Official Title of Study:

A Phase 2 Study of Cabiralizumab (BMS-986227, FPA008) Administered in Combination with Nivolumab (BMS-936558) with and without Chemotherapy in Patients with Advanced Pancreatic Cancer)

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Clinical Protocol CA025006

A Phase 2 Study of Cabiralizumab (BMS-986227, FPA008) Administered in Combination with Nivolumab (BMS-936558) with and without Chemotherapy in Patients with Advanced Pancreatic Cancer

Short Title: A Study of Cabiralizumab Given With Nivolumab With and Without Chemotherapy in Participants With Advanced Pancreatic Cancer

Revised Protocol 04

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Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 04	17-Jun-2019	The following are major changes to the protocol: • Clarified that BICR will be used to assess the primary endpoint of PFS per RECIST v1.1. • Clarified the assessment (Investigator/BICR) used for each efficacy evaluation included as a secondary endpoint. • Time of on-treatment biopsy was changed to an earlier time point on Cycle 2 Day 8.
Revised Protocol 03	24-Apr-2018	The following are major changes to the protocol: • Removal the cross over post disease progression for participants treated with chemotherapy only. [redacted] • Additional data added to support the combination of cabiralizumab and nivolumab.
Revised Protocol 02	09-Mar-2018	The following are major changes to the protocol: • Eligible participants include those that have progressed after only 1 line of chemotherapy • All participants must have fresh tumor biopsy taken during screening. Up to approximately 8 participants/cohort (~20%) will be allowed on treatment with pretreatment biopsies that do not yield adequate tumor tissue [redacted] • If ONIVYDE-based regimen is not available per institution/country guidelines, FOLFIRI can be used in Arm A. • Adequate organ function is defined as ALT and AST < 2 x ULN
Revised Protocol 01	28-Nov-2017	[redacted], the following section have been revised: • Expanded rationale for combining immunotherapy and chemotherapy agents • Removed criteria excluding participants who had any GI surgery and an inability to tolerate oral medication • Added criteria for permanent dose discontinuation and exceptions [redacted]
Original Protocol	13-Oct-2017	Not applicable

OVERALL RATIONALE FOR THE REVISED PROTOCOL 04

This protocol has been revised to clarify that blinded independent central review (BICR) will be used to assess the primary endpoint of progression-free survival (PFS) per RECIST v1.1. In addition, this revision clarifies the assessment (Investigator/BICR) used for each efficacy evaluation included as part of the secondary endpoints.

On-treatment tumor biopsy samples will now be collected at an earlier time point on Cycle 2 Day 8 to increase the number of biopsies collected.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04

