10, 150	30 min IV infusion	4 doses, given weekly
0787-12002	Yes	TK	Cynomolgus monkey, n=3/sex/group for Terminal Sacrifice n=2/sex group for Recovery Sacrifice	50 and 150	30 min IV infusion	4 doses, given weekly
0787-13315	Yes	TK	Cynomolgus monkey n=4/sex/group for Terminal Sacrifice n=2/sex group for Recovery Sacrifice	20, 50, and 100	30 min IV infusion	13 doses, given weekly

- When given as a single IV bolus dose, cabiralizumab exhibited target-mediated clearance in the dose range of 3–150 mg/kg. Maximum observed serum concentration (Cmax) increased proportionally to dose at all dose levels tested. Area under plasma concentration curve extrapolated to infinity (AUCinf) increases were greater than dose proportional from 3 mg/kg to 10 mg/kg and were dose proportional from 10 mg/kg to 150 mg/kg. The total clearance is approximately 0.21 mL/h/kg (5.0 mL/day/kg) in the dose range of 10–150 mg/kg. Since all eight animals were anti-cabiralizumab antibody (ADA) positive and the presence of ADA affects the total exposure for some animals, the relative attribution of non-specific clearance to target-mediated clearance or to ADA-mediated clearance is unknown.

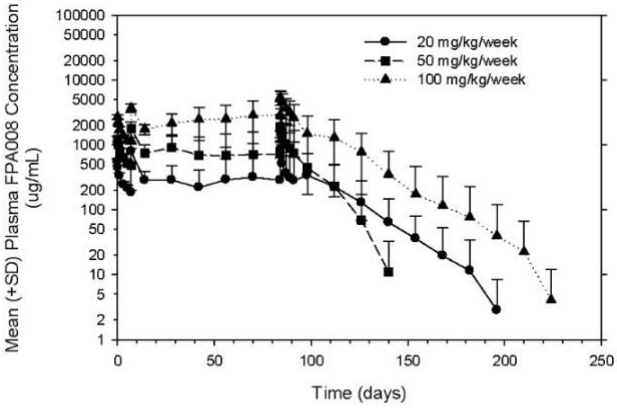
- When given as weekly repeat IV infusion administration in three toxicology studies in the dose range of 3–150 mg/kg, the TK profile following the first dose was similar to what was observed in the single-dose PK study. Cmax increased proportionally to dose at all dose levels tested. AUC increased dose proportionally from 10 mg/kg to 150 mg/kg, but less than dose proportionally from 3 mg/kg to 10 mg/kg, suggesting that there was a limited contribution of target-mediated clearance to the total clearance at higher dose levels. The mechanism of prolonged exposure following last dose in comparison to PK data from the single dose is unknown, but is likely caused by the decreases in target-mediated clearance due to the reduction of CSF1R expressing cells of the monocyte/macrophage lineage in the presence of cabiralizumab (Figure 3 and Figure 4). Target-mediated clearance of cabiralizumab was caused by these CSF1R expressing cells. Estimated clearance at steady state (CLss) was 8.74, 2.78, and 5.34 day* g/mL for ADA-negative cynomolgus monkeys dosed at 20, 50, and 100 mg/kg, respectively, based on the data from the 13-week repeat-dose GLP toxicology study. A nearly 2-fold accumulation was observed between the first and last dose for Cmax and AUC except the ones affected by ADAs.

Figure 3: Individual Plasma Cabiralizumab Concentration-Time Profile in Cynomolgus Monkeys after 4-Week Repeat Dosing



Vertical dash lines indicate dose days (1, 8, 15, and 22). Each animal received four weekly doses: 50 mg/kg weekly doses were given to 2M07, 2M09, 2F23, 2F24 and 150 mg/kg weekly doses were given to 3M14, 3M15, 3F29, and 3F30.

Figure 4: Group Mean (+SD) Plasma Cabiralizumab Concentration-Time Profile in Cynomolgus Monkeys after 13-Week Repeat Dosing



Symbols represent mean observed concentrations. Error bars represent +SD from mean. n=5-6/sex/group from first dose to terminal sacrifice on Study Day 92 and n=2/sex/group for recovery period.

- ADAs were detected in the toxicity studies for animals administered cabiralizumab (4 out of 4, 6 out of 20, and 20 out of 36 positive for the samples tested for the 4-week pilot toxicity study, the 4-week GLP toxicity study, and 13-week GLP toxicity study, respectively). In general, the presence of ADAs was associated with lower plasma concentrations of cabiralizumab (Figure 3 and Figure 4). However, the TK data supported that the adequate exposure was observed for most of the animals in two GLP toxicity studies.

- Cabiralizumab concentration-dependent PD effect was observed for CD16+ monocytes reduction in cynomolgus monkeys. The lowest plasma concentration of cabiralizumab with maximum reduction of CD16+ monocytes in cynomolgus monkeys after weekly repeat IV infusion of cabiralizumab is approximately 10 µg/mL. Based on the findings from cynomolgus monkeys, the cabiralizumab concentration-effect for the reduction of CD16+ monocytes in humans was evaluated as an exploratory PD marker.

- The starting dose for the first-in-human single IV administration in healthy volunteers was 0.2 mg/kg based on evaluation of the minimum anticipated biological effect level (MABEL).

2.2.1.2 Distribution, Metabolism, and Excretion

The expected consequence of metabolism of biotechnology-derived pharmaceuticals such as cabiralizumab is the degradation to small peptides and individual amino acids following receptor-mediated endocytosis. Therefore, the metabolic pathways are generally understood.

Following a single administration of cabiralizumab at 0.2, 1, 3, and 10 mg/kg, total clearance decreased with increasing dose and ranged from 1.60 to 0.105 mL/h/kg in healthy volunteers. The total clearance of 0.105 mL/h/kg at 10 mg/kg is within the range for a typical human IgG monoclonal antibody. Following multiple dose administration of cabiralizumab in different populations, the accumulation of cabiralizumab exposure was observed for doses 2 mg/kg with every two week dosing

2.2.1.3 Toxicology

Cabiralizumab was generally well-tolerated in the toxicology studies in cynomolgus monkeys. Test article-related findings included clinical observations, hematology and clinical chemistry changes, and histopathologic changes. The majority of these observations were considered non-adverse. The most prominent clinical observation was reversible periorbital edema, seen after prolonged exposure to cabiralizumab. The onset of edema did not show a clear relationship to exposure levels; however edema resolved after systemic clearance of the drug. Periorbital edema is a known side effect with drugs affecting the CSF1 pathway.[24] The main hematologic change was a decrease in circulating CD16+ monocytes, which was considered a PD effect, and the decreased cell numbers normalized with clearance of cabiralizumab from circulation. Cabiralizumab-related clinical chemistry effects included reversible increased ALT, AST, CK, and LDH values. These laboratory abnormalities were not associated with evidence of tissue injury or histopathologic changes and were attributed to decreased clearance of the ALT, AST, CK, and LDH molecules from serum due to a decreased number of liver macrophages (Kupffer cells). Kupffer cells are the cells responsible for clearance of short-lived serum enzymes such as ALT, AST, CK, and LDH. The connection between elevated serum enzymes, inhibition of CSF1R, and reduction of Kupffer cell numbers have been previously demonstrated in nonclinical studies.[25] Similar findings of increased serum enzymes have been reported for several CSF1R pathway antagonists, for example, PD-0360324, which is a human IgG2 monoclonal antibody to CSF1. During preliminary safety studies of this antibody in humans, dose-related increases in the levels of AST and CK were observed in the absence of other liver or muscle injury markers. These serum enzyme elevations were also attributed to reductions in Kupffer cell numbers. Accordingly, the ALT, AST, CK, and LDH elevations are considered non-toxic and an indirect PD effect of cabiralizumab exposure.

The most noteworthy necropsy findings in both pivotal studies was the histopathological observation of reversible expansion of the submucosal collagen fibers by clear space and varying amounts of a blue, granular ECM. This was most abundantly seen in the esophagus but was also present in a large variety of other tissues. This change was not associated with inflammatory cells or with any sign of degeneration or other alteration of the collagen fibers, fibroblasts, or the smooth muscle cells within the area of expansion. Most likely the reduction of tissue macrophages causes the observed accumulation of ECM due to a decreased clearance of glycosaminoglycans, especially hyaluronic acid, that are prominent in connective tissue and are normally catabolized by macrophages. A similar observation was also seen in *op/op* mice that lack functional CSF1.[25] This change is considered an indirect effect of cabiralizumab. There was no evidence that the accumulation of the blue granular ECM was adverse. There were no correlative clinical observations or organ weight changes, and the findings were fully reversible during a drug-free recovery period. Therefore, these observations were not considered adverse.

The no-observable-adverse-effect level (NOAEL) was determined to be 100 mg/kg for cynomolgus monkey, when administered for 13 weekly doses.

No reproductive or developmental toxicity studies have been conducted with cabiralizumab at this stage. Examinations of the reproductive organs in the 4-week and 13-week toxicology studies have shown no evidence of reproductive target toxicity. Male fertility assessment at the end of the dosing phase in the 13-week toxicity study did not show any effect of cabiralizumab on male fertility.

2.2.1.4 Pharmacodynamics

Cabiralizumab binds specifically to the extracellular domain (ECD) of human and cynomolgus monkey CSF1R as determined by direct binding enzyme-linked immunosorbent assay (ELISA) and Biacore analysis. Cabiralizumab binds in a dose-dependent manner to the ECD of human CSF1R fused to IgG1 Fc (CSF1R-Fc) and to cynomolgus monkey CSF1R-Fc with comparable half-maximal response (EC50) values. Cabiralizumab binds to human and cynomolgus monkey CSF1R-Fc with KD values in the low nanomolar (nM) range.

Cabiralizumab did not bind to human c-Kit-Fc or to human PDGFRβ-Fc in direct binding ELISAs, demonstrating specificity of cabiralizumab for CSF1R. cKit and PDGFRβ are proteins with the closest amino acid sequence homology to CSF1R in their ECDs.

Cabiralizumab blocks binding interactions between CSF1R and its two known ligands, CSF1 and IL34, as determined by competitive binding ELISAs. Cabiralizumab IC50 values were similar for both CSF1 and IL34 in these assays, indicating cabiralizumab blocks binding of both ligands with equal potency.

Cabiralizumab inhibited both CSF1 and IL34-induced CSF1R phosphorylation in a recombinant cell line engineered to overexpress CSF1R (CHO-CSF1R) in cell-based assays, demonstrating cabiralizumab blocks the activation of ligand-induced CSF1R signaling pathways. Cabiralizumab also inhibits CSF1 and IL34-induced proliferation/survival of peripheral blood IL34 signaling pathways, but also the subsequent physiologic responses of primary human monocytes to these ligands.

To assess the activation potential of cabiralizumab, CHO-CSF1R cells were incubated with cabiralizumab in the absence of CSF1 or IL34, and CSF1R phosphorylation was quantified from cell lysates using a phospho-CSF1R ELISA. To test if cross-linking of cabiralizumab could result in CSF1R activation, in some studies cell bound cabiralizumab was cross-linked with a secondary antibody or with a biotinylated secondary antibody followed by tertiary avidin cross- linking. Under no condition tested was the induction of CSF1R phosphorylation observed, consistent with a lack of cabiralizumab agonist activity. In conclusion, the data from both the recombinant cell line and primary monocytes suggest that cabiralizumab lacks the potential to activate CSF1R signaling either directly or when cross-linked.

To further assess the activation potential of cabiralizumab, freshly isolated peripheral blood monocytes were incubated with cabiralizumab in the absence of CSF1 or IL34, and its effects on monocyte proliferation/survival were assessed. In this case, cabiralizumab cross-linking may be facilitated by Fc receptors expressed on monocytes themselves. Under no condition tested did cabiralizumab induce monocyte proliferation/survival, consistent with a lack of cabiralizumab agonist activity.

Effect on CD16+ Monocytes in Cynomolgus Monkeys

CD16+ monocytes were reduced in monkeys receiving four weekly IV infusions of 50 mg/kg or 150 mg/kg cabiralizumab, consistent with CSF1R pathways being necessary to support the growth and maintenance of this monocyte subpopulation *in vivo*. CD16+ monocyte inhibition occurred within one week of dosing and was sustained throughout the dosing and exposure period. The CD16+ monocytes were restored to normal baseline levels after cabiralizumab cleared with no evidence of a rebound effect. The CD16- monocyte subpopulation remained unaffected by administration of cabiralizumab.

Effect on CSF1 Serum Levels in Cynomolgus Monkeys

Plasma levels of CSF1 are a measure of cabiralizumab target engagement. CSF1 is cleared from circulation under normal physiological conditions by macrophages (primarily liver Kupffer cells) via CSF1R-mediated endocytosis and intracellular degradation (Bartocci 1987). Cabiralizumab binds to and blocks CSF1R, resulting in a large, rapid increase in circulating CSF1 concentration, after which CSF1 levels reach a new steady state. The data (for Day 8 and Day 15) show that a minimum biological effect occurred at 5 µg/mL, and a half-maximal response (EC50) was 8 µg/mL cabiralizumab. While

cabiralizumab elevates CSF1, FivePrime believes that these elevations will have no consequence because:

- The receptor through which CSF1 signals is blocked by cabiralizumab.
- The levels of CSF1 fall dramatically once cabiralizumab is cleared.
- In the presence of cabiralizumab, when CSF1 is elevated, the potential for extremely high concentrations of CSF1 to displace cabiralizumab from the CSF1R receptor was evaluated in the cabiralizumab cell potency assay. The data showed that concentrations as high as 10 µg/mL CSF1 had no impact on cabiralizumab potency or maximal inhibition of CSF1R signaling.

Cabiralizumab Effect on Bone Resorption in Cynomolgus Monkeys

Treatment with cabiralizumab will potentially decrease the osteoclastic activity in RA that contributes to bone destruction. Plasma and urine markers of bone resorption were evaluated in monkeys following repeat dosing with cabiralizumab. Urine Collagen-type I N-terminal telopeptide (NTx) and plasma CTx, NTx, and Trap5b were all decreased at Day 28 after four weekly doses in the male monkeys. A similar trend was observed in the female monkeys, but the result was not statistically significant. At the recovery termination on Day 245, urinary NTx was restored to baseline in all monkeys.

2.2.1.5 Efficacy in Human Disease Tissues

The ability of cmFPA008 to enhance anti-PD1 efficacy was studied in an orthotopic pancreatic tumor model. KRasG12D/Ink4a-/- pancreatic ductal adenocarcinoma (PDAC) cells were surgically implanted into the pancreas of immunocompetent mice. To determine the effect of CSF1R blockade on macrophages, tumor bearing mice were treated with cmFPA008 alone for eight days at which point tumors were excised and analyzed by flow cytometry. Murine PDAC tumors contain a distinct subset of immunosuppressive TAMs identified as CD206Hi and a subset of immunostimulatory TAMs identified as CD206Low. Quantification of CD206Hi and CD206Low TAM subsets revealed that cmFPA008 led to a significant reduction of CD206Hi immunosuppressive TAMs whereas CD206Low immunostimulatory TAMs were less affected. To determine the effect of CSF1R blockade on the T cell checkpoint blockade, tumor cells were analyzed for PDL1 expression. cmFPA008 treatment increased the number of PDL1+ tumor cells. Taken together, these results suggest that although cmFPA008 reprograms the TAM compartment towards immune stimulation, this reprogramming also leads to upregulation of PDL1 on tumors cells which could limit an anti-tumor T cell response.

To test the effects of CSF1R blockade on anti-PD1 efficacy, mice bearing established tumors were treated with cmFPA008, anti-PD1, or the combination together with gemcitabine (GEM). Anti-PD1 or

cmFPA008 alone showed only limited efficacy at decreasing the progression of established tumors. In contrast, the combination of cmFPA008 and anti-PD1 significantly reduced tumor progression. Similar results were seen in KRasG12Dp53-/- tumors. These data suggest that CSF1R blockade can reprogram the immunosuppressive TAM compartment and significantly enhance anti-PD1 therapy.

2.2.2 Clinical Data to Date

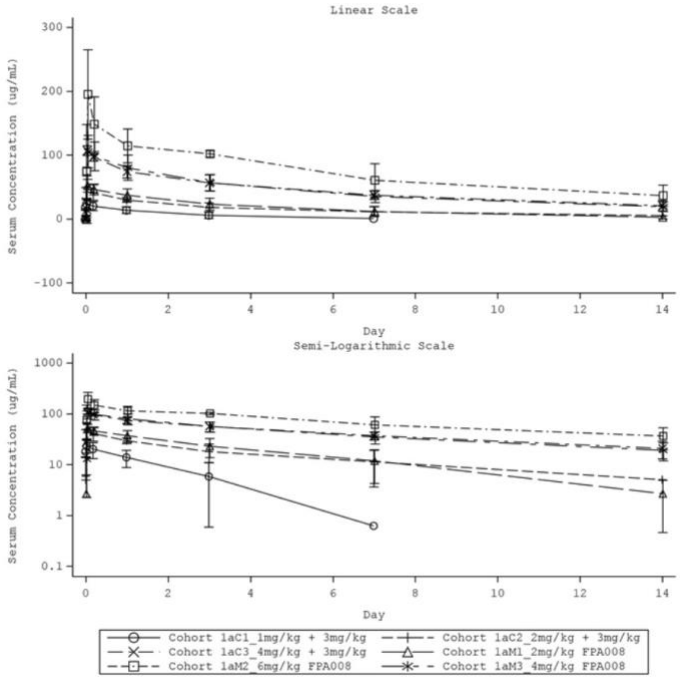
2.2.2.1 Pharmacokinetics

The PK and ADA of cabiralizumab were characterized in three studies: FPA008-001, FPA008- 002, and FPA008-003. These data are described in detail in the Investigator's Brochure. The cabiralizumab serum concentrations were quantitatively measured by a validated enzyme-linked immunosorbent assay (ELISA). PK parameters were estimated for each patient using noncompartmental analysis (NCA) by Phoenix® WinNonlin® (Version 6.3, Certara L.P., St. Louis, MO). The pharmacokinetic (PK) profile of cabiralizumab is characterized by linear and nonlinear clearance pathways, with the latter likely mediated by binding to CSF1R on cells. As monocyte and macrophage cells are dependent on CSF1R for viability, these target-bearing cells are reduced in number following cabiralizumab treatment, resulting in a decrease of target-mediated clearance. Once target-mediated clearance is saturated at high or repeat doses, cabiralizumab clearance is similar to other human IgG antibodies.

Following a single administration of cabiralizumab at 0.2, 1, 3, and 10 mg/kg, total clearance decreased with increasing dose and ranged from 1.60 to 0.105 mL/h/kg in healthy volunteers. The total clearance of 0.105 mL/h/kg at 10 mg/kg is within the range for a typical human IgG monoclonal antibody. Following multiple dose administration of cabiralizumab in different populations, the accumulation of cabiralizumab exposure was observed for doses 2 mg/kg with every two week dosing. The PK characteristics observed in healthy volunteers and patients with RA, PVNS, and cancer support dosing of cabiralizumab every two weeks or less frequently.

In Phase 1a, patients with cancer were administrated cabiralizumab at doses of 2, 4, and 6 mg/kg every two weeks as monotherapy and at 1, 2, 4 mg/kg every two weeks in combination with 3 mg/kg nivolumab every two weeks. Cabiralizumab serum concentration vs nominal time data is displayed in Figure 5.