Section Number & Title	Description of Change	Brief Rationale
Synopsis	Synopsis was updated.	Synopsis was updated to reflect the changes in the body of the protocol as summarized below.
Table 2-1 Screening Procedural Outline; [redacted]	Included that fresh pretreatment tumor biopsies must be obtained from a metastatic tumor lesion or from an unresectable primary tumor lesion.	Included for clarity.
Table 2-1 Screening Procedural Outline; Section 9.1.1 Imaging Assessment for the Study	Timing of body imaging/baseline tumor assessments at screening was changed – now must be performed 30 days prior to first dose of study treatment.	Changed to align with BMS protocol standards.
Table 2-2 On-Treatment Procedural Outline; Table 2-3 Follow-up Procedural Outline	Brain Imaging row was removed. Brain Scan was added to "Others" row.	Brain metastases are an exclusion criteria in this study; therefore, Procedural Outline is not required for participants with a history of brain metastases.
Table 2-2 On-Treatment Procedural Outline; Section 5.1.2 Treatment Period	Updated text: Randomization should occur no more than 3 business days prior to the first day of treatment on Cycle 1 Day 1, unless otherwise agreed upon with the Medical Monitor. Previously, randomization occurred on Cycle 1 Day 1.	Changed to allow sufficient time for sites to prepare for study treatments.
Section 3.1.1.1 Rationale for the 2L Cohort; Section 5.4.1 Rationale for Chemotherapy-only Regimens;	Revised text for rationale for the 2L Cohort.	Updated rationale for the 2L Cohort for improved readability.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.2.1.3 Clinical Summary; Section 5.4.2 Rationale for Cabiralizumab and Nivolumab Combination Therapy	Study CA025001 was added to the list of studies evaluating cabiralizumab in Section 3.2.1.2. Safety and efficacy summaries for Study FPA008-003 were updated with data from the latest Investigator Brochure for cabiralizumab (IB version 6, October 2018).	Updated to provide latest information on the safety profile of cabiralizumab.
Section 3.1.5 Rationale for Combining Immunotherapy and Chemotherapy Regimens; Section 3.3 Benefit Risk Assessment; Section 5.1.2 Treatment Period; Section 5.2 Number of Participants	Updated text for the preliminary safety cohort in participants receiving cabiralizumab in combination with nivolumab and chemotherapy (2L Cohort Treatment Arms C and D).	Updated to clarify treatment arms included in the safety cohort and to indicate that the predefined 4-week observation period for the safety cohort has been completed. Review of the preliminary data from the safety cohort indicated that the combination of cabiralizumab with nivolumab and chemotherapy is well tolerated.
Table 4-1 Objective and Endpoints	Clarified that BICR will be used to assess the Primary Endpoint of PFS per RECIST v1.1. Clarified that investigator assessment will be used to assess the Secondary Endpoint of PFS per RECIST v1.1 and that BICR and investigator assessment will be used to evaluate the Secondary Endpoints of ORR, DOR, and PFSR per RECIST v1.1. [redacted]	Updated to clarify assessments used for efficacy endpoints. [redacted]
Section 5.1.3 Treatment Beyond Progression	Section was moved from 7.4.7 to 5.1.3 and language was updated.	Moved and updated as part of an update to BMS protocol standards.
Section 5.2 Number of Participants	Changed randomized to treated. Sentence now reads: “Approximately 160 participants will be treated (approximately 40 participants in each treatment arm).”	Updated to clarify the number of participants determined based on the statistical justification highlighted in Section 10.1.
Section 6.1 Inclusion Criteria	Updated criterion 4) f) to: Azoospermic males are required to use a condom for the duration of the study.	Male contraceptive requirements modified to require condom use for all males, including azoospermic males, who are sexually active with WOCBP to align with BMS protocol standards.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04