Figure 5: Mean (±SD) Cabiralizumab Serum Concentration vs. Time in Patients with Solid Tumor following First Dose Administration



Based on preliminary analyses, following the first dose in patients with cancer at 2, 4, and 6 mg/kg as monotherapy or at 1, 2, and 4 mg/kg in combination with nivolumab, Cmax increased dose proportionally while AUC and Cmin increased more than dose proportionally, suggesting target-mediated clearance. Accumulation was observed for Cmax and Cmin ZLWK 2 mg/kg every two week dosing. Exposure was similar at 4 mg/kg for cabiralizumab as monotherapy and in combination with nivolumab.(see figure 6) Furthermore, exposure with cabiralizumab 4mg/kg in the presence of nivolumab was similar in the pancreatic cancer cohort compared to other tumor types (see figure 7) The PK of cabiralizumab was similar among patients with pancreatic cancer and other cancers. [26]

Figure 6: Pharmacokinetic Parameters of Cabiralizumab +/- Nivolumab

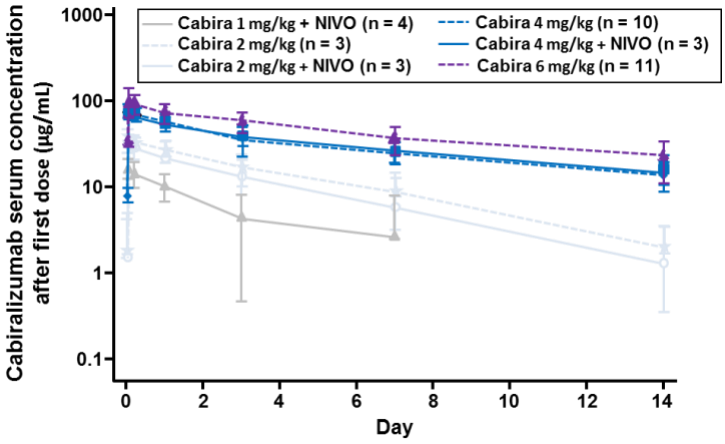
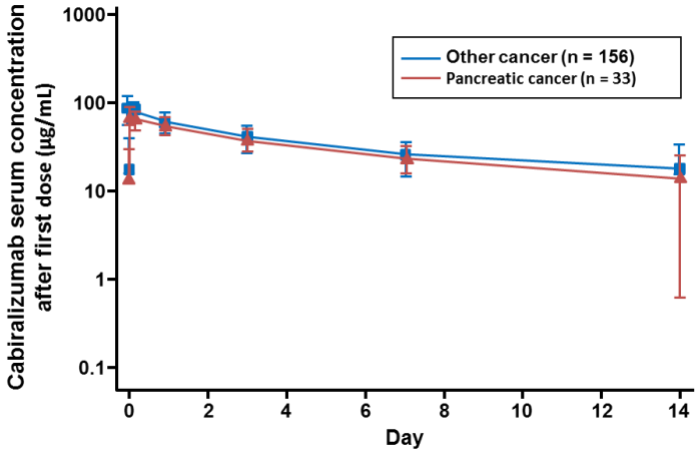


Figure 7: Pharmacokinetic Parameters of Cabiralizumab 4mg/kg + Nivolumab in pancreatic cohort vs other solid tumors



2.2.2.2 Pharmacodynamics

Three pharmacodynamic (PD) biomarkers correlate with cabiralizumab exposure in nonclinical studies: CSF1 serum levels, circulating CD16-positive peripheral blood monocytes (CD16+ monocytes), and serum markers of bone resorption.

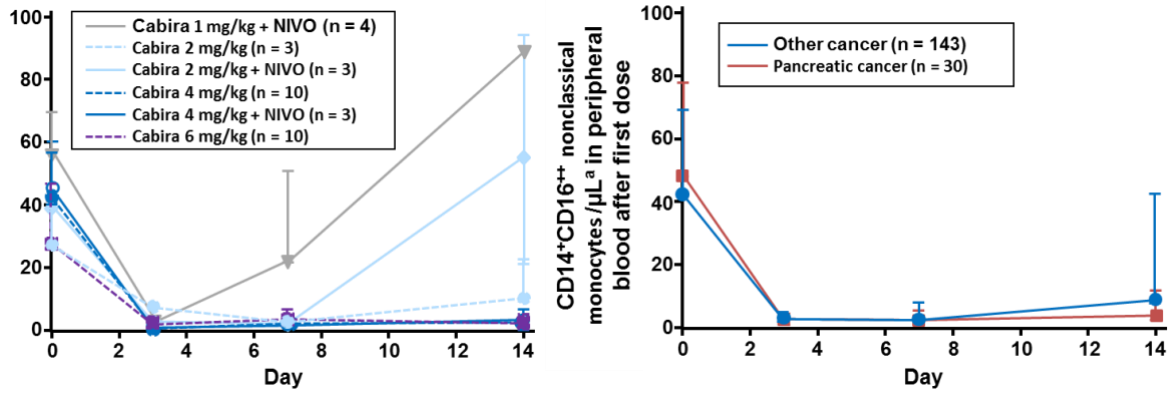
CSF1 and IL34 Ligands
Cabiralizumab blocks binding interactions between CSF1R and its two ligands, CSF1 and IL34. In nonclinical studies, cabiralizumab dosing resulted in a rapid and sustained increase in serum CSF1 that was readily reversible. The consequences of extremely high CSF1R ligand levels have been considered and are not anticipated to cause any adverse effects. Both CSF1 and IL34 were measured in the serum from all subjects in Parts 1, 2 (healthy volunteers) and Part 3 (patients with RA) of the study using commercially available ELISAs. The results were comparable to what was observed in nonclinical studies, marked by a rapid and sustained elevation of serum CSF1R ligands that was restored to baseline upon

clearance of cabiralizumab. The data prove that both CSF1R ligands have high turnover in humans and that CSF1R is a dominant mechanism of ligand clearance.

Effects on CD16+ Monocytes

- Human peripheral blood monocytes can be divided into three subgroups based on surface expression of CD14 and CD16; classical monocytes (CD14++CD16-), intermediate monocytes (CD14++CD16+), and nonclassical monocytes (CD14+CD16++). Nonclassical CD16+ monocytes are dependent on CSF1R signaling for survival and/or differentiation and are reduced upon CSF1R inhibition. Nonclassical CD16+ monocyte levels in peripheral blood have been or are being assessed in all three clinical studies described above as pharmacodynamic markers of CSF1R inhibition; FPA008-001 in healthy volunteers and patients with RA, FPA008-002 in patients with PVNS, and FPA008-003 in patients with advanced cancer. In general across all three studies, cabiralizumab treatment results in a transient increase in nonclassical CD16+ monocytes at four hours followed by complete reduction, to the limits of the assay, by 72 hours. The duration of nonclassical CD16+ monocyte reduction is dose and concentration dependent and levels return to normal once drug has decreased below approximately 10 µg/mL. Cabiralizumab 4 mg/kg Q2W was the minimal dose required to consistently deplete circulating nonclassical monocytes throughout the dosing interval; results were similar with cabiralizumab 4 mg/kg + nivolumab.(see figure 10). These decreases in levels of nonclassical monocytes were similar in the pancreatic cancer cohort as compared to other tumor types. Cabiralizumab does not reduce classical CD16- monocyte levels.

Figure 8: Cabiralizumab-mediated Reduction of Nonclassical CD16+ Monocytes in Patients with Cancer in Study FPA008-003



Bone Turnover Markers

Cabiralizumab may be of therapeutic benefit in patients with RA by targeting pro-inflammatory monocytes/macrophages and bone-destructive osteoclasts. A surrogate marker for inhibition of osteoclast activity is the measurement of bone resorption markers such as NTx, CTx and Trap5b in serum or urine. A decrease in urine NTx and plasma CTx, NTx and Trap5b was observed in monkeys following repeat dosing of cabiralizumab. A dose-dependent reversible decrease in urinary NTx was a reported pharmacodynamics (PD) effect of PD- 0360324, a neutralizing monoclonal antibody to CSF1, in healthy volunteers (Sadis 2009). CTx and Trap5b were measured by ELISA in serum samples collected from healthy volunteers following dosing with placebo or cabiralizumab in Parts 1 and 2 of study FPA008-001 and from patients with RA dosed with cabiralizumab in Part 3. A decrease in both serum CTx and Trap5b was observed at 3 mg/kg and 10 mg/kg in healthy volunteers. There was no statistically significant change in either marker following one or two doses of 1 mg/kg cabiralizumab in healthy volunteers (placebo subjects not shown). In Part 3 of this study, eighteen patients with RA were enrolled into five cohorts: 1 mg/kg for two doses, 3 mg/kg for two doses, 3 mg/kg for three doses, 6 mg/kg for two doses,

and 6 mg/kg for three doses. Data is available for the first three cohorts in Part 3. A dose-dependent decrease in both serum CTx and Trap5b was observed with cabiralizumab in patients with RA.

2.2.2.3 Safety and Efficacy

The clinical summary of safety and efficacy is based on three clinical studies:

1. 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.
2. Study FPA008-002 is evaluating the safety and efficacy of cabiralizumab monotherapy for 6 months in approximately 40 subjects with pigmented villonodular synovitis (PVNS).
3. 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.

Study FPA008-001 – Healthy Volunteers and Rheumatoid Arthritis

Thirty six healthy volunteers and 18 RA subjects received cabiralizumab in Study FPA008-001. No dose-limiting toxicities (DLTs) were reported and no unexpected treatment-related adverse events (AEs) have been reported from RA subjects treated with three doses up to 6 mg/kg.

In healthy volunteers and patients with RA, adverse events related to treatment with cabiralizumab have included edema, skin findings and elevations in circulating levels of certain enzymes. The edema described is mostly facial and periorbital (including eyelid) edema; the onset and duration of the edema varies, and does not appear to correlate with the serum concentration of cabiralizumab. Edema has been reported in other compounds targeting CSF1R pathway. Skin findings include pruritus and rash. Enzyme elevations include CK, lactate dehydrogenase (LDH) and AST. These enzyme elevations have been noted in a majority of patients, but have been reversible and clinically asymptomatic without evidence of other underlying organ dysfunction in most patients.

Study FPA008-002 – Pigmented Villonodular Synovitis

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 (FivePrime, 2017)

Study FPA008-003 – Advanced Cancers (Cabiralizumab/Nivolumab)

As of 01-Aug-2017, cabiralizumab-related AEs were reported in 169 of 195 subjects (87%) treated Q2W in Phase 1b of Study FPA008-003. The AEs reported in more than 10% of the subjects included: CK increased (77 subjects, 40%); periorbital edema (73 subjects, 73%); AST increased (65 subjects, 33%); fatigue (61 subjects, 31%); ALT increased and pruritus (32 subjects each, 16%); amylase increase and rash (30 subjects each, 15%); lipase increase (29 subjects, 15%); nausea (27 subjects, 14%); and LDH increased (20 subject, 10%).

Cabiralizumab-related $\geq$ 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 $\geq$ Grade 3 and reported in 2 or subjects ($\geq$ 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 ($\geq$ 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) 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 patients with respiratory failure (unrelated), 1 patient with acute respiratory distress (related), and 1 patient with acute respiratory failure (related).

Between 15 December 2016 and 15 February 2017, an additional 34 patients have been enrolled in the pancreatic tumor expansion phase of FPA008-003. The type, incidence, and severity of all AEs and AEs leading to discontinuation in these additional patients were generally consistent with the expected safety profile. All cabiralizumab-related AEs in Phase 1b were Grade 1 or 2, with the exception of: six Grade 4 CK increases, one Grade 4 LDH increase, three Grade 3 CK increases, three Grade 3 AST increases, three Grade 3 lipase increases, three Grade 3 hypertension, one Grade 3 diarrhea, one Grade 3 hypopituitarism. SAEs related to cabiralizumab were reported in six additional patients (for a total of eight treatment- related SAEs) in these additional patients. The new treatment-related SAEs reported in one patient each were pneumonitis, dyspnea, hypopituitarism, hyperbilirubinemia, hyponatremia, and seizure.

The study is still ongoing in the Phase 1b dose expansion and efficacy data for both phases of the study are preliminary. In this heavily pretreated pancreatic cancer population durable clinical benefit was observed in 5 of 31 (16%) evaluable patients.[27] All 4 confirmed responses were in patients with microsatellite stable tumors and were accompanied by steep declines in levels of the pancreatic tumor marker CA19-9 over baseline.

2.2.3 Dose Rationale

Cabiralizumab 4mg/kg dose was selected based on preliminary analyses. Following the first dose in patients with cancer at 2, 4, and 6 mg/kg as monotherapy or at 1, 2, and 4 mg/kg in combination with nivolumab, Cmax increased dose proportionally while AUC and Cmin increased more than dose proportionally, suggesting target-mediated clearance. Accumulation was observed for Cmax and Cmin with ≥ 2 mg/kg every two week dosing. Exposure was similar at 4 mg/kg for cabiralizumab as monotherapy and in combination with nivolumab (limited data, Cabiralizumab Investigator's Brochure Version 4 May 2017). Furthermore, the 4mg/kg every 2 week dose achieved the concentration ($\geq$10 μg/mL) necessary for maximum reduction of nonclassical CD16+ monocytes between dose intervals in a majority of patients when overall tolerability and safety allowed.

2.3 Nivolumab

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.[28] Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

The clinical use of monoclonal antibodies to T-cell inhibitory receptors has provided transformative information on the nature of the immune system and cancer. An emerging picture suggests that endogenous immune responses can mediate effective tumor regression and/or improved survival even in patients with large volume tumors resistant to other forms of therapy. Some of the unique features of this type of therapy, based largely on experience in advanced melanoma, include: improved overall survival (OS) with or without radiographic responses or improved progression-free survival (PFS); responses that may be delayed or occur after radiographic disease progression; combinations of immune modulators with enhanced or novel activities (in the example of ipilimumab and nivolumab); and toxicity that is almost exclusively immune or inflammatory in nature. It is not yet clear what factors determine responses and which components of the immune system are needed for this to occur. It seems likely that both memory helper and effector cells would be needed to sustain long-term responses. Increasing emphasis has been placed on understanding the relationships of the tumor, cellular infiltrate, and immunologic milieu surrounding each tumor.

PD-1, a 55-kDa type 1 transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors that include Ig super family member CD28, CTLA-4, inducible co-stimulator (ICOS), and B and T lymphocyte attenuator (BTLA) (Investigator Brochure, 2014). PD-1 is transiently but highly expressed on activated T cells functioning to limit immune effectors at the site of activation. Chronic stimulation may prevent the re-methylation of the PD-1 gene leading to continuous expression and characterizes a state of “exhausted” T cells that lose function and proliferative capacity while enhancing a suppressive tumor microenvironment. PD-1 may act together with other T-cell modulating molecules, including CTLA-4, TIM-3, lymphocyte-activation gene 3 (LAG-3) as well as indoleamine-pyrrole 2, 3-dioxygenase 1 (IDO-1), cytokines, and transforming growth factor beta (TGF-beta).

Two ligands specific for PD-1 have been identified: PD-ligand 1 (PD-L1, also known as B7-H1 or CD274, expressed on tumor, antigen-presenting cells [APCs], and dendritic cells [DCs]) and PD-L2 (also known as B7-DC or CD273, expressed on endothelial cells). The interaction of PD-1 with PD-L1 and PD-L2 results in negative regulatory stimuli that down-modulate the activated T-cell immune response through SHP-1 phosphatase.

PD-1 knockout mice develop strain-specific lupus-like glomerulonephritis (C57BL/6) and cardiomyopathy (BALB/c). In transplantable tumor models that expressed PD-1 and LAG-3 on tumor-infiltrating CD4+ and CD8+ T cells dual anti-LAG-3/anti-PD-1 antibody treatment cured most mice of established tumors that were largely resistant to single antibody treatment.[29] Despite minimal immunopathologic sequelae in PD-1 and LAG-3 single knockout mice, dual knockout mice abrogated self-tolerance with resultant autoimmune infiltrates in multiple organs, leading to eventual lethality.

PD-L1 expression is found on a number of tumors, and is associated with poor prognoses based on OS in many tumors, including melanoma,[30] renal,[31] esophageal,[32] gastric,[33] ovarian,[34] pancreatic,[35] lung [36] and other cancers (Investigator Brochure, 2014).

The PD-1/PD-L1 axis plays a role in human infections, particularly in hepatitis C virus (HCV) and human immunodeficiency virus (HIV). In these cases, high expression levels of PD-1 were found in viral-specific CD8+ T cells that also display a non-responsive or exhausted phenotype. Non-responsive PD-1-high T cells were observed in simian immunodeficiency virus (SIV) infection in rhesus macaques. Treatment of SIV-infected macaques with an anti-PD-1 mAb (3 mg/kg x4) resulted in decreased viral loads and increased survival along with expanded T cells with increased T-cell functionality.

Nivolumab is approved for the treatment of several types of cancer in multipleregions including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014). Nivolumab is also being investigated in various other types of cancer as monotherapy or in combination with other therapies, and as single-dose monotherapy for the treatment of sepsis.

2.3.1 Preclinical Data

Nivolumab has been shown to bind specifically to the human PD-1 receptor and not to related members of the CD28 family. Nivolumab inhibits the interaction of PD-1 with its ligands, PD-L1 and PD-L2, resulting in enhanced T-cell proliferation and interferon-gamma (IFN-γ) release in vitro[37] Nivolumab binds with high affinity to activated human T-cells expressing cell surface PD-1 and to cynomolgus monkey PD-1.2 In a mixed lymphocyte reaction (MLR), nivolumab promoted a reproducible concentration-dependent enhancement of IFN-γ release.[38] In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab was well tolerated at doses up to 50 mg/kg, administered weekly for 5 weeks, and at doses up to 50 mg/kg, administered twice weekly for 27 doses. While nivolumab alone was well tolerated in cynomolgus monkeys, combination studies have highlighted the potential for enhanced toxicity when combined with other immunostimulatory agents. In addition, an enhanced pre- and postnatal development (ePPND) study in pregnant cynomolgus monkeys with nivolumab was conducted. Administration of nivolumab at up to 50 mg/kg 2QW was well tolerated by pregnant monkeys; however, nivolumab was determined to be a selective developmental toxicant when administered from the period of organogenesis to parturition at $\geq$ 10 mg/kg (area under the concentration- time curve [AUC] from time zero to 168 hours [AUC(0-168 h)] 117,000 μg*h/mL). Specifically, increased developmental mortality (including late gestational fetal losses and extreme prematurity with associated neonatal mortality) was noted in the absence of overt maternal toxicity. There were no nivolumab-related changes in surviving infants tested throughout the 6-month postnatal period. Although the cause of these pregnancy failures was undetermined, nivolumab-related effects on pregnancy maintenance are consistent with the established role of PD-L1 in maintaining fetomaternal tolerance in mice.[39]

2.3.2 Clinical Data to Date

2.3.2.1 Pharmacokinetics

The PK of nivolumab was studied in subjects with cancer over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. Nivolumab clearance (CL) decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of approximately 24.5% (47.6%) resulting in a geometric mean steady state clearance (CLss) (CV%) of 8.2 mL/h (53.9%); the decrease in CLss is not considered clinically relevant. The geometric mean volume of distribution at steady state (Vss) was 6.8 L (27.3%), and geometric mean elimination half-life (t1/2) was 25 days (77.5%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3.7-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. Additionally, nivolumab has a low potential for drug-drug interactions. The clearance of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1 status, solid tumor type, baseline tumor size, and hepatic impairment. Although ECOG status, baseline glomerular filtration rate (GFR), albumin, and body weight had an effect on nivolumab CL, the effect was not clinically meaningful. PPK analysis suggest that nivolumab CL in subjects with cHL was approximately 32% lower relative to subjects with NSCLC; however, the lower CL in cHL subjects was not considered to be clinically relevant as nivolumab exposure was not a significant predictor for safety risks for these patients. When nivolumab is administered in combination with ipilimumab, the CL of nivolumab was increased by 29%, whereas there was no effect on the clearance of ipilimumab.