Section Number & Title	Description of Change	Brief Rationale
Section 6.1 Inclusion Criteria; Appendix 4 Women of Childbearing Potential Definitions and Methods of Contraception	Inclusion Criterion 4) d) and Appendix 4 were revised to extend the duration of posttreatment contraception in WOCBP to 6 months for participants receiving ABRAXANE. Participants receiving any other study treatment must use contraception for 5 months posttreatment. Duration of posttreatment contraception required for male participants was changed to 7 months.	The duration of posttreatment contraception in WOCBP who received ABRAXANE was extended to 6 months to align with the US prescribing information for ABRAXANE. Aligned with Inclusion Criterion 4) e)
Section 6.2 Exclusion Criteria; Section 7.6.1 Prohibited and/or Restricted Treatments	Exclusion criterion 4) b) was updated to indicate that receipt of a live/attenuated vaccine within 30 days of first treatment is not permitted.	Updated per BMS protocol standards.
Section 6.3 Lifestyle Restrictions	The following sentence was added: Male participants receiving gemcitabine, ABRAXANE, and fluorouracil should seek advice regarding cryoconservation of sperm prior to treatment because of the possibility of infertility.	Statement added to alert potential male participants of infertility following treatment with gemcitabine, ABRAXANE, and fluorouracil.
Table 7-1 Study Treatments for CA025006	Added new dosage strength of cabiralizumab (140 mg/vial).	The dosage strength of 140 mg/vial was introduced to accommodate a larger quantity of drug per vial, to minimize waste during preparation in the clinic.
Section 7.1 Treatments Administered	Provided additional details for ONIVYDE dosing, as follows: The recommended starting dose of ONIVYDE in participants known to be homozygous for the UGT1A1*28 allele is 50 mg/m^2 administered by intravenous infusion over 90 minutes. Increase the dose of ONIVYDE to 70 mg/m^2 as tolerated in subsequent cycles.	Updated [redacted] to clarify irinotecan dosing in patients known to be homozygous for the UGT1A1*28 allele.
Section 7.4.1 Dose Delay for Cabiralizumab and Nivolumab	The following criterion was added: If symptoms or signs of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) appear, nivolumab should be withheld and the patient referred for specialized care for assessment and treatment.	Dose Delay criterion was added to align with the nivolumab Investigator Brochure v17.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.4.4 Dose Discontinuation Criteria for Cabiralizumab and Nivolumab	The following two discontinuation criteria were removed: Adrenal insufficiency requires discontinuation regardless of control with hormone replacement. Any Grade 3 or higher drug-related diarrhea or colitis, which does not resolve to Grade 1 or baseline within 28 days.	Removed for consistency [redacted]
Section 7.4.4 Dose Discontinuation Criteria for Cabiralizumab and Nivolumab	The following criteria were added: Confirmed Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) will result in permanent discontinuation of nivolumab. Any Grade 3 or higher myocarditis will result in permanent discontinuation of nivolumab.	Discontinuation criteria were added to align with the nivolumab Investigator Brochure v17.
Section 7.4.6 Dose Modification for Chemotherapy	The following criterion was added: In addition, if participants experience tolerability issues for 5-FU / leucovorin and ONIVYDE, and FOLFIRI, dose modifications for these 2 regimens should be performed according to their respective SmPCs and institutional guidelines.	Dose modification guidelines were clarified for 5-fluorouracil / leucovorin and ONIVYDE, and FOLFIRI [redacted]
Section 8.1 Discontinuation from Study Treatment	Modified text related to pregnancy cases to include that BMS/Medical Monitor must be notified within 24 hours of a pregnancy event.	Modified in-the-case-of-pregnancy instructions to clarify expectations for reporting pregnancy.
Section 9.2 Adverse Events	Added the following paragraph on IMAEs: “IMAEs are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant’s CRF.”	Updated per BMS protocol standards.
Section 9.2.1 Time Period and Frequency for Collecting AE and SAE Information	Provided additional details on SAE collection and safety references for all study drugs	Updated to include appropriate references to the Reference Safety Information for all investigational products administered in CA025006.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.2.5 Pregnancy	Modified second paragraph related to treatment continuation and pregnancy to: • Remove redundant text related to timing of notifying BMS Medical Monitor/designee of pregnancy. • Add text for circumstances in which continuation of study treatment may be discussed.	Updated text related to treatment continuation and pregnancy to clarify the circumstances for continuation of study treatment in the case of pregnancy.
Table 9.4.4-1 Clinical Laboratory Tests	Included that pregnancy tests should also be performed monthly during treatment and safety follow-up periods in WOCBP.	Updated [redacted]
Table 2-1 Screening Procedural Outline; Table 2-2 On-treatment Procedural Outline; Table 2-3 Follow-up Procedural Outline; Table 9.4.4-1 Clinical Laboratory Tests	Thyroid panel (TSH, free T3, and free T4) was added.	Included as part of BMS protocol standards.
[redacted]		

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Table 10.3.1-1 Efficacy - Statistical Analyses	Updated the Statistical Analysis Method text. Added row for OS.	Updated/added for clarity.
Appendix 2 Study Governance Considerations	Updated language around reporting potential serious breaches and added section on Scientific Publications.	Updated per BMS protocol standards.
Appendix 3 Adverse Events and Serious Adverse Events Definitions and Procedures for Recording, Evaluating, and Follow-up and Reporting	Added the following new sections: • Events Meeting the AE Definition. • Events Not Meeting the AE Definition. • Definition of Serious Adverse Event (SAE). Modified the following sections: • SAEs (text related to pregnancy and drug-induced liver injury). • Evaluating AEs and SAEs (updated and rearranged bulleted information). Reporting of SAEs to Sponsor or Designee (updated and rearranged bulleted information related to pregnancy and paper report forms).	Modifications made to information related to AEs and SAEs to align with the [redacted] Common Protocol Template, regulatory definition EMA GVP Module VI (EMA/873138/2011) and ICH E2A, and clarify the instructions for reporting pregnancy.
Appendix 7 Adverse Event Management for Cabiralizumab and Nivolumab Combination Therapy Cohorts	Gastrointestinal Adverse Event Management: option to delay treatment with Grade 3-4 event was removed - discontinue cabiralizumab and nivolumab per protocol. Renal Adverse Event Management: updated range for Grade 1 and combined row for Grades 2 and 3. For Grade 4, added monitor creatinine daily Hepatic Adverse Event Management Algorithm: Footnote stating I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN was removed.	Updated to better align with nivolumab protocol standards. Language was modified to align protocol with current Nivolumab Investigator Brochure and nivolumab program safety parameters.
All sections	Minor typographical errors were corrected and edits were made for consistency and clarity.	Minor changes, therefore they have not been summarized.