PPK and exposure response analyses have been performed to support use of nivolumab 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W dosing regimens in subjects with cancer in addition to the 3 mg/kg Q2W regimen. A flat dose of nivolumab 240 mg Q2W was selected since it is identical to a dose of 3 mg/kg for subjects weighing 80 kg, the observed median body weight in nivolumab treated cancer patients, while the nivolumab 360 mg Q3W and 480 mg Q4W regimens allow flexibility of dosing with less frequent visits and in combination with other agents using alternative dosing schedules to Q2W. Using a

PPK model, the overall distributions of nivolumab exposures (Cavgss, Cminss, Cmaxss, and Cmin1) are comparable after treatment with either nivolumab 3mg/kg or 240 mg Q2W. Following nivolumab 360 mg Q3W and 480 mg Q4W, Cavgss are expected to be similar to those following nivolumab 3 mg/kg or 240 mg Q2W, while Cminss are predicted to be 6% and ~16% lower, respectively, and are not considered to be clinically relevant. Following nivolumab 360 mg Q3W and 480 mg Q4W, Cmaxss are predicted to be approximately ~23% and ~43% greater, respectively, relative to that following nivolumab 3 mg/kg Q2W dosing. However, the range of nivolumab exposures (median and 90% prediction intervals) following administration of 240 mg flat Q2W, 360 mg Q3W, and 480 mg Q4W regimens across the 35 to 160 kg weight range are predicted to be maintained well below the corresponding exposures observed with the well tolerated 10 mg/kg nivolumab Q2W dosing regimen.

The PK of single-dose nivolumab monotherapy in subjects with sepsis is under evaluation; however, no data are currently available.

2.3.2.2 Clinical Efficacy

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy and in combination with ipilimumab in several tumor types, including NSCLC, melanoma, RCC, cHL, SCLC, gastric cancer, SCCHN, urothelial cancer, HCC, and CRC. In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in subjects with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or SCCHN. Nivolumab in combination with ipilimumab improved PFS and ORR over ipilimumab alone in subjects with unresectable or metastatic melanoma. No efficacy data are currently available for nivolumab treatment in subjects with sepsis.

2.3.2.3 Clinical Safety

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 16,900 subjects treated to date.

For monotherapy, the safety profile is similar across tumor types. There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. In Phase 3 controlled studies, the safety profile of nivolumab monotherapy is acceptable in the context of the observed clinical efficacy, and manageable using established safety guidelines. Clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and timely immunosuppressive therapy or other supportive care. Based on preliminary data from an ongoing Phase 1 study, there have been no unexpected safety findings to date in patients with sepsis who received a single dose of nivolumab monotherapy. In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve. The most advanced combination under development is nivolumab + ipilimumab, which is approved in subjects with unresectable or metastatic melanoma and being studied in multiple tumor types. Results to date suggest that the safety profile of nivolumab+ipilimumab combination therapy is consistent with the mechanisms of action of nivolumab and ipilimumab. The nature of the AEs is similar to that observed with either agent used as monotherapy; however, both frequency and severity of most AEs are increased with the combination.

2.3.3 Dose Rationale

The safety and efficacy of 240 mg Q2W flat dose of nivolumab is expected to be similar to the3 mg/kg Q2W dosing regimen in subjects with cancer. A flat dose of nivolumab 240 mg Q2W was selected since it is identical to a dose of 3 mg/kg for subjects weighing 80 kg, the observed median body weight in nivolumab treated cancer patients. Using a PPK model, the overall distributions of nivolumab exposures (Cavgss, Cminss, Cmaxss, and Cmin1) are comparable after treatment with either 3 mg/kg or 240 mg nivolumab. The predicted range of nivolumab exposures (median and 90% prediction intervals) resulting from a 240 mg flat dose across the 35 to 160 kg weight range is maintained well below the corresponding exposures observed with the well tolerated 10 mg/kg nivolumab Q2W dosage. Across the various tumor types in the clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy and safety has been found to be relatively flat. Given the similarity of nivolumab PK across tumor types and the similar exposures predicted following administration of 240 mg flat dose compared to 3 mg/kg Q2W regimen, it is expected that the safety and efficacy profile of 240 mg Q2W nivolumab will be similar to that of 3 mg/kg nivolumab. Hence, a flat dose of 240 mg nivolumab has been incorporated into the oncology clinical studies.

2.4 Sterotactic Body Radiation Therapy (SBRT)

SBRT is an important recent advance in the treatment of localized pancreatic cancer. While studies using conventional chemoradiation for non-metastatic pancreatic cancer have had conflicting results, SBRT is a contemporary form of RT that involves a short course of radiation delivered at a higher dose than conventional RT. Studies of SBRT have been encouraging and suggest that it can cause tumor regression away from involved vasculature, thereby improving the chances of negative surgical margins. Importantly, because the radiation course is short, the potential for delay of definitive surgery is reduced.

Additionally, shorter courses of radiation may be immunologically preferential, resulting in acute rather than chronic antigen exposure and thereby reducing T cell anergy, exhaustion, and senescence.

2.4.1 Clinical Data to Date

Results of SBRT in patients with LAPC are encouraging. Early phase I/II studies using single-fraction SBRT (25 Gy in 1 fraction) demonstrated excellent freedom from local progression (FFLP) at 1 year (>90%) and minimal acute toxicity in patients with locally advanced disease, but resulted in high late grade 2-4 gastrointestinal (GI) toxicity[40-42] [43, 44]. A single-arm phase II multi-institutional study to determine whether gemcitabine with fractionated SBRT (in 5 fractions of 6.6 Gy, total 33.0 Gy) would achieve reduced late grade 2-4 GI toxicity compared with a historical cohort of patients treated with gemcitabine and a single 25 Gy-fraction of SBRT was subsequently conducted.[45] Forty-nine LAPC patients received up to 3 doses of gemcitabine (1,000 mg/m2) followed by a one-week break and SBRT (33.0 Gy in 5 fractions). Following SBRT, patients continued gemcitabine until progression or toxicity. Rates of acute and late (primary endpoint) grade ≥2 gastritis, fistula, enteritis, or ulcer toxicities were 2% and 11%, respectively. QLQ-C30 global quality of life scores remained stable from baseline to after SBRT (67 at baseline, median change of 0 at both follow-ups; P>.05 for both). Patients reported a significant improvement in pancreatic pain (P<.001) 4 weeks after SBRT on the QLQ-PAN26 questionnaire. Median plasma CA19-9 was reduced following SBRT (median time post-SBRT 4.2 weeks, 220 vs. 62 U/mL, p<0.001). Median overall survival was 13.9 months (95% CI, 10.2-16.7). FFLP at 1 year was 78%. Four patients with LAPC at diagnosis (8%) underwent margin- and node-negative resections.

2.4.2 Dose Rationale

At this time, there is no clear consensus regarding an optimal fractionation schedule for patients with locally advanced pancreas cancer.[40, 46] To date, Stanford has treated more than 150 patients with SBRT, and this treatment has resulted in local control rates of >90% with acceptable acute GI toxicity. A single fraction of Linac-based SBRT (25 Gy x 1) has resulted in excellent tumor control. However, close to 50% of these patients developed late grade 2-5 duodenal toxicity within one year, primarily because of the proximity of the duodenum to the pancreas. Delivering hypofractionated radiation (5 or 6.6 Gy over 5 days) instead of single fraction treatment appears to result in similar tumor control with less late toxicity (≤20%) [45, 47-49]

Using the linear-quadratic formulation, the biologically equivalent dose (BED) of the proposed fractionation schedules are given in comparison to other commonly used schemes (Table 3). The proposed 6.6 Gy x 5 schedule (BED early/late 54.8/105.6) closely approximates that of standard chemoradiation (BED early/late 60/83.3), but without concurrent chemotherapy and treating a smaller tumor margin (0.3 cm vs. ~2 cm). Furthermore, the proposed 6.6 Gy x 5 fractionation schedule has a much lower late BED (105.6 vs. 146.7) with a similar early BED (54.8 vs. 70) as the previous 40 Gy x 5 regimen. In this study, we will refine our current understanding of radiation tolerance of the pancreas and adjacent organs.

Table 3: Estimated biological equivalent dose (BED) of Fractionation Schedules

Dose / fractions	Nodes Tx	Chemo	BED early	BED late
			α/β=10	α/β=-3
50 Gy/25	Yes	Yes	60	83.3
30 Gy/10	Yes	Yes	39	60
25 Gy/5	**Yes**	**No**	**37.5**	**66.7**
33 Gy/5	**No**	**No**	**54.8**	**105.6**
40 Gy/5	No	No	70	146.7

The dose 6.6 Gy x 5fx has been shown to be safe and effective in the treatment of LAPC and is a commonly used regimen for the delivery of SBRT. Furthermore, it approximates the pre-clinical model we have used which employed 3 doses of 6 Gy at 48-hour intervals.

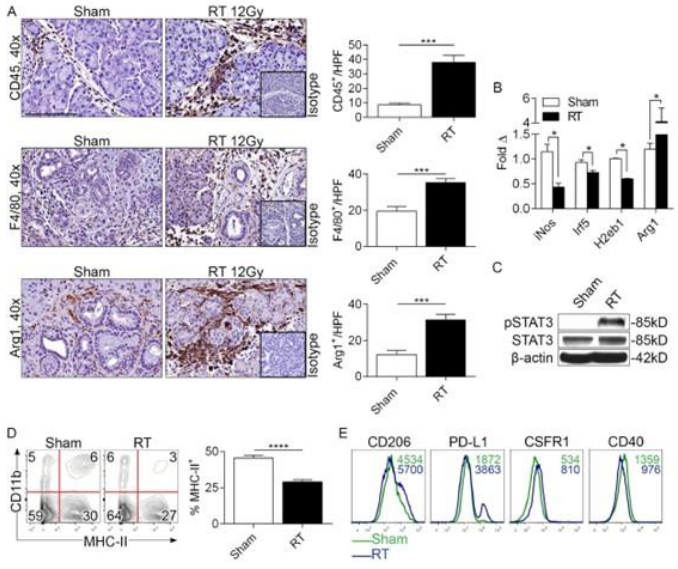
2.5 Rationale

2.5.1 Rationale for Study Population and Interventional Treatment

Pancreatic cancer remains a deadly malignancy despite incremental gains made with the increased use of multi-agent chemotherapy in the metastatic setting. Disease in the localized setting remains the optimal opportunity to improve the number of patients cured of this deadly disease. Surgery continues to provide the best opportunity for cure, but only 15-20% of patients with pancreatic cancer present with upfront, resectable disease.[2] However, even with the integration of multi-agent chemotherapy, gains have remained modest. In resectable disease, the addition of capecitabine to gemcitabine in the postoperative setting has improved median survival from 25.5 months to 28 months.[50] Given the majority of patients present with advanced disease, with 30-40% having locally advanced unresectable disease and median overall survival of 15-16 months, there is certainly need for improved therapy[2]. Treatment for LAPC most commonly involves either chemotherapy alone or combined with radiation therapy(RT). What has been demonstrated is that patients with LAPC who can be downstaged and undergo R0 resection have a significant improvement in overall survival. However, conventional chemoradiation converts less than 10% of patients with locally advanced disease to resectable.[10] If the tumoricidal effects of radiation can be augmented then higher R0 resection rates may be achieved and in turn, improved survival rates. **We hypothesize that the clinical efficacy of RT in pancreatic cancer is limited by its promotion of innate and adaptive immune suppression and CSF1R blockade with cabiralizumab combined with PD-1 blockade with nivolumab will enhance the efficacy of SBRT by reprogramming the TAM compartment in tumors, thereby preventing an immune suppressive phenotype and augmenting T-cell mediated anti-tumor response.**

Immunosuppressive effect of radiation in pancreatic cancer:
In preclinical model systems with an intact tumor microenvironment, we have shown that RT in pancreatic cancer leads to marked immune suppression within the tumor microenvironment (TME) via expansion of immune suppressive tumor associated macrophages (TAMs)[51]. Phenotypic analysis of TAMs from a pre-invasive pancreatic model (p48Cre;LSL-KrasG12D, KC mice) treated with12Gy RT, demonstrated a reduction in iNos, Irf5, and H2eb1 expression but upregulation in Arg1, consistent with M2-like macrophage differentiation. Further, RT increased STAT3 phosphorylation, diminished MHCII expression in TAMs, and increased TAM expression of CD206, PD-L1, and CSFR1, but modestly diminished CD40 expression (Figure 9).

Figure 9: RT increases TAM infiltration and induces M2-polarization in pre-invasive PDA.



(a) KC mice underwent pancreas-directed RT or sham treatment at 6 weeks of life and pancr were assayed 3 days later (n=10/group). IHC on paraffin-embedded pancreatic sections performed using mAbs directed against CD45+-pan leukocytes, F480+ cells, and Arg1+ c Cellular infiltrates were quantified by examining 10 HPFs per slide. (b) mRNA levels of iNos, H2Eb1, and Arg1 were tested in RT- or sham-treated pancreata by nanostring assay. (c) ST phosphorylation was evaluated by western blotting. (d) Gr1–F4/80+ cells in sham- and RT-tre pancreata from KC mice were gated and tested for co-expression of CD11b and MHCII. fraction of Gr1– F4/80+CD11b+ TAMs expressing MHCII was quantified. (e) Gr1–F4/80+CD1 TAMs from sham or RT-treated KC pancreata were gated by flow cytometry and tested expression of CD206, PD-L1, CSFR1, and CD40. Representative histogram overlays are sho MFIs are indicated for each respective treatment group.

A similar increase in M2 polarized TAMs following RT was also seen in an invasive model of pancreatic cancer with KPC-derived orthotopic pancreatic tumors (p48Cre;LSL-KrasG12D;LSL-Trp53R172H , KPC mice).(Figure 10)

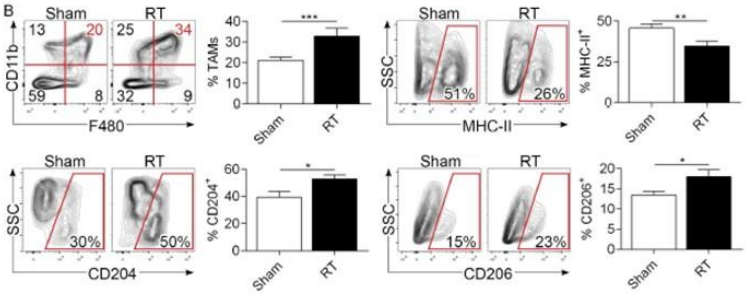
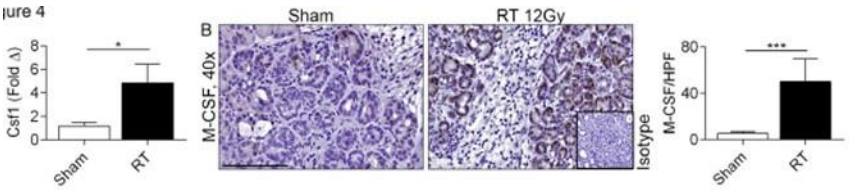


Figure 10: RT increases infiltration of TAMs and induces M2-like polarization in invasive PDA.

The fraction of Gr1–F4/80+CD11b+ TAMs among CD45+ leukocytes in the TME was determined by flow cytometry. TAMs were then gated and tested for expression of MHC II, CD204, and CD206. Representative contour plots and summary data are shown.

This M2 reprogramming was also observed when invasive tumors were treated with fractionated RT given as 3 doses of 6 Gy at 48 hour intervals. It was then shown that this change in TAM infiltration and M2-phenotype was modulated by RT-induced expression (about 5 fold) of M-CSF from pancreatic tumor cells (Figure 11).

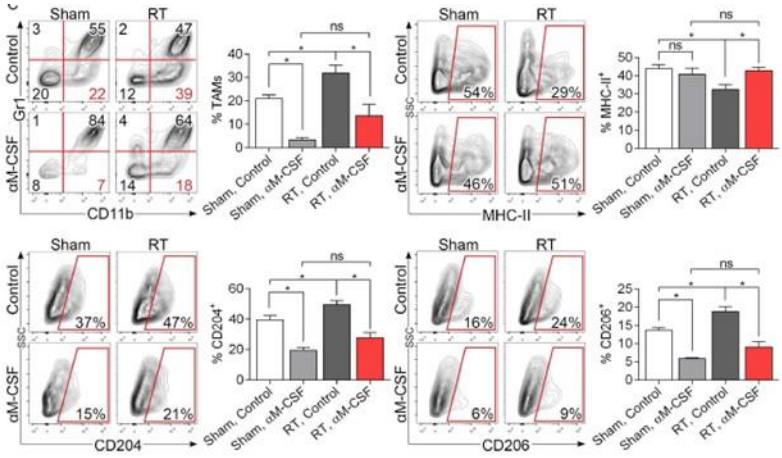
Figure 11: RT-induced M-CSF expression from pancreatic tumor cells.



a) qPCR for CSF1 was performed on RT- and sham-treated orthotopic PDA tumors on day 3 after RT (n=3/group). (b) IHC for M-CSF was performed on day 3 in pancreata of irradiated and sham-treated KC mice (n=3/group).

Furthermore, blockade of M-CSF reduced TAM infiltration in RT treated pancreatic tumors and reversed their M2 reprogramming (Figure 12).

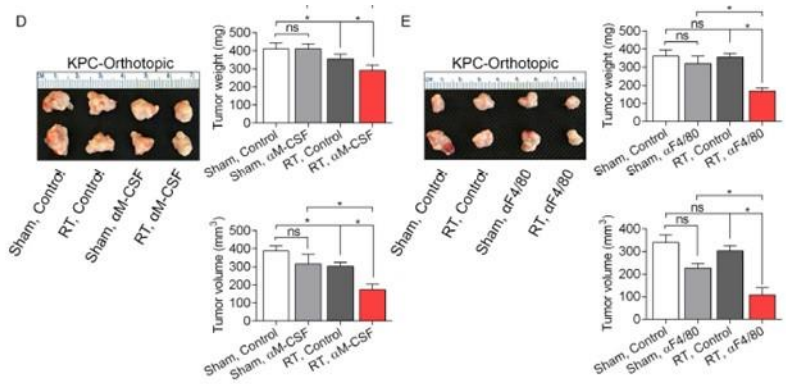
Figure 12: M-CSF blockade mitigates the M2 macrophage reprogramming associated with RT.



WT mice were orthotopically implanted with KPC-derived tumors and cohorts were treated with tumor-focused RT or sham-treated at 18 days. Select cohorts were additionally treated with a neutralizing α-M-CSF mAb. Mice were sacrificed on day 21 and tested for the fraction of tumor infiltrating Gr1–F480+CD11b+ TAMs. Further, TAMs were then gated and tested for MHCII, CD204, and CD206 expression.

Next, we demonstrated that blockade of M-CSF enhanced the anti-tumor efficacy of RT in invasive pancreatic cancer (Figure 13).

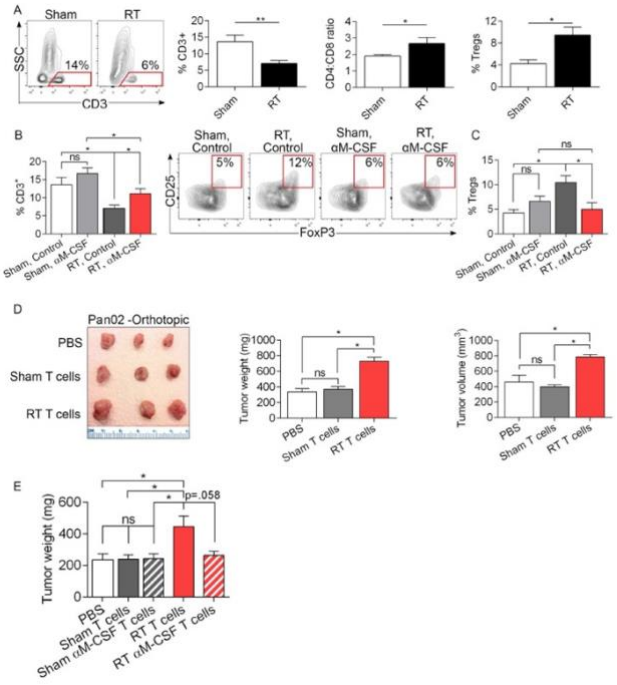
Figure 13: M-CSF blockade enhances the effect associated with RT



WT mice were orthotopically implanted with KPC-derived tumors and cohorts were treated with tumor-focused RT or sham-treated at 18 days. Select cohorts were additionally treated with (D) a neutralizing α-M-CSF mAb or (E) a neutralizing α-F4/80 mAb. Representative photographs of PDA tumors, average tumor weights, and tumor volumes are shown (n=12/group).

Finally, we showed that RT induced M2-polarized macrophages induce T cell anergy and ineffectual adaptive immunity, thereby limiting the efficacy of RT treatment. This was able to be reversed using concurrent blockade of M-CSF with RT to prevent the generation of tumor promoting T cell populations and increase the therapeutic effect of RT (Figure 14).

Figure 14: RT programs tumor-infiltrating T cells in invasive PDA into tumor promoting entities in an M-CSF dependent manner



(a) Sham- or RT-treated orthotopic KPC-derived tumors were assayed on day 3 after treatment for the fraction of tumor-infiltrating CD3+ T cells the CD4:CD8 T cell ratio, and the fraction of tumor-infiltrating Tregs. (b) Select cohorts of sham- or RT-treated orthotopic KPC-derived tumors were additionally treated with a neutralizing α-M-CSF mAb and tested for the fraction of tumor-infiltrating CD3+ T cells and (c) CD4+CD25+FoxP3+ Tregs on day 3 after treatment (n=10/group; *p<0.05, **p<0.01). (d) WT mice were administered a subcutaneous injection of Pan02-derived tumor + PBS, Pan02 cells + T cells harvested from day 21 sham-treated orthotopic KPC-derived PDA (10:1 ratio), or Pan02 cells + T cells harvested from RT-treated PDA. Animals were sacrificed on day 35 and subcutaneous tumors harvested. Representative images of tumors from each treatment cohort, average tumor weight, and tumor volume are shown (n=5/cohort). (e) WT mice were administered a subcutaneous injection of KPC-derived tumor cells + PBS, KPC cells + T cells harvested from sham-treated KPC-derived PDA (10:1 ratio), KPC cells + T cells harvested from αM-CSF-treated PDA, KPC cells + T cells harvested from RT-treated PDA, or KPC cells + T cells harvested from αM-CSF + RT-treated PDA. Animals were sacrificed at day 17 & subcutaneous tumors were weighed (n=5/cohort; *p<0.05).

These observations highlight the necessity to reprogram macrophages toward an M1- like phenotype to overcome the immunosuppression and resultant tumor regrowth after RT. The early infiltration of M2-polarized TAMs following RT, leads to a T-cell suppressive response. Besides directing CD4+ T-cell differentiation toward a Th2 or Treg phenotype, tumor-infiltrating myeloid cells can also induce apoptosis or exhaustion in tumor-specific cytotoxic T lymphocytes via PD-L1– PD1 ligation. We found that RT induces up-regulation of PD-L1 in PDA-infiltrating TAMs, which is potentially another mode of immune suppression that can account for radioresistance in PDA. A similar finding has been demonstrated by Twyman-Saint Victor et al. in which they show that RT alone has only modest efficacy in PDA cell lines implanted in the flank, but combination therapy with PD-1 and CTLA4 inhibition offers impressive tumor protection.[11] Similarly, in models of colorectal and breast cancer, RT has been shown to up-regulate

PD-L1 on myeloid cells, whereas the efficacy of radiation is synergistically enhanced when combined with blockade of the PD-L1– PD1 axis.[12] These reports highlight a fundamental and seemingly paradoxical principal of immunotherapy: accentuating immune suppression by RT-induced up-regulation of PD-L1 can enhance the therapeutic efficacy of immunotherapeutics targeting PD-L1 or PD1. Similarly, our data imply that although αMCSF immunotherapies have only modest efficacy in absence of RT, it can impressively diminish tumor growth when combined with RT. Hence, RT may enhance the therapeutic efficacy of immunotherapy not only via the mechanisms discussed here, but also through modulation of the immune contexture of the TME, which provides targets for immunotherapeutic manipulation. Therefore, in order to improve the effect of radiation therapy by preventing an immune suppressive phenotype and augmenting T-cell mediated anti-tumor response, we propose to investigate the combination of cabiralizumab, nivolumab and radiotherapy in the treatment of locally advanced pancreatic cancer

2.5.2 Rationale for Correlative Science

2.5.2.1 Determination of Pharmacodynamic Biomarkers

Plasma levels of CSF1 are a measure of cabiralizumab target engagement. CSF1 is cleared from circulation under normal physiological conditions by macrophages (primarily liver Kupffer cells) via CSF1R-mediated endocytosis and intracellular degradation.[52] Cabiralizumab binds to and blocks CSF1R, resulting in a large, rapid increase in circulating CSF1 concentration, after which CSF1 levels reach a new steady state. Prior studies measuring both CSF1 and IL34 in the serum from all subjects receiving cabiralizumab demonstrated results comparable to what was observed in nonclinical studies: marked by a rapid and sustained elevation of serum CSF1R ligands that was restored to baseline upon clearance of cabiralizumab. The data show that a minimum biological effect occurred at 5 µg/mL, and a half-maximal response (EC50) was 8 µg/mL cabiralizumab. In this study plasma levels of CSF1 will be measured at multiple timepoints to determine target engagement by carbiralizumab at administered dose.

Another measure of target engagement by cabiralizumab are noncalssical CD16+ monocytes. Nonclassical CD16+ monocytes are dependent on CSF1R signaling for survival and/or differentiation and are reduced upon CSF1R inhibition. Nonclassical CD16+ monocyte levels in peripheral blood have been or are being assessed in all three clinical studies with cabiralizumab as pharmacodynamic markers of CSF1R inhibition. In general across all three studies, cabiralizumab treatment results in a transient increase in nonclassical CD16+ monocytes at four hours followed by complete reduction, to the limits of the assay, by 72 hours. The duration of nonclassical CD16+ monocyte reduction is dose and concentration dependent and levels return to normal once drug has decreased below approximately 10 µg/mL. Cabiralizumab does not reduce classical CD16- monocyte levels. In this study blood will be serially collected for flow cytometry analysis to monitor monocyte subsets over time.

2.5.2.2 Treatment effect on innate and adaptive immunity

We and others have shown that the volume of CD8+ T cells in the pancreatic tumor microenvironment (TME) correlates with a favorable outcome as does a high CD8+/CD4+ratio.[53-55] Furthermore, CD8+ T cells and Th1-polarized CD4+ T cells have anti-tumor properties, whereas the Th2, Treg, and Th17 CD4+ T cell subsets are pro-tumorigenic in human and murine pancreatic cancer. T cell cytotoxic potential can be inferred from their expression of activating receptors. Our experiments will measure the effects of CSF1R and PD-1 blockade in combination with SBRT on T cell subset infiltration, differentiation, and activation by comparing pre- and on- treatment biopsies. We will measure pathologic response, characterized by degree of tumor necrosis as previously described.[56] Changes in immune infiltrate will be assessed by IHC against the following markers including, but not limited to, CD3, CD4, CD8, Foxp3, PD-1, PD-L1, Granzyme B, CD68, CD163, ARG1 and iNOS.

The relative composition and function of the tumor and its immune infiltrate before and on treatment will be further elucidated using a novel 3-D microfluidic system (patient-derived organotypic tumor spheroids (PDOTS), pioneered by the Wong lab, that allows for *ex vivo* culture of organotypic spheroids freshly isolated from patient or murine tumors, which contain autologous tumor-infiltrating myeloid and lymphoid immune cells.[57] They have recently shown that this system can predict therapeutic responses to checkpoint blockade by observing tumor cell killing. Additionally, the microfluidic nature of the device allows for the accurate quantification of cytokine release, providing a quantitative assessment of early immune activation. By using this 3D microfluidic culturing system, the Wong lab has performed proof-of-principle studies in a large collection of human tumors to successfully create PDOTS (including primary human PDAC) as well as have shown that murine-derived organotypic tumor spheroids (MDOTS) derived from various models can respond to checkpoint blockade. After culturing, we can quantify total immune cells (CD45+), viable cells (Calcein) among total cells (Hoechst 32242). This data serves as proof-of-principle that the MDOTS/PDOTS system is a viable method for assessing the anti-tumor immune response *ex vivo*. We will utilize the PDOTS system to evaluate both before and after treatment, the immune responses using various readouts, including viability, and cytokine/chemokine secretion changes to determine changes in the tumor cells as well as infiltrating immune cells in the tumor microenvironment. PDOTS will be derived from the pre- and on-treatment biopsies as well as from those tumors which undergo surgical resection. This will allow us to understand the biology and therapeutic implications of remaining viable tumor cells as well as the effects of the changes in the TME such as alterations in the populations of immune cells. Freshly collected biopsy specimens from patients will be partially digested into organoids and loaded into 3D microfluidic devices and treated with the therapeutic combinations in the accompanying clinical trial. These biopsy samples will be also evaluated for immune composition profiles by flow cytometry prior to the *ex vivo* treatment (immune profiling – above). After the treatment, spheroids will be stained for AO/PI live/dead staining, to quantify cell death. Furthermore, we will quantitatively profile the secreted chemokines/cytokines production in these same conditions using the multiplex Luminex platform at different time points after treatments. Changes in various types of immune cells, including T cell activation/expansion, such as Th1 cytokines responding to type I interferon (IFNγ, CXCL9, CXCL10, IL-12, etc.), and those related to effector T cells function versus T regulator cells expansion (IFNγ, IL-2, TGF-β, IL-10, etc.) will be evaluated. For myeloid cells, we will focus on those involved in inflammation and myeloid activation (IL6, IL-1β, Flt-3L, G-CSF, GM-CSF etc.) versus immunosuppression (CCL2, CXCL1, CCL22, PDGF, IL-10 etc.). Based on the generated data, we will further evaluate detailed changes of different immune cell populations using high-throughput single cell RNA transcriptomic quantification platform 10x genomics, which will be run at the NYU Genome Technology Center. Different immune populations will be identified based on the transcriptional signatures using unsupervised density based clustering on t-Distributed Stochastic Neighbor Embedding (t-SNE) analysis. This will be used to further evaluate key immune populations and signaling pathways that respond to the treatment.

Despite the recent success of checkpoint blockade-based monotherapy in human melanoma and non-small cell lung cancer (NSCLC), many patients do not experience durable clinical benefit.[58] Nevertheless, recent evidence suggests that even in the absence of clinical response, most melanoma and NSCLC patients receiving anti-PD-1 do mount a biologic response that is detectable in the periphery.[59, 60] Furthermore, we have previously shown that changes in immunogenicity in the pancreatic tumor microenvironment is reflected to a lower extent in the systemic immune circulation.[61] Patients who fail treatment despite this response often have substantial tumor burden requiring a reinvigoration beyond that provided by nivolumab alone. It is conceivable then that in this study of patients with LAPC, some patients may mount an inflammatory immune response to cabiralizumab, nivolumab and SBRT detectable in the periphery without evidence of tumor response. These patients might benefit from agonistic or alternative checkpoint immunotherapies. Moreover, it may be possible to identify early biomarkers of response to be utilized in patients who might benefit from combination therapy. Given this possibility, we will collect blood specimens from enrolled subjects at multiple pre-specified time points. Flow cytometry will be performed on isolated leukocytes for a panel of established markers including, but not limited to, CD45, CD56, CD3, CD8, CD4, CD45RA, CD45RO, CCR7, CD27, PD-1, CTLA-4, PD-1, TIM3, LAG3, 2B4, CTLA-4, Tbet, Eomes, Foxp3, Gata-3, Rorγt, CD38, Ki-67, CD33, CD14, CD15, HLA-DR, CD11b, CD11c, CD80, CD86, CD36 and CD206. Serum cytokines IFN-γ, TNF, IL-17, IL-10, IL-4, IL-1, and IL-6 will be measured by cytometric bead array (CBA). The

characteristics of various immune subsets present in blood corresponding to baseline, treatment with dual immunotherapy and SBRT plus dual immunotherapy can be compared to distinguish the contribution of each treatment modality in the peripheral immune response. Moreover, we will correlate the degree of response in the periphery measured by fold change in inflammatory and differentiation markers to baseline tumor characteristics including size and nodal status as well as the degree of pathologic and radiographic response.

2.6 Potential Risks & Benefits

2.6.1 Known Potential Risks

2.6.1.1 Cabiralizumab

The following paragraphs explain the side effects that have been observed when cabiralizumab was given alone.

The most common side effects of cabiralizumab (occurring in 10% or more of the patients):

- Increased blood level of an enzyme (creatine phosphokinase) from muscle damage
- Increased blood level of liver enzymes (asparate aminotransferase, alanine aminotransferase, and gamma-glutamyltransferase) associated with liver function
- Swelling (also called edema) including swelling of eye/eyelid, face, arms, legs and/or localized to some part of the body
- Skin problems including itching and/or rash (discolored area and/or raised bumps)
- Fatigue and tiredness
- Increased blood level of fat-digesting enzyme (lipase)
- Nausea or the urge to vomit
- Vomiting
- Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)
- Decreased appetite

Less common side effects of cabiralizumab in this study (occurred in more than 5% to less than 10% of patients):

- Increased blood level of an enzyme (lactate dehydrogenase) that helps turn sugar into energy
- Increased blood level of a digestive enzyme (amylase)
- Joint pain
- Increased blood level of a liver or bone enzyme (alkaline phosphatase)
- Lack of enough red blood cells (anemia)
- Increased blood level of a liver pigment (bilirubin) often a sign of liver problems
- Inflammation of the lungs that may cause difficulty breathing and can be life-threatening
- Decreased blood level of magnesium

Most of the above less common reported events were mild, and resolved on their own without treatment.

There may be side effects that we cannot predict and in some cases they may be serious, long-lasting, or fatal.

2.6.1.2 Nivolumab

Frequently reported categories of adverse events in clinical studies of nivolumab are listed below:

Likely
- Fatigue

Less Likely
- Anemia
- Adrenal insufficiency
- Endocrine disorders (hypophysitis)
- Hyperthyroidism
- Hypothyroidism
- Uveitis
- Abdominal Pain
- Colitis
- Diarrhea
- Dry mouth
- Nausea
- Pancreatitis
- Fever
- Infusion-related reaction
- Injection site reaction
- Increased alanine aminotransferase
- Increased aspartate aminotransferase
- Increased blood bilirubin
- Increased creatinine
- Increased lipase
- Decreased lymphocyte count
- Decreased neutrophil count
- Decreased platelet count
- Increased serum amylase
- Anorexia
- Arthralgia
- Pleural effusion
- Pneumonitis
- Pruritis
- Rash (maculo-papular)
- Skin hypopigmentation
- Sweet's syndrome

Rare but serious
- Cardiomyopathy
- Myocarditis
- Pericardial tamponade
- Pericarditis
- Diplopia
- Graves ophthalmopathy
- Optic neuritis retrobulbar
- Colonic perforation
- Gastritis
- Allergic reaction
- Autoimmune disorder
- Cytokine release syndrome

- Sarcoid granuloma
- Hyperglycemia
- Diabetes mellitus with ketoacidosis
- Polymyositis
- Rhabdomyolysis
- Myositis
- Encephalopathy
- Facial nerve disorder
- Demyelination myasthenic syndrome
- Encephalitis
- Guillain-Barre syndrome
- Meningoencephalitis
- Meningoradiculitis
- Myasthenia gravis
- Myasthenic syndrome
- Peripheral motor neuropathy
- Peripheral sensory neuropathy
- Acute kidney injury
- Bronchiolitis obliterans with organizing pneumonia
- Erythema multiforme

2.6.1.3 SBRT

Because of the short duration of treatment, acute side effects of SBRT typically occur after completion of treatment, but not during the course of radiation.

- Fatigue, acute and mild
- Dermatitis (skin irritation, redness, itchiness, discomfort), acute and mild
- Asymptomatic, temporary changes in blood work (decrease in blood counts, increase in liver enzymes)
- Nausea
- Vomiting
- Diarrhea
- Weight loss
- Anorexia
- Abdominal pain
- Gastric, esophagus, small bowel or large bowel irritation/ulceration, bleeding, fistula, obstruction or changes in motility following therapy
- Chest wall pain
- Indigestion
- Radiation fibrosis
- Liver damage
- Kidney damage
- Late second malignancy
- Delayed wound healing

2.6.2 Other Risks of Study Participation

Additional risks associated with participation in this study, include the risk of phlebotomy and breach of confidentiality. Risks associated with phlebotomy include weaknesses, redness, pain, bruising, bleeding,

or infection at the needle site. Privacy protection procedures are in place and good clinical practice guidelines are followed for the study to minimize risks associated with research procedures and participation.

2.6.3 Known Potential Benefits

Blockade of CSFR-1 with cabiralizumab and PD-1 with nivolumab may enhance the efficacy of SBRT in LAPC by preventing an immune suppressive phenotype and augmenting T-cell mediated anti-tumor response. As a result, a more effective local therapeutic modality may improve R0 resection rates and therefore improve survival rates. In addition, some subjects may develop memory T cells that can exert long-term anti-tumor effects even after patients are off treatment, which may lead to possible long term survival of the participants.

It is possible that some study subjects who receive the study therapies may experience an improvement in their pancreatic cancer during the study. However, if the patient receives such benefit, because the study therapy is not FDA-approved for pancreatic cancer, the study doctor cannot prescribe it after he/she finishes the study. Also, patients may not get any benefit from being in this research study. Others with pancreatic cancer may benefit in the future from what is learned in this study.

3 Objectives and Purpose

3.1 Primary Objectives

1) To determine the safety and tolerability of combined cabiralizumab, nivolumab and radiotherapy in the treatment of locally advanced pancreatic cancer.

2) To estimate the R0 surgical resection rate following treatment with combined cabiralizumab, nivolumab and radiotherapy in subjects with locally advanced unresectable pancreatic cancer.

3.2 Secondary Objectives

1) To evaluate preliminary anti-tumor activity of combined cabiralizumab, nivolumab and radiotherapy in subjects with locally advanced unresectable pancreatic cancer.

3.3 Exploratory Objectives

1) To evaluate the pharmacodynamic (PD) effect of the combination regimen on biomarkers in peripheral blood samples and tumor biopsy specimens.

2) To evaluate the effect of cabiralizumab, nivolumab and radiotherapy on innate and adaptive immunity in peripheral blood samples and tumor biopsy specimens.

4 Study Design and Endpoints

4.1 Description of Study Design

This is a multi-center, single arm, open label Phase II interventional study of cabiralizumab, nivolumab and SBRT in subjects with locally advanced unresectable pancreatic cancer. The study will consist of 3 periods: Screening (up to 4 weeks), Treatment (up to 2 years), and Survival Follow-up (up to 60 months after final subject completes treatment). Subjects will be enrolled into the study following completion of 2- 6 months of multi-agent chemotherapy (gemcitabine/nab-paclitaxel or FOLFIRINOX) with documentation of stable or responsive disease. Subjects will undergo baseline imaging to confirm locally advanced unresectable disease as defined by NCCN Guidelines 3.2017. Core baseline tissue biopsies will be obtained at time of endoscopic fiducial placement. Cabiralizumab and nivolumab will be administered on D1 of a 14 day cycle. SBRT will commence on D8 and be administered as 6.6 Gy x 5 consecutive fractions. Patients will have a biopsy, then restaging imaging will be performed 4 weeks after initiation of treatment Subjects will continue on treatment with cabiralizumab and nivolumab every 2 weeks and subsequent imaging will then be conducted every 8 weeks at which time participants will be evaluated with CT chest, abdomen and pelvis for response based on RECIST 1.1 criteria and potential for surgical resection. If at any response assessment, tumor is deemed resectable, subject may discontinue cabiralizumab and nivolumab and proceed to definitive surgical resection. A total of 6 subjects will be included in the preliminary safety cohort. The 6 subjects will be monitored for up to 6 weeks before additional subjects may be treated. Unacceptable toxicities will be assessed during this time.(see section 7.3) If there are fewer than three unacceptable toxicities in the first 6 subjects enrolled, then study will proceed to the expansion phase with an additional 14 subjects. If more than 2 of the first 6 subjects experience an unacceptable toxicity, enrollment will be paused and different doses/schedules considered in collaboration with study sponsor and BMS.