TABLE OF CONTENTS

TITLE PAGE 1
DOCUMENT HISTORY 3
OVERALL RATIONALE FOR THE REVISED PROTOCOL 04 4
SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04 4
TABLE OF CONTENTS 10
1 SYNOPSIS 14
2 SCHEDULE OF ACTIVITIES 20
3 INTRODUCTION 32
3.1 Study Rationale 32
3.1.1 Rationale for Selection of Patients with Advanced Pancreatic Cancer 32
3.1.1.1 Rationale for the 2L Cohort 33
3.1.2 Rationale for Inhibiting CSF1R in Cancer 33
3.1.3 Rationale for Immunotherapy 34
3.1.4 Rationale for Combining Cabiralizumab and Nivolumab 35
3.1.5 Rationale for Combining Immunotherapy and Chemotherapy Regimens 35
3.2 Background 37
3.2.1 Cabiralizumab 37
3.2.1.1 Mechanism of Action 37
3.2.1.2 Preclinical Summary 38
3.2.1.3 Clinical Summary 39
3.2.2 Nivolumab 43
3.2.3 Clinical Experience Involving Serum Enzyme Elevations 45
3.2.3.1 Serum Enzyme Elevations with Cabiralizumab 46
3.2.3.2 Management of Isolated Laboratory Abnormalities 46
3.3 Benefit/Risk Assessment 46
4 OBJECTIVES AND ENDPOINTS 48
5 STUDY DESIGN 49
5.1 Overall Design 49
5.1.1 Screening Period 50
5.1.2 Treatment Period 51
5.1.3 Treatment Beyond Disease Progression 52
5.1.4 Follow-up Period 53
5.1.4.1 Safety Follow-up Period 53
5.1.4.2 Imaging Follow-up Period 54
5.1.4.3 Survival Follow-up Period 54
5.1.5 Data Monitoring Committee and Other External Committees 54
5.2 Number of Participants 55
5.3 End of Study Definition 55
5.4 Scientific Rationale for Study Design 55
5.4.1 Rationale for Chemotherapy-only Regimens 56
5.4.1.1 Treatment Arm A 56
5.4.2 Rationale for Cabiralizumab and Nivolumab Combination Therapy 56

5.4.3 Rationale for Cabiralizumab in Combination with Nivolumab and Gemicitabine + Nab-paclitaxel or FOLFOX 57
5.5 Justification for Cabiralizumab Dose 57
5.6 Justification for Nivolumab Dose 58
5.6.1 Rationale for Infusion Times for Cabiralizumab and Nivolumab 59
6 STUDY POPULATION 59
6.1 Inclusion Criteria 59
6.2 Exclusion Criteria 62
6.3 Lifestyle Restrictions 65
6.4 Screen Failures 65
6.4.1 Retesting During Screening 65
7 TREATMENT 66
7.1 Treatments Administered 68
7.2 Method of Treatment Assignment 69
7.3 Blinding 69
7.4 Dosage Modification 69
7.4.1 Dose Delay for Cabiralizumab and Nivolumab 69
7.4.2 Management Algorithms for Immuno-oncology Agents 70
7.4.3 Dose Reduction for Cabiralizumab and Nivolumab 70
7.4.4 Dose Discontinuation Criteria for Cabiralizumab and Nivolumab 70
7.4.5 Criteria to Resume Treatment with Cabiralizumab and Nivolumab 72
7.4.6 Dose Modification for Chemotherapy 73
7.4.6.1 Dose Modification for Gemcitabine + Nab-paclitaxel 73
7.4.6.2 Dose Modification for FOLFOX 74
7.4.7 Treatment of Cabiralizumab and Nivolumab-Related Infusion Reactions 76
7.5 Preparation/Handling/Storage/Accountability 78
7.5.1 Dosing of Cabiralizumab and Nivolumab 79
7.5.2 Retained Samples for Bioavailability/Bioequivalence/Biocomparability 79
7.6 Concomitant Therapy 79
7.6.1 Prohibited and/or Restricted Treatments 79
7.6.2 Other Restrictions and Precautions 79
7.6.2.1 Imaging Restrictions and Precautions 80
7.7 Treatment After the End of the Study 80
8 DISCONTINUATION CRITERIA 81
8.1 Discontinuation from Study Treatment 81
8.1.1 Follow-up after Conclusion of Study Treatment 82
8.2 Discontinuation from the Study 82
8.3 Lost to Follow-Up 82
9 STUDY ASSESSMENTS AND PROCEDURES 83
9.1 Efficacy Assessments 83
9.1.1 Imaging Assessment for the Study 83
9.1.2 Methods of Measurement 84
[redacted] 85
9.2 Adverse Events 85
9.2.1 Time Period and Frequency for Collecting AE and SAE Information 86

9.2.2 Method of Detecting AEs and SAEs 87
9.2.3 Follow-up of AEs and SAEs 87
9.2.4 Regulatory Reporting Requirements for SAEs 87
9.2.5 Pregnancy 87
9.2.6 Laboratory Test Result Abnormalities 88
9.2.7 Potential Drug-Induced Liver Injury 88
9.2.8 Other Safety Considerations 89
9.3 Overdose 89
9.4 Safety 89
9.4.1 Physical Examinations 89
9.4.2 Vital signs 90
9.4.3 Electrocardiograms 90
9.4.4 Clinical Safety Laboratory Assessments 90
9.4.5 Imaging Safety Assessment 92
[redacted] 92
[redacted] 94
[redacted] 94
[redacted] 94
[redacted] 96
[redacted] 96
[redacted] 96
[redacted] 96
[redacted] 97
[redacted] 97
[redacted] 97
[redacted] 97
[redacted] 97
[redacted] 99
10 STATISTICAL CONSIDERATIONS 99
10.1 Sample Size Determination 99
10.2 Populations for Analyses 100
10.3 Statistical Analyses 101
10.3.1 Efficacy Analyses 101
10.3.2 Safety Analyses 102
[redacted] 102
[redacted] 103
[redacted] 103
[redacted] 103
10.3.7 Interim Analyses 103
11 REFERENCES 104
12 APPENDICES 108
APPENDIX 1 ABBREVIATIONS AND TRADEMARKS 109
APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS 114

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING 122
APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION 126
APPENDIX 5 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) WITH BMS MODIFICATIONS 130
APPENDIX 6 ECOG PERFORMANCE STATUS 138
APPENDIX 7 ADVERSE EVENT MANAGEMENT FOR CABIRALIZUMAB AND NIVOLUMAB COMBINATION THERAPY ARMS 139
APPENDIX 8 LABORATORY ABNORMALITIES MANAGEMENT TABLE 152
APPENDIX 9 TNM STAGING 153
APPENDIX 10 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY 154

1 SYNOPSIS

Protocol Title: A Phase 2 Study of Cabiralizumab (BMS-986227, FPA008) Administered in Combination with Nivolumab (BMS-936558) with and without Chemotherapy in Patients with Advanced Pancreatic Cancer

Short Title: A Study of Cabiralizumab Given With Nivolumab With and Without Chemotherapy in Patients With Advanced Pancreatic Cancer

Study Phase: 2

Rationale:

Pancreatic ductal adenocarcinoma (PDAC) remains a dreadful diagnosis due to its often advanced stage at diagnosis and poor sensitivity to chemotherapy. Treatment options for patients with metastatic pancreatic cancer are limited. Currently FOLFIRINOX (combined regimen of oxaliplatin, irinotecan, fluorouracil, and leucovorin) and gemcitabine combined with nab-paclitaxel (ABRAXANE®) are globally recognized as the standard of care for patients with advanced pancreatic cancers. In newly diagnosed patients, gemcitabine + nab-paclitaxel is currently considered the treatment option of choice, with a reported median progression-free survival (PFS) of 5.5 months and a median overall survival (OS) of 8.5 months, as well as a more tolerable safety profile and the potential to be administered in patients with advanced age and comorbidities. However, progression after 1L chemotherapy is inevitable in patients with advanced pancreatic cancers, and treatment options for patients who progress after 1L chemotherapy are limited and associated with significant toxicity. Development of novel therapies is therefore needed to treat this chemotherapy-refractory disease.

Immunotherapy has emerged as a therapeutic approach that offers effective and durable treatment options for subsets of patients with various types of cancer. However, perhaps due to a lack of pre-existing T-cell immunity and/or a highly immunosuppressive tumor microenvironment (TME), patients with PDAC have not experienced similar benefits with immunotherapy. [redacted] For example, in heavily pretreated participants with advanced/metastatic PDAC, preliminary data from Study FPA008-003 showed that cabiralizumab (BMS 986227; a monoclonal antibody [mAB] targeting colony-stimulating factor 1 receptor [CSF1R]) in combination with nivolumab (a checkpoint blocking antibody [anti-programmed death-1 [PD-1] mAb) provided durable clinical benefit (partial response or stable disease), including prolonged, sustained partial responses in a population that has not benefited from anti-PD-1 therapy alone. Furthermore, the addition of standard-of-care (SOC) chemotherapy could further potentiate the anti-tumor effects of immunotherapy approaches by reducing the tumor burden, exposing antigens, and directly affecting the immunosuppressive TME compartment.

To explore the synergy of the proposed combinatorial approach, participants with locally advanced/metastatic pancreatic tumors who have progressed during or after no more than 1 line of

systemic chemotherapy in the metastatic setting will receive cabiralizumab administered in combination with nivolumab, nivolumab and gemcitabine + nab-paclitaxel, or nivolumab and oxaliplatin/5-fluorouracil (5-FU)/leucovorin (calcium folinate; FOLFOX), or investigator's choice of reference SOC chemotherapy alone.

Study Population:

Participants must be at least 18 years old and have histological or cytological confirmed diagnosis of locally advanced or metastatic adenocarcinoma of the pancreas, which has progressed during or after no more than 1 prior line of systemic chemotherapy in the metastatic setting (gemcitabine or FU-based regimens).

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the PFS of cabiralizumab administered in combination with nivolumab with and without chemotherapy relative to investigator's choice of chemotherapy in participants with advanced/metastatic pancreatic cancer who progressed on or after the first line of chemotherapy (either gemcitabine-based or 5-FU-based chemotherapy).	• PFS per RECIST v1.1 by BICR
Secondary	
• To evaluate the anti-tumor activity of cabiralizumab administered in combination with nivolumab with or without chemotherapy relative to investigator's choice of chemotherapy in participants with advanced/metastatic pancreatic cancer who progressed on or after the first line of chemotherapy (either gemcitabine-based or 5-FU-based chemotherapy) using RECIST v1.1.	• PFS per RECIST v1.1 by investigator assessment; ORR, DOR, and PFSR at 6, 9, and 12 months per RECIST v1.1 by BICR and investigator assessment
• To assess OS.	• OS and OSR at 6 months, 1 year, and 2 years
• To assess the safety of cabiralizumab administered in combination with nivolumab with or without chemotherapy in participants with advanced/metastatic pancreatic cancer who progressed on or after the first line of chemotherapy (either gemcitabine-based or 5-FU-based chemotherapy).	• Incidence of AEs, SAEs, AEs leading to discontinuation, death, and laboratory abnormalities
[redacted]	

Objectives	Endpoints
[redacted]	