Subjects who withdraw from the study during the initial 42 days for reasons other than an unacceptable toxicity will be replaced. No dose escalations or de-escalations are permitted within each subject's treatment. Cabiralizumab dose adjustments are allowed if there has been +/- 10% weight change since the previous treatment.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

1) Adverse events will be graded according to the NCI's Common Terminology Criteria for Adverse Events (CTCAE v. 5.0). Unacceptable toxicity will be assessed during the first 42 days of treatment. (see section 7.3)

2) R0 resection rate, determined by blinded pathologic assessment.

4.2.2 Secondary Study Endpoints

1) Overall response rate
2) Progression free survival rate
3) Overall survival rate
4) Distant metastasis free survival rate

RECIST 1.1 assessments will be used to determine overall response rate, distant metastasis free survival rate, and progression free survival.

5) Plasma and tissue levels of CSF1 measured at multiple time points to determine target engagement by carbiralizumab
6) Nonclassical CD16+ monocyte levels in peripheral blood and tissue measured at multiple time points to determine target engagement by carbiralizumab

4.2.3 Exploratory Endpoints

Immune changes within blood and tissue following treatment and correlation with clinical endpoints

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

Participants must meet the following criteria on screening examination in order to be eligible to participate in the study:

5.1.1 Histologically confirmed locally advanced, unresectable pancreatic cancer as defined by NCCN Guidelines 3.2017

Locally advanced unresectable disease is defined by the NCCN as:

- Tumors of the head that have greater than 180 degrees of SMA encasement or any celiac abutment, unreconstructable SMV or portal occlusion, or aortic invasion or encasement.
- Tumors of the body with SMA or celiac encasement of greater than 180 degrees, unreconstructable SMV or portal occlusion, or aortic invasion.
- Tumors of the tail with SMA or celiac encasement of greater than 180 degrees. Irrespective of location, all tumors with evidence of nodal metastasis outside of the resection field are deemed unresectable.

5.1.2 Age > 18 years

5.1.3 Patients must agree to pretreatment and on treatment tumor biopsy

5.1.4 ECOG performance status of 0 or 1

5.1.5 Completion of at least 2 months, but no more than 6 months of standard induction chemotherapy for LAPC, which must include either FOLFIRINOX or gemcitabine and nab-paclitaxel, preferably within 2-4 weeks but no longer than 8 weeks.

5.1.6 Normal organ and marrow function as defined below:

- absolute neutrophil count ≥ 1,500/mm3
- platelets ≥ 100,000/mm3
- total bilirubin ≤ 1.5 x institutional upper limit of normal (except participants with Gilbert's syndrome who must have normal direct bilirubin)
- AST(SGOT) and ALT(SGPT) ≤ 2 × institutional upper limit of normal
- creatinine ≤ 1.5 mg/ dL
  OR
- creatinine clearance≥ 30 mL/min (as estimated by Cockcroft Gault Equation)

$$\text{Creatinine clearance for males} = \frac{(140 - \text{age [yrs]})\ (\text{body wt [kg]})}{(72)\ (\text{serum creatinine [mg/dL]})}$$

Creatinine clearance for females = 0.85 x male value

5.1.7 Ability to understand and sign a written informed consent document. Participant must have willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other study procedures.

5.1.8 Women of childbrearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study treatment.

5.1.9 WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment(s) and for a total of 5 months post-treatment completion.

5.1.10 Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (see appendix 1) 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.

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

5.2.1 Resectable, borderline resectable or metastatic disease

5.2.2 Medical history and concurrent disease as below:

- 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.
- Interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected treatment-related pulmonary toxicity.
- Current or history of clinically significant muscle disorders (eg, myositis), recent unresolved muscle injury, or any condition known to elevate serum CK levels
- 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 (eg, 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.
- Evidence of uncontrolled, active infection, requiring parenteral anti-bacterial, anti-viral or anti-fungal therapy ≤ 7 days prior to administration of study medication.
- Any uncontrolled inflammatory GI disease including Crohn's Disease and ulcerative colitis.

5.2.3 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 after discussing with the Principal Investigator.

5.2.4 Restricted Concomitant Therapies:

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

b. Non-oncology vaccine therapies for prevention of infectious diseases (eg, human papillomay virus vaccine) within 4 weeks of study drug administration. The inactivated seasonal influenza vaccine can be given to patients 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 principal investigator and may require a study drug washout period prior to and after administration of vaccine.

5.2.5 Known human immunodeficiency virus (HIV), known active hepatitis A, or known hepatitis B or C infection.

5.2.6 History of acute diverticulitis within the last 6 months, or current chronic diarrhea

5.2.7 Pregnant or lactating women.

5.2.8 Women of childbearing potential (WOCBP) with either a positive or no pregnancy test (serum or urine) at baseline. (Postmenopausal women must have been amenorrheic for at least 12 months to be considered of non-childbearing potential.)

5.2.9 WOCBP who are **unwilling or unable** to use an acceptable method to minimize the risk of pregnancy (see appendix 1) for the entire study period and for at least 5 months after the last dose of investigational product. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, but still must undergo pregnancy testing as described in section 5.1.8.

5.2.10 Sexually active fertile men not using effective birth control if their partners are WOCBP

5.2.11 History of primary immunodeficiency.

5.2.12 History of organ allograft or allogeneic bone marrow transplant.

5.2.13 Any prior radiation therapy, immunotherapy, or biologic ('targeted') therapy for treatment of the patient's pancreatic tumor. Patient should have received either FOLFIRINOX or gemcitabine and nab-paclitaxel prior to enrollment.

5.2.14 Treatment for other invasive carcinomas within the last five years who are at greater than 5% risk of recurrence at time of eligibility screening. Carcinoma in-situ and basal cell carcinoma/ squamous cell carcinoma of the skin are allowed.

5.2.15 Participation in any investigational drug study within 4 weeks preceding the start of study treatment.

5.2.16 Major surgery, excluding laparoscopy, within 4 weeks of the start of study treatment, without complete recovery.

5.2.17 History of allergy to study treatments or any of its components

5.2.18 Known history of sensitivity to infusions containing Tween 20 (polysorbate 20) and Tween 80 (polysorbate 80)

5.3 Inclusion of Women and Minorities

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

5.4 Vulnerable Subjects

Vulnerable subjects will not be eligible for enrollment into the study. Locally advanced pancreatic cancer does not occur in children, therefore they are excluded. Pregnant women are not included in the study given the unknown safety effects of radiation therapy and study drugs to the developing fetus. Prisoners or subjects who are involuntarily incarcerated are not eligible. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness are not eligible as they will be unable to adhere to the study timeline.

5.5 Strategies for Recruitment and Retention

The study will be posted on the NYU Perlmutter Cancer Center website and on clinicaltrials.gov. Any language that will be used to advertise this study on the NYU Perlmutter Cancer Center Website will first be submitted for IRB review and approval prior to posting. The patients who are eligible for this research study come directly from the study investigators' clinical patient population. Thus, the investigators are very familiar with their patients' disease status and potential eligibility given the protocol's inclusion and exclusion criteria. The investigator will approach eligible potential subjects and explain the study in a private room, including the reasons why subjects will be eligible, risks, benefits, and the regimes to be evaluated. Consent will be obtained in a private room by the PI, Co-I, or research coordinator/research nurse at the time of the subject's visit prior to any study assessments/procedures. The subjects will be given a chance to ask questions to the person consenting him/her and will be able to take the consent home to discuss it with family/friends prior to signing. If the subject agrees s/he will sign the consent form either at the first contact (if the investigator/delegate is convinced that the subject understands) or at the time of a return visit after having had time to study the consent in more depth. Study procedures will not begin until after the consent form has been properly obtained. The subject is entitled to decide not to participate in the trial, without affecting their right to other medical care, and may discontinue participation in the trial at any time without penalty or loss of benefits to which they are entitled.

All efforts will be made to actively recruit and retain women and members of minority groups in this study. The inclusion and exclusion criteria in this study should not have a negative effect on the enrollment of the desired populations.

Target enrollment for this study is 10-12 patients over 2 years. The target accrual goal is 5-6 patients per year at NYU Langone Health. Patients will be recruited from physicians participating in this study. Consenting, screening, and treatment will take place at the NYU Langone Health PCC or participating sub-sites under the supervision of the Site PI.

The Principal Investigator will:

1. Obtain signed and dated informed consent from the potential subject before any study specific procedures are performed.

2. Determine patient eligibility; see Section 5.1 and 5.2

3. Submit registration to NYU Langone Health Perlmutter Cancer Center CTO

4. Receive registration confirmation from the NYU Langone Health Perlmutter Cancer Center CTO, including a unique study identification number assigned to the patient that will be distributed to the study team upon registration of the patient.

The informed consent process and documentation follows, established procedures of the NYU Langone Health Perlmutter Cancer Center Clinical Trials Office.

5.6 Registration Procedures

5.6.1 General Guidelines

Each patient must sign and date an informed consent form before undergoing any study specific procedure unless a procedure is being performed as part of the patient's standard of care.
Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrollment occurs upon confirmation of registration from the NYULH PCC Clinical Trials Office. The following materials must be submitted to the CTO for subject registration:

1. Complete signed and dated informed consent form
2. Complete signed and dated eligibility checklist
3. All supporting documentation verifying each eligibility criterion has been met

Registration will occur within 48 hours of research coordinator receipt of all of the above documents. A written confirmation of enrollment including a unique study identification number assigned by the research coordinator will be disbursed to the study team upon registration.

Once eligibility is verified, a unique patient study number will be issued within 24 hours of receiving all required registration material. The patient will not be identified by name. This is the point, at which, the patient is considered accrued on study.

5.6.2 Multi-Site Surveillance

As the lead investigator in a multi-site trial, the Principal Investigator is responsible for organizing and conducting monthly teleconferences with all participating sites. The PI will also be responsible for including data from all of the participating sites within the overall trial's quarterly Data and Safety Monitoring report to the DSMC to include minutes from monthly PI teleconferences. Each participating site will be responsible for submitting the results and recommendations from the DSMC's quarterly

reviews to their IRB of record at the time of continuing review. Additionally, the NYU Langone Health PCC Clinical Trial Office, Quality Assurance Unit will provide remote extensive monitoring including real-time review of all eCRFs to ensure completeness and compliance with the protocol (100% source documentation verification). Additionally, a first subject audit is to be completed within four weeks of enrollment.

5.6.3 Patient Registrations at Additional Sites

Enrollment at addition sites can begin once each site's IRB has approved this protocol, a copy of each site's IRB approval, Citi training certificates, Medical Licenses and signed CVs are provided to NYU Langone Health Perlmutter Cancer Center (PCC) Clinical Trials Office. Once, all required documents are provided to NYU Clinical Trials Office an activation notification will be sent to the PI and research coordinator of that site. Central registration for this study will take place at NYU Langone Health PCC Quality Assurance Unit (PCC-QAU@nyumc.org).

Each patient must sign and date an informed consent form before undergoing any study specific procedures unless a procedure is being performed as part of the patient's standard of care. Once a patient has signed consent, each site must notify the NYU Langone Health PCC Quality Assurance Unit and forward a copy of the signed consent to NYU Langone Health PCC Clinical Trials Office within 24 hours.

Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrollment occurs upon confirmation of registration from the NYU Langone Health PCC Clinical Trials Office. The following materials must be submitted to the Quality Assurance Unit at NYU Langone Health via email (PCC-QAU@nyumc.org):

1. Complete signed and dated informed consent form
2. Complete signed and dated informed consent checklist
3. Complete signed and dated eligibility checklist
4. All supporting documentation verifying each criterion has been met.

Registration will occur once the Senior Research Nurse for Quality Assurance conducts a central review of the submitted materials. Once eligibility is verified, a unique subject study number will be issued within 48 hours of receiving all required registration material. This number is unique to the participant and must be written on all data and correspondence for the participant. The NYU Langone Health PCC CTO will return a signed eligibility confirmation worksheet email with the subject's unique study number.

The subject will not be identified by name. This is the point, at which, the patient is considered accrued on study. Protocol treatment should begin within designated timeframe; issues that would cause treatment delays should be discussed with the overall PI, Dr. Cohen. All screen failures/ineligible subjects, as well as subject's who withdraw consent prior to initiation of protocol therapy must be submitted to the CTO in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

Subjects must not start any protocol procedures prior to registration; each participating institution will order the study agent directly from the supplier, Bristol-Myers Squibb (Nivolumab and Carbiralizumab).

Each site is responsible for reporting all unexpected problems involving risks to participants or others to NYU Langone PCC Clinical Trials Office and to their IRB as per site institutional policy.

Please email all SAEs to NYUPCCsafetyreports@nyumc.org, Dr. Cohen, PCC Assigned Medical Monitor, and the NYU Langone Health CTO regulatory specialist.

5.7 Duration of Study Participation

Subjects may remain on study therapy for a maximum of 2 years, or until progressive disease (occurring within 2 years) as

determined by RECIST criteria, withdrawal due to toxicity, withdrawal of consent, or at the discretion of the investigator.

Subjects tolerating therapy may continue on study until disease progression(when occurring within 2 years) or eligible for surgical resection. It is well known that patients who receive immunotherapy can experience pseudoprogression, which is initial progression of disease based on RECIST 1.1 criteria, but later achievement of tumor regression based on RECIST 1.1 criteria. Any patients with no clinical deterioration and progression of disease based on RECIST 1.1 criteria are allowed to continue treatment until a second scan is done within 6 weeks of the prior scan. If the second scan confirms progression of disease by RECIST 1.1, then the patient will be taken off study.

5.8 Total Number of Participants and Sites

There will be 3 sites participating in the study, including NYUMC. A total of 6-22 patients will be enrolled.

5.9 Participant Withdrawal or Termination

5.9.1 Reasons for Withdrawal or Termination

Subjects will be treated until progression, intolerable toxicities or definitive surgical resection; however, if the patient does not experience any of the below (listed) reasons, they can be treated for 2 years, and then be considered for continuation of treatment beyond 2 years if no excessive toxicities occur and following discussion with and approval by the sponsor. If approval is granted, subjects will continue treatment and follow-up, all procedural assessments will continue as previously outlined in the study calendar. A subject has the right to voluntarily discontinue study treatment or withdraw from the study at any time, for any reason, and without repercussion. The investigator and sponsor have the right to discontinue a patient from study treatment or withdraw a patient from the study at any time.

Reasons for subject withdrawal from the study may include, but are not limited to:

- Significant noncompliance on the part of the patient
- Refusal of the patient to continue treatment or observations
- Concurrent illness that prevents further administration of treatment
- Disease progression
- Unacceptable adverse events regardless of grade
- Termination of study
- Patient consent withdrawal
- Decision by the investigator that termination is in the participant's best medical interest
- Unrelated medical illness or complication
- Patient is deceased
- Pregnancy or intent to become pregnant

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up

- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). All patients who withdraw from study drug prematurely will undergo end-of-treatment assessments within 30 days after the last dose, if possible. Regardless of the reason for withdrawal, effort shall be made to follow safety events from the time of withdrawal through resolution or until the event stabilizes. Subjects who discontinue study drugs will continue to be followed for adverse events for up to 100 days and for survival every 12 weeks (+/- 1 week) from the date of last dose of study drug(s), either in person or by telephone contact, up to 18 months, then every 6 months thereafter until the participant's death or until the participant is lost to follow-up or until study closure (approximately 60 months after last subject terminates treatment).

5.9.2 Handling of Participant Withdrawals or Termination

Withdrawal from the study can be made in writing to the Principal Investigator, Dr. Deirdre Cohen. Any samples/specimens remaining after formal withdrawal, will be destroyed/discarded per Institutional guidelines.

5.10 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to Dr. Deirdre Cohen, BMS, the IND/IDE sponsor and any regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

6 Study Agents

Table 4 Study treatments				
Product Description / Class and Dosage Form	**Potency/Route of Administration**	**Blinded or Open Label**	**Packaging / Appearance**	**Storage Conditions (Per Label)**
Nivolumab (BMS-936558-01) Solution for Injection	100 mg (10 mg/mL)	Open label	Vial	Refer to the label on container and/or Investigator Brochure
Nivolumab (BMS-936558-01) Solution for Injection	40 mg (10 mg/mL)	Open label	Vial	Refer to the label on container and/or Investigator Brochure
Cabiralizumab (BMS-986227) Solution for Injection	100 mg (20 mg/mL)	Open label	Vial	Refer to the label on container and/or Investigator Brochure

6.1 Cabiralizumab

6.1.1 Acquisition

Cabiralizumab will be supplied by BMS directly and shipped to the investigational pharmacy at the respective ordering participating institution.

6.1.2 Formulation, Appearance, Packaging, and Labeling

For details on shipping, storage, and maintenance, please refer to the Investigator Brochure. Cabiralizumab drug product is supplied for IV administration as a sterile, aqueous, colorless to pale yellow, clear to slightly opalescent, pyrogen-free solution in 5 mL glass vials stoppered with coated stoppers, and equipped with aluminum seals. Light (few) particulates (consistent in appearance to proteinaceous particles) may be present. Each vial contains a minimum of 5 mL of a 20 mg/mL solution of cabiralizumab (approximately 100 mg per vial).

6.1.3 Product Storage and Stability

Cabiralizumab drug product is shipped refrigerated at 2–8°C and stored refrigerated at 2–8°C until time of use. The contents of the vials supplied are sterile, pyrogen-free, and contain no preservatives. Vials are for single-use only. Drug product should be protected from light. The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that the investigational product must only be dispensed to study participants. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study treatment is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study treatment arise, the study treatment should not be dispensed, and BMS should be contacted immediately

6.1.4 Preparation

Solutions of cabiralizumab for IV infusion are prepared by dilution of the drug product in 0.9% sodium chloride or 5% dextrose injection. Since cabiralizumab solution contains no preservatives, diluted solutions for infusion should be administered or discarded within four hours after preparation. The IV administration set for cabiralizumab infusion must contain a 0.2 or 0.22 µm in-line filter or a 0.2 or 0.22 µm syringe filter. Please refer to the current version of the Investigator Brochure and/or pharmacy manual for complete preparation, storage, and handling information.

6.1.5 Route of Administration

Injection,for intravenous use. Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents and administration sets).

6.2 Nivolumab

6.2.1 Acquisition

Nivolumab will be supplied by BMS directly and shipped to the investigational pharmacy at the respective ordering participating institution

6.2.2 Formulation, Appearance, Packaging, and Labeling

Nivolumab Injection, 100 mg/10 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^{TM} 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.

6.2.3 Product Storage and Stability

Nivolumab should be stored between 2 and 8^{o}C and should be protected from light, freezing, and shaking. If stored in a glass front refrigerator, vials should be stored in the carton.

6.2.4 Preparation

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection. When the dose is based on patient weight (ie, mg/kg), nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (eg, 240 mg, 360 mg, or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 120 mL.

During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, pharmacy manual, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

Please refer to the current version of the Investigator Brochure and/or pharmacy manual for complete preparation, storage, and handling information.

6.2.5 Route of Administration

Administer the infusion over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).

Do not co-administer other drugs through the same intravenous line.

Flush the intravenous line at end of infusion.

6.3 Study Agent Accountability Procedures

Drug should be destroyed at the site, after the investigator approves the drug destruction policy at the site. Drug will not be returned. Destruction will be documented in the Drug Accountability Record Form.

At the end of the study period, Bristol-Myers Squibb Company will not continue to supply study drug to subjects/investigators unless the Sponsor-Investigator chooses to extend their study. The investigator is responsible to ensure that the subject receives appropriate standard of care or other appropriate treatment in the independent medical judgement of the Investigator to treat the condition under study.

7 Treatment Plan

7.1 Cabiralizumab and Nivolumab Administration

Cabiralizumab and Nivolumab will be initiated on Cycle 1 Day 1 prior to the initiation of SBRT on Day 8. Subjects will receive nivolumab flat dose of 240mg IV over 30 minutes followed by cabiralizumab 4mg/kg IV over 30 minutes. The time in between infusions is expected to be approximately 30 minutes but can be more or less depending on the situation. Dosing calculations should be based on the body weight assessed at Cycle 1 Day 1 prior to the first dose of cabiralizumab. If the subject'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. Treatment with combined immunotherapies will continue every 14 days (+/- 2 days) unless a further delay is mandated by toxicity criteria. 1 cycle is considered to be 14 days. Treatment will continue until unacceptable toxicity, disease progression, conversion to and eligible for surgical resection or completion of two years of treatment. The first six subjects enrolled will be evaluated for unacceptable toxicity in the first 42 days on study.

7.2 SBRT

7.2.1 Fiducial Placement

Treatment on this protocol requires placement of 1-5 gold (99.9% pure, 1-5 mm length, visicoils, or other) fiducials for targeting purposes. The fiducials will be used as surrogates for targeting the daily tumor position during treatment. The fiducials will be placed directly into the tumor and/or periphery under endoscopic ultrasound or CT guidance. Fiducials may be implanted prior to enrollment as this is an acceptable standard of care procedure for any patient receiving radiotherapy for pancreatic cancer. Also, if a patient had an attempted surgical resection that was aborted, fiducials may have been implanted intraoperatively, which is also allowable prior to study enrollment.

If fiducials are not placed intraoperatively and/or prior to enrollment, placement will be done and is expected to be done on an outpatient basis. In rare occurrences when fiducials/clips cannot be placed, patients may be treated at the discretion of the PI.

Fiducials must be placed prior to Cycle 1 Day 1 of study treatment.

7.2.2 Simulation

Patients will be simulated supine with the addition of a 4D CT if appropriate. A stereotactic immobilization device with abdominal compression will be used. Oral contrast will be delivered approximately one hour prior to simulation to allow opacification of small bowel unless contraindicated. Intravenous (IV) contrast may be delivered for the simulation if deemed necessary by the treating radiation oncologist.

As long as the specified dosimetric parameters for SBRT are reached, patients may be treated on any IGRT-enabled machine.

7.2.3 Treatment Planning

Volume definitions
GTV: The gross tumor volume (GTV) will be defined as all gross disease evident on imaging and examination at the site of treatment (pancreas).

PTV: The planning target volume (PTV) will be a 3-5 mm concentric expansion on the GTV. An additional margin of up to 3 mm may be added as needed if 4D CT reveals extensive respiratory motion of the target.

Dose specification
The PTV doses should meet the following criteria:

1) 93% of the PTV should receive at least 93% of the prescribed dose
2) < 5% of the PTV should receive more than 110% of the prescribed dose. Efforts will be made to reduce heterogeneity if possible.

Normal Structures The following dose goals will apply for normal tissues:

- Kidney: mean dose < 10 Gy (total kidney volume)
- Small bowel: maximum 35 Gy, mean <25Gy, V30< 5cc, V35Gy <1cc
- Duodenum: maximum 35Gy, mean <25Gy, V30< 5cc, V35Gy <1cc
- Stomach: 35 Gy, mean <25Gy, V30< 5cc, V35Gy <1cc
- Large bowel: maximum 35Gy, mean <25Gy, V30< 5cc, V35Gy <1cc
- Liver: V30<10%

- Spinal cord: maximum 20Gy

7.2.4 Treatment

Treatment will be delivered on 5 consecutive days (Day 8 cycle 1 to Day 12 cycle 1) except during holidays or inclement weather conditions. SBRT will be dose at 6.6 Gy for 5 days. In the event that a treatment is postponed due to machine malfunction, holiday, or inclement weather condition, the missed treatment will be delivered the following business day. Localization will be verified with pretreatment imaging prior to every fraction. Ideally, this will include Tomotherapy localization or cone beam CT, although kV/kV imaging may be used if necessary.

7.3 Definition of Unacceptable Toxicity

Adverse events (AE) will be graded according to the NCI's Common Terminology Criteria for Adverse Events (CTCAE v. 5.0). During the initial safety lead in, unacceptable toxicity will be assessed for the first six subjects enrolled into the study for the initial 42 days of treatment. This observation interval is based upon inclusion of the known median times to onset of common immune-related adverse events attributed to nivolumab and allows for an adequate amount of time for unexpected toxicities with the combined administration of cabiralizumab, nivolumab, and SBRT to emerge. Subjects who do not complete the safety lead in observation period for reasons other than drug-related toxicity will be replaced. Replacement subjects will receive the same treatment but will be assigned a new subject number. During the safety observation (within 42 days of initiation of study therapy), subjects, who for reasons other than study-drug related toxicity, either miss 1 or more of their scheduled doses of nivolumab or cabiralizumab, or do not complete planned SBRT, will not be considered evaluable for safety for the purposes of the safety lead in and will be replaced. The safety observation period includes Day 1 Cycle 1 to Day 14 of Cycle 3 (6 weeks).

The combination of nivolumab and cabiralizumab has demonstrated a tolerable safety profile, with elevations in creatine kinase and serum liver enzymes (without elevation in bilirubin) being the most common treatment related adverse events seen (see Table 5)[26].

Table 5: Safety profile for cabiralizumab and nivolumab

	Cabiralizumab + nivolumab All solid tumors (n = 205)		Cabiralizumab + nivolumab Pancreatic cancer (n=33)	
	Any grade, n (%)	Grade 3–4, n (%)	Any grade, n (%)	Grade 3–4, n (%)
Any TRAE	184 (90)	100 (49)	31 (94)	20 (61)
AEs leading to discontinuation	15 (7)	10 (5)	3 (9)	3 (9)
Clinical TRAEs (≥ 15% of pts treated with combination)				
Periorbital edema	84 (41)	1 (<1)	10 (30)	0
Fatigue	74 (36)	11 (5)	14 (42)	1(3)
Rash	38 (19)	8 (4)	7(21)	0
Pruritus	34 (17)	2 (1)	n/a	n/a
Nausea	30 (15)	0	n/a	n/a
Treatment-related laboratory abnormalities of interest				
Serum enzyme elevations[a]	103 (50)	40 (20)	17 (52)	11 (33)
Pancreatic enzyme elevations[b]	42 (20)	24 (12)	2 (6)	1 (3)
Treatment-related deaths	3 (1.5)[c]		0	

[a] Includes AE terms indicative of elevated CPK, AST, ALT, and LDH. [b] Includes AE terms indicative of elevated amylase and lipase.
[c] Includes pneumonitis in a patient with thyroid cancer (cabiralizumab 1 mg/kg + nivolumab 3 mg/kg), and respiratory distress (n = 1, cabiralizumab 4 mg/kg + nivolumab) and acute respiratory distress (n = 1, cabiralizumab 4 mg/kg + nivolumab) in 2 patients with lung cancer.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; LDH = lactate dehydrogenase; TRAE, treatment-related adverse event

The addition of SBRT to cabiralizumab and nivolumab is hypothesized not to significantly increase the rate of adverse events. Toxicity of SBRT alone includes anorexia, fatigue, abdominal pain, diarrhea, ulceration, hemorrhage, fistula, perforation, stenosis, nausea, vomiting and dermatitis. As a result, unacceptable toxicity of the combination of SBRT, nivolumab and cabiralizumab will be defined as the following:

Unacceptable Toxicity

- Grade 3 fatigue lasting >2 weeks
- Grade 3 nausea lasting >7 days despite maximal medical management
- Grade ≥ 3 anorexia
- Grade ≥ 3 vomiting
- Grade ≥ 3 diarrhea
- Grade ≥ 3 pancreatitis
- Grade 3 abdominal pain
- Grade ≥ 3 radiation dermatitis
- Grade ≥ 3 GI hemorrhage
- Grade ≥ 3 GI fistula
- Grade ≥ 3 GI stenosis
- Any Grade GI perforation

8 Dosing Delays/Dose Modifications

Dose delays and modifications will be made using the following recommendations. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off-study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

8.1 Cabiralizumab and Nivolumab Dose Adjustments

There are no dose reductions for cabiralizumab or nivolumab. Subjects will receive nivolumab 240mg IV followed by cabiralizumab 4mg/kg IV every two weeks. Unacceptable toxicity as defined in Section 7.3 will be assessed for the first 42 days on study in the initial 6 patients. During and following the safety lead in assessment period, 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 2). Please discuss with the PI as needed;
- For dose delays or modifications for all other AEs, please refer to the AE management table in Appendix 3.

Patients who require a dose delay of cabiralizumab/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 patient 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 Section 8.5 and Appendix 3. If the causality of the AE requiring a dose delay is confirmed to be due to one of the study drugs of the combination therapy, the non-offending drug may be continued per protocol taking into account the safety and clinical benefit to the patient.

8.2 Management Algorithms for Cabiralizumab and Nivolumab

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 3 and are applicable to immune-related AEs for all immuno-oncology study treatment combinations.

For subjects who require more than 4 weeks of corticosteroids or other immunosuppressants to manage an adverse event, consider the following recommendations:

- Antimicrobial/antifungal prophylaxis per institutional guidelines to prevent opportunistic infections such as Pneumocystis jiroveci and fungal infections.

- Early consultation with an infectious disease specialist should be considered. Depending on the presentation, consultation with a pulmonologist for bronchoscopy or a gastroenterologist for endoscopy may also be appropriate.

- In patients who develop recurrent adverse events in the setting of ongoing or prior immunosuppressant use, an opportunistic infection should be considered in the differential diagnosis.

8.3 Dose Discontinuation Criteria for Cabiralizumab and Nivolumab

For comprehensive discontinuation rules, refer to Appendix 3 (AE management) and Appendix 2 (laboratory abnormalities).

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

  - ➢ Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
  - ➢ Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - o 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). See Appendix 2 and Appendix 3 for guidelines and possibility of restarting therapy
  - ➢ ALT or AST > 20 x ULN
  - ➢ Total bilirubin > 3 x ULN
- 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 PI 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 PI.
  - ➢ 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 patient with a dosing delay lasting > 6 weeks from the previous dose, the PI 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 PI. Prior to re-initiating treatment in a patient with a dosing delay lasting > 6 weeks, the PI must be consulted. Tumor assessments should continue per-protocol every 8 weeks (± 3 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 patient 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 PI.
- 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 one of the study drugs in the combination therapy, the other drug 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 patient based on investigator assessment.

8.4 Criteria to Resume Treatment with Cabiralizumab and Nivolumab

Patients may resume treatment with cabiralizumab and/or nivolumab when the drug-related AE resolves as noted in the AE management tables in Appendix 3 or the abnormal laboratory management table in Appendix 2.

8.5 Treatment of Cabiralizumab and Nivolumab Infusion Reactions

Cabiralizumab and nivolumab may induce infusion or hypersensitivity reactions. If such reactions occur, they may manifest with fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension or hypertension, bronchospasm, or other symptoms.

Infusion reactions should be graded according to CTCAE v5.0 guidelines. It may be unclear if an infusion reaction is due to cabiralizumab, nivolumab, or to both study drugs. Therefore, one set of treatment recommendations (based on the most conservative treatments for infusion reactions due to either study drug) is provided below and may be modified based on clinical judgment, local treatment standards and guidelines, and/or specific symptoms, as appropriate:

For Grade 1 symptoms: Mild reaction (eg, localized cutaneous reactions including mild pruritus, flushing, and rash), requires infusion rate to be decreased; intervention may be indicated.

- Decrease the rate of the study drug infusion until recovery from symptoms.
- Remain at bedside and monitor the patient's vital signs until resolution of symptoms. Diphenhydramine 50 mg may be administered at the discretion of the treating physician.
- When symptoms resolve, restart the infusion at the original infusion rate.
- If a patient has an infusion reaction with nivolumab, cabiralizumab can be given (without prophylactic medications) if the infusion reaction resolves within 3 hours. For scheduling purposes, the cabiralizumab infusion may be given the next day. Prophylactic pre-infusion medications should be given prior to all subsequent nivolumab infusions.
- If a patient has an infusion reaction with cabiralizumab, prophylactic pre-infusion medications should be given prior to all subsequent cabiralizumab and nivolumab infusions.
- The following prophylactic pre-infusion medications are recommended prior to future infusions of cabiralizumab and nivolumab: diphenhydramine 50 mg (or equivalent) and/or paracetamol (acetaminophen) 325 mg to 1000 mg at least 30 minutes before additional study drug administrations.

For Grade 2 symptoms: Moderate reaction (ie, any symptom not listed above [mild symptoms] or below [severe symptoms] such as generalized pruritus, flushing, rash, dyspnea, and hypotension with systolic blood pressure >80 mmHg), requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, and IV fluids); prophylactic pre-infusion medications indicated for $\leq$ 24 hours.

- Interrupt the study drug infusion.
- Begin an IV infusion of normal saline and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol (acetaminophen) 325 mg to 1000 mg.
- Remain at bedside and monitor the patient's vital signs until resolution of symptoms. Corticosteroid therapy may be administered at the discretion of the treating physician.

- When symptoms resolve, restart the infusion at 50% of the original infusion rate; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate.
- Monitor the patient closely. If symptoms recur, immediately discontinue the infusion; no further study drug will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the patient until resolution of symptoms.
- If a patient has an infusion reaction with nivolumab infusion, cabiralizumab infusion can be given (without prophylactic medications) if the infusion reaction resolves within 3 hours. For scheduling purposes, the cabiralizumab infusion may be given the next day. Prophylactic pre infusion medications should be given prior to all subsequent nivolumab infusions.
- If a patient has an infusion reaction with cabiralizumab, prophylactic pre-infusion medications should be given prior to all subsequent cabiralizumab and nivolumab infusions.
- The following prophylactic pre-infusion medications are recommended prior to future infusions of cabiralizumab and nivolumab: diphenhydramine 50 mg (or equivalent) and/or paracetamol (acetaminophen) 325 mg to 1000 mg should be administered at least 30 minutes before additional study drug administrations. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.
- The amount of study drug infused must be recorded.

For Grade 3 or Grade 4 symptoms: Severe reaction such as bronchospasm, generalized urticaria, systolic blood pressure <80 mmHg, or angioedema; Grade 3 symptoms including prolonged symptoms, which require 6 or more hours to respond to symptomatic medication and/or discontinuation of infusion; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae, such as renal impairment, pulmonary infiltrates; Grade 4: life-threatening; pressor or ventilation support indicated.

- Immediately discontinue the study drug infusion. No further study drug will be administered. The amount of study drug infused must be recorded on the CRF.
- Begin an IV infusion of normal saline and treat the patient as follows: Recommend bronchodilators, epinephrine 0.2 mg to 1.0 mg of a 1:1,000 solution for subcutaneous administration or 0.1 mg to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed.
- Remain at bedside and monitor the patient's vital signs until recovery from symptoms.
- The patient should be monitored until the investigator is comfortable that the symptoms will not recur.
- Investigators should follow their institutional guidelines for the treatment of anaphylaxis.

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

8.6 Radiation Dose Adjustments

Radiation therapy will be stopped for any ≥ grade 4 toxicities with exception of laboratory abnormalities. Radiation therapy will be held for Grade 3 nausea that is not well controlled with anti- emetic support, until nausea resolves to Grade 2 or less. It will then be resumed at same dose.

9 Study Procedures and Schedule

9.1 Laboratory Procedures/Evaluations

9.1.1 Clinical Laboratory Evaluations

- ***Hematology:*** *hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count.*
- ***Comprehensive Metabolic Panel:*** *creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate*
- *aminotransferase (AST), alkaline phosphatase (ALP), albumin, blood urea nitrogen (BUN), Calcium, Carbon Dioxide (Bicarbonate), chloride, glucose, potassium, sodium, total protein*
- ***Biochemistry:*** *CPK and LDH, amylase and lipase, Free T4, TSH, CA 19-9, PT/PTT*
- ***Urinalysis:*** *dipstick urinalysis, including protein, hemoglobin and glucose; if dipstick is abnormal, complete urinalysis with microscopic evaluation is required.*
- ***Pregnancy test****, usually to be done within 24 hours prior to study intervention and results must be available prior to administration of study product.*

9.1.2 Other Assays or Procedures

Three to four core biopsy samples will be taken at the pre-treatment time point using sterile technique. Each core will provide material for histologic analysis and PDOT creation and analysis. Post-treatment core biopsy samples and/or surgically resected specimens will be sectioned for the same analyses. Pathologic response will be characterized by degree of tumor necrosis. Tissue will be evaluated for expression of CSF1 using IHC. Changes in immune infiltrate will be assessed by IHC against, including but not limited to, CD3, CD4, CD8, Foxp3, PD-1, PD-L1, Granzyme B, CD68, CD163, ARG1 and iNOS. PDOT's will be used to evaluate tumor cell viability, the relative composition and function of the tumor immune infiltrate, cytokine/chemokine profiles and single cell RNA sequencing.

9.1.2.1 Specimen Preparation, Handling, and Storage

9.1.2.2 Tissue

Tumor tissue for pathology analysis will be processed by the appropriate department at each participating institution. All tumor tissue for research will be processed by the NYU Center for Biospecimen Research and Development (CBRD) and then sent to the lab of either Dr. George Miller or Dr. Kwok Wong for analysis.

Please note: Dr. Kwok Wong will not have access to PHI, and will only be handling samples per professional service.

Please see laboratory manual for full details on tissue collection, handling and storage. Pre-treatment biopsies and post-treatment biopsies and/or surgically resected specimens from each subject will be obtained for a total of two to three tissue samples per patient. For fixed tissue, paraffin embedding, sectioning, immunohistochemistry and scanning will be performed by the NYU Experimental Pathology Research Laboratory. Staining will be manually quantified after analysis on a digital image database. Fresh tissue will be used to establish PDOT's in the laboratory of Dr. Wong.

9.1.2.3 Research Blood Sample Collection

Four green-top tubes, one-red top tube, and one lavender top tube will be collected from each patient per

week. Peripheral blood leukocytes will be isolated with the assistance of the George Miller Lab in accordance with established lab practice and stored at -80C until the end of the study period for a maximum of 4 cycles per subject.

Serum will be harvested and stored at -80C for a total of a maximum of 4 cycles per subject. Flow cytometry and cytometric bead array will be performed for all participant samples at the end of the study period. Staining will be performed using an established panel and protocol in the George Miller Lab. Data will be acquired on an LSR II and analyzed in FlowJo software.

9.1.3 Specimen Shipment

See laboratory manual for full details on specimen shipment.

9.2 Study Schedule

9.2.1 Screening

Screening Visit (Day -28 to -1)

- Obtain informed consent of potential participant verified by signature on informed consent form.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria.
- Complete history and physical examination, including weight and height, and ECOG performance status
- Clinical laboratory tests (hematology, complete serum chemistry panel, hepatic panel, LDH, CPK, amylase, lipase, TSH and free T4, PT/PTT, urinalysis, CA 19-9)
- Baseline imaging study with CT chest, abdomen and pelvis
- Pregnancy test (serum or urine) for women of childbearing potential
- 12 lead ECG
- AE assessment
- Fiducial placement and pre-treatment tissue biopsy
- Research blood draw for pharmacodynamics markers and immune monitoring
- Schedule study visits for participants who are eligible and available for the duration of the study.

9.2.2 Enrollment/Baseline

Enrollment/Baseline Visit (Cycle 1, Day 1) Pre-Treatment Evaluations

Results of clinical and laboratory evaluations must be reviewed to confirm that the subject continues to meet eligibility criteria before drug administration. The pre-treatment evaluations consist of the following:

- Physical examination, including weight
- WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study treatment.
- Record vital signs, ECOG performance status
- Review of concomitant medications
- Clinical laboratory tests (hematology, complete serum chemistry panel, hepatic panel, LDH, CPK, amylase, lipase, TSH and free T4, CA 19-9)
- Scientific correlate blood samples (to be collected within 30 minutes, pre-dose)

- AE assessment
- Administer the study treatment with cabiralizumab and nivolumab.

9.2.3 Intermediate Visits

9.2.3.1 Cycle 1, Day 8 (+/- 1 day)

- physical examination, including weight
- Record vital signs, ECOG performance status
- Clinical laboratory tests (hematology, complete serum chemistry panel, hepatic panel, LDH, CPK, amylase, lipase)
- Scientific correlate blood samples
- AE assessment
- SBRT administration (Day 8-12)

9.2.3.2 Cycle 2, Day 1 (+/- 1 day)

- physical examination, including weight
- Record vital signs, ECOG performance status
- Clinical laboratory tests (hematology, complete serum chemistry panel, hepatic panel, LDH, CPK, amylase, lipase, TSH and free T4)
- Scientific correlate blood samples
- AE assessment
- Administer the study treatment with cabiralizumab and nivolumab.

9.2.3.3 Cycle 2, Day 8 (+/- 1 day)

- physical examination, including weight
- Record vital signs, ECOG performance status
- Clinical laboratory tests (hematology, complete serum chemistry panel, hepatic panel, LDH, CPK, amylase, lipase)
- Scientific correlate blood samples
- AE assessment
- Tumor Biopsy (+/- 3 days)

9.2.3.4 Cycle 2, Day 12 (+/- 2 days)

- CT chest, abdomen and pelvis

9.2.3.5 Cycle 3, Day 1 (+/- 1 day)

- physical examination, including weight
- Record vital signs, ECOG performance status
- Clinical laboratory tests (hematology, complete serum chemistry panel, hepatic panel, LDH, CPK, amylase, lipase, TSH and free T4, CA 19-9)
- Scientific correlate blood samples
- AE assessment
- Administer the study treatment with cabiralizumab and nivolumab.

9.2.3.6 Cycle 3, Day 8 (+/- 1 day)

- physical examination, including weight
- Record vital signs, ECOG performance status
- Clinical laboratory tests (hematology, complete serum chemistry panel, hepatic panel, LDH, CPK, amylase, lipase)
- Scientific correlate blood samples
- AE assessment

9.2.3.7 Cycle 4, Day 1 (+/- 1 day) and all subsequent 14 day cycles

- physical examination, including weight
- Record vital signs, ECOG performance status
- Clinical laboratory tests (hematology, complete serum chemistry panel, hepatic panel, LDH, CPK, amylase, lipase, TSH and free T4)
- Scientific correlate blood samples (maxiumum 4 cycles)
- AE assessment
- Administer the study treatment with cabiralizumab and nivolumab.
- CT chest, abdomen, and pelvis (prior to cycle 6 (+/- 3 days and then every 8 weeks thereafter (+/- 7 days)

9.2.4 Final Study Visit

On the last day of treatment, or on the day when treatment is discontinued, subjects are to return to the study site to complete all end of treatment assessments as follows:

Final Study Visit

- physical examination, including weight
- Record vital signs, ECOG performance status
- Clinical laboratory tests (hematology, complete serum chemistry panel, hepatic panel, LDH, CPK, amylase, lipase, TSH and free T4, CA 19-9)
- Scientific correlate blood samples
- 12 lead ECG
- Review of concomitant medications
- AE assessment

9.2.5 Unscheduled Visit

If additional visits are needed (e.g., for resolution of an adverse event), the following procedures and evaluations may be performed as needed at the discretion of the treatment physician:

- physical examination, including weight
- Record vital signs, ECOG performance status
- Clinical laboratory tests (hematology, complete serum chemistry panel, hepatic panel, LDH, CPK, amylase, lipase, TSH and free T4, CA 19-9)
- Urinalysis

- Urine pregnancy test
- 12 lead ECG
- AE assessment
- Concomitant medications
- CT Scans

9.3 Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

No investigational or commercial agents or therapies other than cabiralizumab and/or nivolumab may be administered with the intent to treat the participant's malignancy. Myeloid growth factors will NOT be used throughout study. Live attenuated vaccines while on study or 30 days following completion of study are NOT permitted.

After confirmation and documentation that a subject has met all the inclusion criteria and note of the exclusion criteria, supportive care treatments (transfusions etc.) can be prescribed as medically appropriate. The following treatments are permitted during study:

- The use of erythropoietin or other specific red blood cell growth factors and red blood cell transfusion will be permitted as clinically indicated during the study after documentation of anemia secondary to study treatment. These agents cannot be used prior to this occurrence.
- Other concomitant medications, including premedication may be given as clinically indicated

9.4 Participant Access to Study Agent at Study Closure

Study agents will be supplied for the study period only.

10 Assessment of Safety

10.1 Specification of Safety Parameters

10.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

10.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

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

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

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

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 i.e IND US trial, reporting will be provided as part of an annual reporting requirement.

Overdose

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

Other Safety Considerations

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

10.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

10.2 Classification of an Adverse Event

10.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

10.2.2 Relationship to Study Agent

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- ***Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.*
- ***Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.*
- ***Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.*

- ***Unlikely to be related*** *– A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).*
- ***Not Related*** *– The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.*

10.2.3 Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin from the time of consent. 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.

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.

10.2.4 Expectedness

The principal investigator and/or sub-investigator(s) will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

10.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 100 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

10.4 Reporting Procedures – Notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

Report Promptly, but no later than 5 working days:
Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events* that are unexpected and related**
  - *Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
  - *Related to the research procedures: An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.*
  - *Harmful: either caused harm to subjects or others, or placed them at increased risk*

Other Reportable events:

The following events also require prompt reporting to the IRB, though ***no later than 5 working days***:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*
  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*
- ***Breach of confidentiality***
- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process
The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or

as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

10.4.1 Adverse Event Reporting

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 100 days following the last administration of study treatment.

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

Potential Drug Induced Liver Injury (DILI)

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

10.4.2 Serious Adverse Event and Unanticipated Problem Reporting

Investigators and the protocol sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported within 5 days of PI notification are those that are:

- related to study participation,
- unexpected, and
- Harmful or have the potential to cause harm (see definitions, section 10.1)

Events should be reported using the NYU CTO Medical Events Form.

Adverse events that do not fit the above immediately reportable criteria must still be reported to the IRB at each annual review, either in a summary or tabular format.

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the overall principal investigator. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the DSMC/study sponsor within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DSMC/study sponsor within 24 hours of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 5 days of the IR's receipt of the report of the problem from the investigator.

Serious adverse event reporting will begin in conjunction with the date of treatment administration. Any SAEs occurring prior to study drug administration that the investigator believes may have been caused by a protocol procedure must be reported immediately to the principal investigator, with a notification email sent to NYUPCCsafetyreports@nyumc.org and recorded on the case report form.

All fatal or life-threatening adverse events must be immediately reported to the Principal Investigator, via appropriate reporting mechanism and the NYU Langone Health IRB by telephone or e-mail. Within 24 hours of the event, the Serious Adverse Event Form must be emailed to NYUPCCsafetyreports@nyumc.org and PCC Assigned Medical Monitor whether full information regarding the event is known or not.

Additional follow-up by the investigator will be required if complete information is not known. De-identified source documentation of all examinations, diagnostic procedures, etc. which were completed with respect to the event should be included with the SAE form. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers (as assigned at the time of study enrollment) are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.

All other serious adverse events must be reported to the sponsor and DSMC's appointed medical monitor within 24 hours by e-mail (NYUPCCsafetyreports@nyumc.org) or fax (212-263-0715). The Serious Adverse Event Form must also be emailed to the principal investigator and Clinical Trials Office (NYUPCCsafetyreports@nyumc.org) or it can be faxed (212-263-0715), this documentation will be forwarded to the DSMC's appointed medical monitor within 24 hours of the event whether full information regarding the event is known or not. Additional follow-up by the investigator will be required if complete information is not known.

Current contact information shall be maintained at the site within the regulatory binder.

All serious adverse events (SAEs) will be evaluated by the DSMC if meeting the requirements for expedited reporting, the study Sponsor will report the adverse event to all regulatory authorities with jurisdiction over ongoing trials with the study drug and to all other investigators involved in clinical trials with the study drug. The investigator is responsible for reporting all SAEs to the appropriate IRB, DSMC, and FDA.

10.4.3 Reporting of Pregnancy

If, following initiation of the investigational product(s), 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. The pregnancy must be reported immediately to the principal investigator, and the Clinical Trials Office, by emailing: NYUPCCsafetyreports@nyumc.org, PCC Assigned Medical Monitor, and the study sponsor (NYU Langone Health PCC) will report to BMS in accordance with the procedures described below. Pregnancy in itself is not regarded as an adverse event unless there is a suspicion that the investigational product may have interfered with the effectiveness of a contraceptive medication. This will be reported to the IRB if necessary. Each pregnancy case will be followed until pregnancy resolution.

The investigator must immediately notify Worldwide.Safety@bms.com of this event via MedWatch or appropriate Pregnancy Surveillance Form in accordance with SAE reporting procedures. The pregnancy, AEs associated with maternal exposure and pregnancy outcomes must be reported and submitted to BMS on a BMS Pregnancy Surveillance Form **or** the MedWatch, or approved site SAE form, and reported to BMS within 24 hours/1 business day by confirmed fax or reported via electronic mail to: Worldwide.Safety@BMS.com. If only limited information is initially available, follow-up reports may be required. Your original forms are to remain on site. Follow-up information should be obtained on pregnancy outcomes for one year following the birth of the offspring.

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 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 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.

10.5 Reporting Procedures – Notifying the Study Sponsor

Since multiple sites will be participating, the following describes events that must be reported to the study sponsor (NYU Langone Health PCC) and the study sponsor reports to BMS in an expedited fashion.

Initial Report: within 24 hours:
The following events must be reported to the study sponsor (NYULMC PCC) by email within 24 hours of awareness of the event using the NYU CTO Medical Events Form:

- Unanticipated problems related to study participation,
- Serious adverse events, regardless of whether they are unexpected.

The investigator shall maintain a copy of the Medical Events Form on file at the study site. All report forms must be signed and dated by the Principal Investigator. If the Principal Investigator is not available at the time of the initial report, then the form can be submitted by a Sub-Investigator. This form should be reviewed by the Principal Investigator, whom sign/date initial report upon return.

Report to:

NYUPCCsafetyreports@nyumc.org
(212) 273-2748

AND

Deirdre Cohen, MD
160 E. 34th Street,
New York, NY 10016
Phone: 212-731-5656
deirdre.cohen@nyumc.org

AND

PCC Assigned Medical Monitor

Events of Clinical Interest (any medical event that is deemed significant via Principal Investigator's expertise, but does not apply to SAE categories) will be reported within 2-5 days, or as per study Sponsor specifications.

Follow-up report:
As a follow-up to the initial report, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event.

Other Reportable events:

- **Deviations from the study protocol**
  Deviations from the protocol must receive both Sponsor and the investigator's IRB approval before they are initiated. Any protocol deviations initiated without Sponsor and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor and to the investigator's IRB as soon as a possible, but ***no later than 5 working days*** of the protocol deviation.

- ***Withdrawal of IRB approval***
  An investigator shall report to the sponsor a withdrawal of approval by the investigator's reviewing IRB as soon as a possible, but ***no later than 5 working days*** of the IRB notification of withdrawal of approval.

- 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 (eg, 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.
- If the BMS safety address is not included in the protocol document (eg, multicenter studies where events are reported centrally), the procedure for safety reporting must be reviewed/approved by the BMS Protocol Manager. Procedures for such reporting must be reviewed and approved by BMS prior to study activation.
- For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection.

Reporting to BMS

Frequency of reconciliation should be every 3 months and prior to the database lock or final data summary. BMS GPV&E will email, upon request from the Investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS.

- In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of a 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 (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.
  - Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

In addition 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).

Adverse Event Reporting

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 an attached '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 that the file contains:

both non-serious Adverse Events and previously submitted Serious Adverse Events (which were submitted to BMS within 24 hours / 1 business day of event awareness within the 3 months).

Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether or not related to the BMS product associated with this study, must be collected, including those thought to be associated with protocol-specified procedures. CIOMS, MedWatch, or site approved form and reported to BMS within 24 hours \ 1 business day to comply with regulatory requirements.

Either the CIOMS, MedWatch, or approved site SAEform should be completed for any event where doubt exists regarding its status of seriousness. Note: Please include the BMS Protocol number on the SAE form or on the cover sheet with the SAE form transmission.

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the DCC/study sponsor within 24 hours of site awareness. See Section 1, Key Roles for contact information.
- Other SAEs regardless of relationship will be submitted to the DCC/study sponsor within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the DCC/study sponsor and should be provided as soon as possible.

Investigators should report to the responsible regulatory authority as appropriate.

All SAEs must be reported by confirmed facsimile (fax) transmission or reported via electronic mail to:

BMS Protocol number must be included on the SAE form or on the cover sheet with the SAE form transmission

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1-609-818-3804

If only limited information is initially available, follow-up reports may be required.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin at initiation of the study. Non-serious AE information should also be collected from the start of the observational period intended to establish a baseline status for the subjects.

Non-serious adverse events must be recorded on the Non-interventional Research AE/SAE Form and individually reported to BMS within 7 business days to comply with regulatory requirements.

All non-serious AEs must be reported by confirmed fax transmission or reported via electronic mail to:

Non-serious AE Email Address: Worldwide.Safety@BMS.com

Non-serious AE Facsimile Number: +1-609-818-3804

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 the BMS product associated with this study and for those present at the end of the study, as appropriate.

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

10.6 Reporting Procedures – Notifying the FDA

The study sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND/IDE safety reports.

The following describes the IND safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 calendar days*** *(via telephone or facsimile report)*
  Any study event that is:
  - associated with the use of the study drug
  - unexpected,
  - fatal or life-threatening

- ***Within 15 calendar days*** *(via written report)*
  Any study event that is:
  - associated with the use of the study drug,
  - unexpected, and
  - serious, but not fatal or life-threatening
    -or-
  - a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

Additional reporting requirements
Sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Reporting Process
Adverse events may be submitted on FDA Form 3500A (MEDWATCH Form; see Attachment 1), or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 8.3. The contact information for submitting IND safety reports is noted below:

NYU Langone Health Contacts:

NYUPCCsafetyreports@nyumc.org

AND
Deirdre Cohen, MD
160 E. 34th Street,
New York, NY 10016
Phone: 212-731-5656
deirdre.cohen@nyumc.org

AND
PCC Assigned Medical Monitor

10.7 Reporting Procedures – Participating Investigators

It is the responsibility of the study sponsor to notify all participating investigators of any adverse event that meets the FDA 15-day reporting requirement criteria as note above. The same materials and timeline used to report to the FDA are used for notifying participating investigators.

10.8 Safety Oversight

All Internal SAEs reported by the CTO, occurring to patients on clinical trials that are not monitored by any other institution or agency, are reported via email: NYUPCCsafetyreports@nyumc.org and reviewed within 48 hours by the medical monitor. Based on the review, one of three determinations will be made:

- SAE report is considered to be adequate
- Queries for clarification to PI regarding treatment attribution and/or resolution of SAE or completeness of other information. The committee may request a cumulative review of

all SAEs on the study to date.

- Request for full DSMC committee review of protocol at the next scheduled meeting.

The DSMC Coordinator will record the committee's decision and incorporate it into the study summary for the next scheduled study review.

11 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan detailed below. Serious adverse events are evaluated regularly by the principal investigator in conjugation with the research team, the DSMC is notified of serious adverse events via email initially, reviewed offline by the designated medical monitor, and presented at the next DSMC monthly meeting. The Data Safety and Monitoring Committee (DSMC) will review the study at least quarterly. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

11.1 Data and Safety Monitoring Committee

This investigator-initiated study will be monitored by the Data Safety Monitoring Committee (DSMC) of the New York University (NYU) Perlmutter Cancer Center (PCC). The DSMC operates based on the National Cancer Institute approved Charter. It is an existing and multidisciplinary committee (consisting of clinical investigators/oncologists, biostatisticians, nurses, and research administration staff knowledgeable of research methodology and design and in proper conduct of clinical trials) that is responsible for monitoring safety, conduct and compliance in accordance with protocol data monitoring plans for interventional clinical trials conducted in the NYULMC Perlmutter Cancer Center that are not monitored by another institution or agency. The DSMC reports to the Director of the NYULMC PCC.

Per the NYU PCC Institutional Data Safety and Monitoring Plan, this phase II trial will be monitored by DSMC *quarterly* (from the date the first patient is enrolled), at protocol-specified interim time points, and at the completion of the study prior to study closure. This review includes accrual data, subject demographics and adverse events. Principal Investigators are required to attend the review of their studies. Additional reviews can be scheduled based on SAE reports, investigator identified issues, external information, etc. The DSMC will review safety data every 3 months. DSMC summary reports are available to facilitate the review and monitoring of this study. These reports include the following: patient listings and summary reports that describe study enrollment and accrual, eligibility, demographic characteristics, dose modifications, adverse experiences, subject's death and additional external published data if applicable to the study. Cumulative toxicities, SAEs, and AEs are reviewed, to identify possible adverse events with elevated frequency that is unexpected. Once a recommendation is made if further action is required, the Investigator's must respond within 10 business days of receipt of DSMC letter.

12 Statistical Considerations

12.1 *Statistical and Analytical Plans (SAP)*

All variables will be summarized with tabular and graphical descriptive statistics. Assessment of variable distributions will be conducted, and potential transformations sought if data do not approximate normality.

12.2 *Statistical Hypotheses*

The co-primary outcomes are safety and efficacy, assessed using the R0 resection rate. Adverse events will be tabulated. The current expected R0 resection rate is 5%. We will consider this regimen promising if we can achieve an R0 resection rate of 20% or higher. With 20 patients, the lower bound of a 95% confidence interval around the R0 resection rate will exceed 5% when the true R0 resection rate is 20% or higher.

The secondary outcomes are the overall response rate, progression free survival, overall survival, and distant metastasis free survival rate.

12.3 *Analysis Datasets*

The Safety Analysis Dataset will include all participants who receive any dose of the proposed investigational therapy. The Efficacy Analysis Dataset will include all participants who receive at least 75% of the first three planned cycles of cabiralizumab and nivolumab and 75% of planned SBRT dose.

12.4 *Description of Statistical Methods*

12.4.1 General Approach

All variables will be summarized with tabular and graphical descriptive statistics. Assessment of variable distributions will be conducted, and potential transformations sought if data do not approximate normality.

12.4.2 Analysis of the Primary Efficacy Endpoint(s)

Safety will be evaluated by tabulating the type and severity of all dose-limiting toxicities and adverse events. If more than two of the first six patients experience an unacceptable toxicity, accrual will be temporarily halted while the study team investigates potential dose modifications. The rate of R0 resection will be calculated as the proportion of enrolled patients who achieve R0 resection. The rate of R0 resection will be estimated with its associated exact 95% confidence interval. If the lower bound of the confidence interval exceeds the null rate of 5%, the therapy will be deemed worthy of further investigation.

12.4.3 Analysis of the Secondary Endpoint(s)

Overall response will be tabulated according to RECIST criteria. Progression-free survival will be measured as the time from enrollment until the occurrence of the earlier of progression or death. Overall survival will be measured as the time from enrollment until death from any cause. Distant metastasis-free survival will be as the time from enrollment until the occurrence of the earlier of distant metastasis or death. PFS, OS, and DMFS will be estimated using the Kaplan-Meier method.

12.4.4 Safety Analyses

The rate of unacceptable toxicity will be estimated, both within the safety run-in cohort of six patients and continuously in the entire cohort of 20 patients. A Bayesian monitoring rule will be applied, such that accrual will be temporarily suspended if the posterior probability that the unacceptable toxicity rate exceeds 0.33 goes above a pre- specified threshold of 75%. We will assume a *Beta*(1,2) prior, which is prior information equivalent to one unacceptable toxicity observed in three treated patients. This minimally informative prior is justified as there is some clinical experience with the combination therapy. Early termination for toxicity will be considered based on a posterior probability above 75% (in

parentheses), that the toxicity rate exceeds 33%. Toxicity will be carefully monitored in the 20 patients. Termination will be considered if unacceptable toxicity is observed in: 2 of 3 patients (0.84), 3 of 6 patients (0.81), 4 of 9 patients (0.79), 5 of 12 patients (0.58), 6 of 15 patients (0.78), 7 of 18 patients (0.77), or 8 of 20 patients (0.77).

12.4.5 Adherence and Retention Analyses

All patients will be followed from enrollment until withdrawal, completion, or death, whichever occurs earlier.

12.4.6 Baseline Descriptive Statistics

Baseline characteristics will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age, gender), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment using descriptive statistics and tabular formats.

12.4.7 Planned Interim Analysis

A single interim analysis is planned after the first six patients have been treated. If there are fewer than two unacceptable toxicities in the first six patient enrolled (as defined in section 7.3), an additional 14 patients will be accrued.

12.4.7.1 Safety Review

A Bayesian monitoring rule will be applied, such that accrual will be temporarily suspended if the posterior probability that the unacceptable toxicity rate exceeds 0.33 goes above a pre-specified threshold of 75%. We will assume a *Beta*(1,2) prior, which is prior information equivalent to one unacceptable toxicity observed in three treated patients. This minimally informative prior is justified as there is some clinical experience with the combination therapy. Early termination for toxicity will be considered based on a posterior probability above 75% (in parentheses), that the toxicity rate exceeds 33%. Toxicity will be carefully monitored in the 20 patients. Termination will be considered if unacceptable toxicity is observed in: 2 of 3 patients (0.84), 3 of 6 patients (0.81), 4 of 9 patients (0.79), 5 of 12 patients (0.58), 6 of 15 patients (0.78), 7 of 18 patients (0.77), or 8 of 20 patients (0.77).

12.4.7.2 Efficacy Review

There will be no interim analyses for efficacy.

12.4.8 Exploratory Analyses

Immune response parameters will be assessed. These analyses will be purely descriptive and hypothesis-generating; no formal hypothesis testing will be conducted.

12.5 Sample Size

We will initially enroll six patients. Should the threshold for continuation be reached (two or fewer patients with unacceptable toxicity in the first six), we will accrue an additional 14 patients for a total of 20 patients. An exact 95% confidence interval around the R0 resection rate will exclude the null rate of 5% if the true rate is 20% or higher.

13 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

TrialMaster, an electronic database capture system will be created to record the data for this trial. Research coordinators will input clinical trial data into the database. This database is password protected and only the PI, assigned study team members, and CTO staff will have access to the database. DataCore, a core resource of the institution, will provide the primary data collection instrument for the study. All data requested in the system must be reported. All missing data must be explained. The quality assurance specialists will monitor this trial every 4-6 weeks for data entry accuracy.

Source documentation should be consistent with data entered into any electronic medical record or Trial master. Relevant source documentation to be reviewed by the DSMC throughout the study includes:

1. Baseline measures to assess pre-protocol disease status
2. Concurrent medications
3. Treatment records
4. Adverse events

14 Quality Assurance and Quality Control

This study will be monitored according to the monitoring plan detailed below, subsite monitoring follows parameters detailed in Section 14.1. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit. A risk-based, data-driven monitoring approach will be used to verify data for this trial which will also include a centralized review of data for quality, trends, consistency and general safety review. A quality assurance specialist will make regularly

scheduled trips to the investigational site to review the progress of the trial, study data and site processes. At each visit, the monitor will review various aspects of the trial including, but not limited to: screening and enrollment logs; compliance with the protocol and study manual and with the principles of Good Clinical Practice; completion of case report forms; source data verification; study drug accountability and storage; facilities and staff.

During scheduled monitoring visits, the investigator and the investigational site staff must be available to meet with the quality assurance specialist in order to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the monitor. In addition to on-site monitoring visits, the Sponsor and/or representatives will also be routinely reviewing data. Any queries identified through this review will be managed within the systems established for query resolution and tracking. Inquiries related to study conduct, which require further information or action will be discussed within the study team for appropriate and documented escalation plans. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Sponsor or representatives, and review/entry of data into the electronic study database.

At any time during the course of the study, representatives of the FDA and/or local regulatory agencies may review the conduct or results of the study at the investigational site. The investigator must promptly inform NYU PCC CTO and BMS of any audit requests by health authorities, and will provide BMS with the results of any such audits and with copies of any regulatory documents related to such audits.

In accordance with HIPAA and associated privacy regulations, a patient's authorization to use personal identifiable health information may be required from each patient before commencement of research activities. This authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose and for what duration.

At the NYU Perlmutter Cancer Center, all investigator-initiated protocols are subject to a standardized data and safety monitoring, which includes scientific peer review, IRB review and DSMC review as well as internal auditing.

The review of AEs and trial conduct for this trial occurs at several levels:

(1) Principal Investigator: Adverse events are evaluated monthly by the principal investigator in conjunction with the research nurses, data manager and research team.

(2) DSMC, quarterly

(3) Institutional Review Board (IRB): An annual report to the IRB is submitted by the trial PI for continuation of the protocol. It includes a summary of all AEs, total enrollment with demographics, protocol violations, and current status of subjects as well as available research data.

In addition, the quality assurance unit will monitor this trial every 4-6 weeks, this includes real- time review of all eCRFs to ensure completeness and to verify adherence to the protocol; the completeness, accuracy and consistency of the data; and adherence to ICH Good Clinical Practice guidelines. Additionally, a first subject audit is to be conducted within four weeks of enrollment.

14.1 *Subsite QC monitoring*

Monitoring visits are done remotely unless otherwise specified, via remote EMR access. If not possible, secure email exchange will be utilized. The quality assurance specialist will confirm an upcoming

monitoring visit with a Subsite Investigator and staff. If remote EMR access is not available, then the Subsite Coordinator will ensure that all source documents for subjects are de-identified and labeled only with the subject ID number(s), and emails all requested documents to the quality assurance specialist by the specified visit date. All documents are reviewed and a monitoring report is submitted within 5 business days from the date of the visit. Any outstanding documents will be listed in the report as a high-priority request for the next monitoring visit. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Sponsor or representatives, and review/entry of data into the electronic study database. Continued non-compliance and failure to submit documentation will result in the suspension of subject enrollment at the site, until the documents have been received.

15 Ethics/Protection of Human Subjects

15.1 *Ethical Standard*

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

15.2 *Institutional Review Board*

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

15.3 *Informed Consent Process*

15.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. The following consent materials are submitted with this protocol Informed Consent.

15.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically

for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

The consenting process and documentation will follow Standard Operating Procedures (Obtaining Informed Consent for Clinical Trials) of the NYULMC PCC CTO.

15.3.3 Informed Consent

Consent will be obtained only by a participating investigator who has completed requisite training for human subject research and has been instructed by the Principal Investigator about the research study and consent process. Investigators will review the informed consent form with patients and address any questions or concerns prior to obtaining written informed consent for participation and HIPAA authorization.

Patients will be given adequate time to read the consent form. They will be given time to ask questions about the study in private exam rooms. Questions will be answered by a participating physician, or qualified research study team member all of whom have completed requisite training for human subject research. Investigators will review the informed consent form with patients and address any questions or concerns prior to obtaining written informed consent for participation. Investigators will stress that participation in the study is completely voluntary and will not affect the care patients receive or result in any loss of benefits to which patients are otherwise entitled.

For non-English speaking patients, institutional translation services will be utilized. All procedures for consenting non-English speaking patients will be in accordance with NYU Langone Health PCC CTO guidelines and policies.

For patients who cannot read; a witness, not related to the research study will be present. The consent will be read to the patient. The patient will also be allowed to ask any questions s/he may have. The investigator will ask the patient questions to ensure s/he understands the study. If the investigator determines the subject understands the study, the patient will mark an X where his/her name would go and the witness will sign the consent form.

15.3.4 Documentation of Consent

The Principal Investigator or IRB approved sub-investigator will be responsible for documentation in the medical record that consent has been obtained from all participants. A signed copy of the consent form will be given to each participant. Original consent forms will be stored in the subject's medical chart.

15.4 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why

- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

15.4.1 Research Use of Stored Human Samples, Specimens, or Data

- Intended Use: Samples and data collected under this protocol may be used to provide a tertiary treatment option for patients with locally advanced unresectable pancreatic cancer. No genetic testing will be performed.
- Storage: Access to stored samples will be limited to the study team. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.
- Tracking: Data will be tracked using Trialmaster.
    - Disposition at the completion of the study: All stored samples will be sent to CBRD . Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking. However, withdrawal of consent with regard to biosample storage will not be possible after the study is completed

15.5 Future Use of Stored Specimens

Data collected for this study will be analyzed and stored at NYU Langone Health. After the study is completed, the de-identified, archived data will be transmitted to and stored via an electronic database

system, under the supervision of Dr. Deirdre Cohen, with the potential for use by other researchers including those outside of the study. Permission of storage of samples, specimens, and data are optional to participate in this future use study and will be included in the informed consent. Subjects have the option to permit/decline the banking of their samples and data for future research (beyond the scope of the study) and will be asked to indicate their decision on the informed consent form. They can choose to/not to allow this long-term storage for future research and still be in the study.

With the participant's approval and as approved by local IRBs, de-identified biological samples will be stored at the NYU Center for Biospecimen Research & Development. These samples could be used for research into the causes of pancreatic cancer, its complications and other conditions for which individuals with pancreatic cancer are at increased risk, and to improve treatment. True genetic testing will not be performed on the samples, however data from the research could potentially predict patterns within the samples. The CBRD will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research..

When the study is completed, access to study data and/or samples will be provided through the supervision of the principal investigator, Dr. Deirdre Cohen, these samples will be stored indefinitely.

16 Data Handling and Record Keeping

16.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Trialmaster, a 21 CFR Part 11-compliant data capture system provided by DataCore. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

16.2 Study Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

16.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

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Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. All protocol deviations must be addressed in study source documents and reported to IRB Program Official at the time of annual continuing review. If a protocol deviation is determined to be reportable new information, the IRB will be notified immediately.

16.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

17 Study Finances

17.1 Funding Source

17.2 Participant Reimbursements or Payments

No subjects will receive payments or stipends for participation in this research study. BMS may provide coverage for tests and/or procedures that are a part of the research study, if it is not covered by the subject's insurance.

18 Study Administration

18.1 Study Leadership

The Steering Committee will govern the conduct of the study. The Steering Committee will be composed of the Study Chairman, the PI of the Coordinating Center, the PI of the clinical sites, and designated members of the study team The Steering Committee will meet monthly to discuss the trial's progress, these meetings are facilitated by CTO's quality assurance specialists.

19 Conflict of Interest Policy

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULH investigators will follow the applicable University conflict of interest policies.

20 Schedule of Events

Activity	Screening/ Baseline	Cycle 1		Cycle 2			Cycle 3		Cycle 4		Subsequent Cycles (cycle = 14 days)		End of Study Visit
	Day -28 to -1	Day 1	Day 8	Day 1 (Day 15)	Day 8 (Day 22)	Day 10-14 (Day 24-28)	Day 1 (Day 29)	Day 8 (Day 36)	Day 1 (Day 43)	Day 8 (Day 50)	Day 1	Day 8	
Study team procedures													
Informed Consent	X												
Eligibility Assessment	X												
Medical History	X												
Physical Exam	X	X	X	X	X		X	X	X		X		X
Height	X												
Weight	X	X	X	X	X		X	X	X		X		X
Vitals signs	X	X	X	X	X		X	X	X		X		X
Performance Status	X	X	X	X	X		X	X	X		X		X
Fiducial Placement	X												
Carbiralizumab		X		X			X		X		X		
Nivolumab		X		X			X		X		X		
SBRT			X										
Cardiology assessments													
Electrocardiogram	X												X
Laboratory Assessments													
Comprehensive metabolic profile[1]	X	X	X	X	X		X	X	X		X		X
CBC with differential[1]	X	X	X	X	X		X	X	X		X		X
LDH[1]	X	X	X	X	X		X	X	X		X		X
CPK[1]	X	X	X	X	X		X	X	X		X		X

Amylase & Lipase[1]	X	X	X	X	X		X	X	X		X		X
Free T4, TSH[2]	X	X		X			X		X		X		X
CA 19-9[3]	X	X					X						X
PT/PTT[4]	X												
Pregnancy Test	X	X											
Urinalysis[4]	X												
Imaging Assessments													
CT chest, abdomen and pelvis[5]	X					X					X[5]		
Correlative Studies[6]													
Research Blood for		X	X	X	X		X	X	X				X
Tumor Biopsy	X				X								
Follow up													
Patient Contact[7]													

1. To be collected at weekly intervals for the first 42 days (ie cycles 1-3) and then Day 1 of every subsequent cycle (ie every 14 days)
2. To be collected on Day 1 of every cycle, ie every 14 days
3. To be collected on Day 1 of every other cycle, ie Cycle 1 day, Cycle 3 Day 1, Cycle 5 Day 1 etc
4. To be collected at screening and then as clinically indicated
5. Baseline imaging with CT chest, abdomen and pelvis with IV contrast to be done within 28 days of Cycle 1 Day 1. Post SBRT imaging to be done Cycle 2 Day 12 (+/- 2 days). CT chest, abdomen, and pelvis (prior to cycle 6 (+/- 3 days and then every 8 weeks thereafter (+/-7 days).
6. Research blood will be collected prior to initiation of treatment on Cycle 1 Day1 and then every week thereafter for the first 6 weeks on study through Cycle 4 Day 1.
7. Patients will be followed for survival every 12 weeks (± 1 week) from the date of last dose of investigational drug(s), either in person or by telephone contact, up to 18 months, then every 6 months thereafter until death or lost to follow-up (for a maximum of 5 years after final patient completes treatment).. Information will be obtained on subsequent cancer treatments, SAE's and AE's possibly or probably related to investigational drug(s) for up to 100 days, date and cause of death (if subject deceased).

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Appendix 1:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male subjects, who are WOCBP, are expected to use one of the highly effective methods of contraception listed below. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner. Acceptable contraception methods of include:

- Progestogen: hormonal contraception associated with inhibition of ovulation
- Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone
- Vaginal Ring
- Injectables
- Implants
- Intrauterine Devices (IUDs) such as Mirena®
- Non-hormonal IUDs, such as ParaGard ®
- Bilateral Tubal Occlusion
- Vasectomised partner with documented azoospermia 90 days after procedure. A Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

- Intrauterine Hormone-Releasing System (IUS).
- Complete Abstinence
  Complete Abstinence is defined as the complete avoidance of heterosexual intercourse. Complete abstinence is an acceptable form

Appendix 2:

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[a] Measure CK isoenzyme panel to identify source of elevation Increase frequency of monitoring (every 48-72 hours or more, as clinically indicated)	**If CK or LDH returns to ≤ 15 x ULN 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 BMS Medical Monitor 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
CK or LDH > 20 xULN	– Discontinue cabiralizumab and nivolumab therapy per protocol	– Follow up until resolution

a. If the AE requiring a dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient.

Appendix 3:

ADVERSE EVENT MANAGEMENT FOR CABIRALIZUMAB AND NIVOLUMAB

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 and nivolumab therapy per protocol – Symptomatic treatment	– Close monitoring for worsening symptoms – Educate patient to report worsening immediately **If worsens:** – Treat as Grade 2 or ¾
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[a] – 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 224 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[b] – 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent[c] – 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] If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient

[b] If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by the patient

[c] 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[a] – Monitor creatinine every 2 to 3 days – 0.5 to 1 mg/kg/day methylprednisolone IV or oral equivalent[b] – Consider renal biopsy if clinically indicated	**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[a] – Monitor creatinine every 2 to 3 days – 0.5 to 1 mg/kg/day methylprednisolone IV or oral equivalent[b] – Consider renal biopsy if clinically indicated	**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 and nivolumab therapy per protocol[c] – 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent[b] – Consult nephrologist – Consider renal biopsy if clinically indicated	**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] If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient.

[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.

[c] If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by the patient.

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[a] – 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[b] – Hospitalization – Pulmonary and infectious disease consults – 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent[c] – 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] If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient.

[b] If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by patient.

[c] 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		
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 – Evaluate for non-drug related causes of the laboratory abnormalities (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 the investigator and Sponsor 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 PI if there are clinical signs of muscle or hepatic injury or other clinical symptoms – Contact the PI if there is a concurrent increase of bilirubin, AST, ALT, or alkaline phosphatase – Notify the PI 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 x ULN ***or*** Isolated total bilirubin > 2 to ≤ 3 x ULN	– Delay cabiralizumab and nivolumab therapy per protocol[a] – 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	**If AST/ALT return to ≤ 12 x 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 therapy per 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

Hepatic Adverse Event Management		
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**
	phosphatase along with ALT, start steroids immediately – Monitor for other clinical symptoms (fatigue, nausea, vomiting, abdominal pain, fever, rash, and/oreosinophilia)	– Consider prophylactic antibiotics for opportunistic infections – Discuss with PI
AST or ALT > 20 xULN **or** **Total bilirubin >3 xULN**	– Discontinue cabiralizumab and nivolumab therapyb – Increase frequency of monitoring to every 1 to 2 days – Consider 1 to 2 mg/kg/day methylprednisolone IV or IV equivalentc – 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

If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient.

[b] If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by the patient.

[c] 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[a] – 1 to 2 mg/kg/day methylprednisolone IV or PO equivalent[b] – 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 therapy per 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 PI 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] If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient.

[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.

[c] If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by the patient.

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, topical steroids) – Continue cabiralizumab and nivolumab therapy per protocol	**If persists >1-2 weeks or recurs:** – Consider skin biopsy – Delay cabiralizumab and nivolumab therapy per 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, and resume 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[b,c] – Consider skin biopsy and dermatology consult – 1 to 2 mg/kg/day IV methylprednisolone IV or IV equivalent[d]	**If improves to Grade 1 within 28 days:** – Taper steroids over at least 1 month and add prophylactic 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] If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient

[c] If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by the patient

[d] 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[a] – Treat symptoms per local guidelines – Consider 0.5 to 1 mg/kg/day methylprednisolone IV or PO[b]	**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[c] – Obtain neurology consult – Treat symptoms per local guidelines 1 to 2 mg/kg/day IV methylprednisolone or PO[b] – 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] If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient.

[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.

[c] If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by the patient.

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[a] – Start systemic treatment including steroids, eye drops, or analgesics as needed[b]	**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 and nivolumab therapy per protocol[c] – Systemic treatment including steroids, eye drops, or analgesics as needed[b] – 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] If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient.

[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.

[c] If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by the patient.

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[a,b] – Systemic treatment including NSAIDs, corticosteroids and antihistamines[c] – 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:** – Discontinue treatment at the visit – Discuss with PI as needed
Grade ≥3	– Discontinue cabiralizumab and nivolumab therapy per protocol[b] – Systemic treatment including NSAID , corticosteroids, and antihistamines[c] – 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, if indicated

[a] If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient

[b] If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by the patient

[c] 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 v5.0)	**Management**	**Follow-Up**
Grade 1	– Observe symptoms – Continue cabiralizumab and nivolumab 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[a,b] – Start antibiotics and inflammatory medications including steroids[c] – Ophthalmologic consult, 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 and start 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 as infliximab, as clinically indicated
Grade ≥3	– Discontinue cabiralizumab and nivolumab therapy per protocol[b] – Start antibiotics and inflammatory medications including steroids[c] – Ophthalmologic consult, 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 as infliximab, as clinically indicated – Follow up until resolution

[a] If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient

[b] If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by the patient

[c] 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.