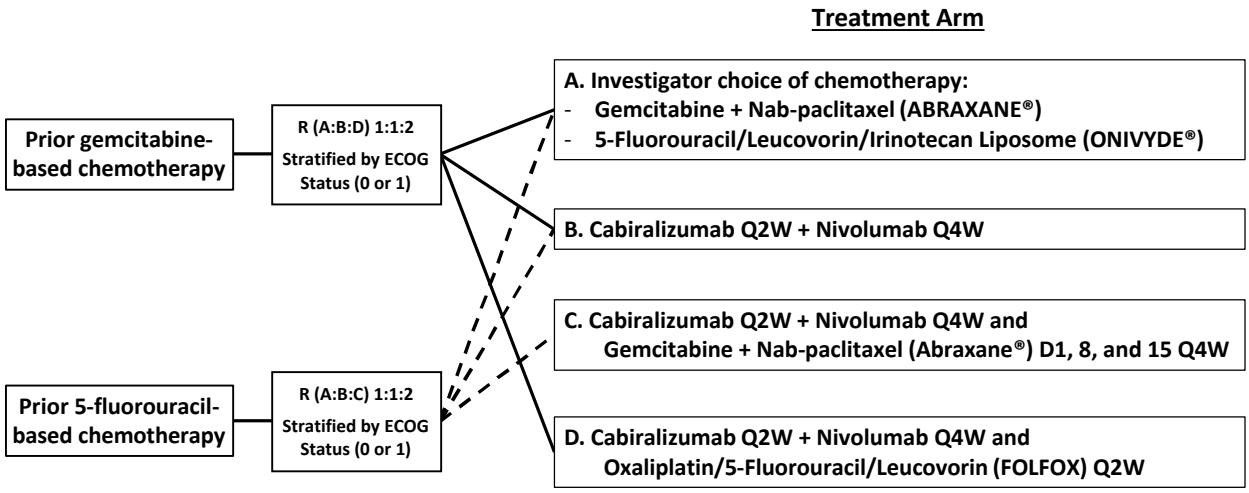
Abbreviations: 5-FU = 5-fluorouracil; [redacted] AE = adverse event; BICR = blinded independent central review; [redacted] ORR = objective response rate; OS = overall survival; OSR = overall survival rate; PFS = progression-free survival; PFSR = progression-free survival rate; [redacted] RECIST = Response Evaluation Criteria In Solid Tumors; SAE = serious adverse event; [redacted]

Overall Design:

This is a Phase 2, open-label, randomized study to evaluate the efficacy, safety, tolerability, [redacted] of cabiralizumab in combination with nivolumab with or without gemcitabine + nab-paclitaxel or oxaliplatin, 5-FU, and leucovorin (calcium folinate; FOLFOX), or an alternative choice of chemotherapy, in participants with locally advanced/metastatic pancreatic tumors who have progressed during or after no more than 1 line of systemic chemotherapy (either gemcitabine-based or 5-FU-based) in the metastatic setting.

The study design schematic is presented below.

Study Design Schematic



Note: ONIVYDE-based regimen can be substituted with FOLFIRI.

Abbreviations: ECOG = Eastern Cooperative Oncology Group; Q2W = every 2 weeks; Q4W = every 4 weeks; R = randomized.

Six participants per arm in both Treatment Arms C and D were treated and monitored for 4 weeks as part of a preliminary safety cohort. [redacted] Enrollment was allowed to proceed after completion of the safety lead-in period.

Number of Participants:

Approximately 160 participants will be treated (approximately 40 participants in each treatment arm). The false positive rate (FPR) is set at approximately 20%, and the false negative rate (FNR) is set at approximately 10%. The median PFS is assumed as 3.1 months in Treatment Arm A based on the NAPOLI-1 study and 5.4 months in Treatment Arms C and D by combining cabiralizumab and nivolumab with chemotherapy. In this setting, it will be required to observe at least 59 PFS events in each of Treatment Arms A and C and Treatment Arms A and D. If assuming a fixed accrual rate of 16 participants per month with equal distribution across 4 treatment arms, a total of approximately 80 participants are needed to be treated for Treatment Arms A and C (or D) in order to achieve the 59 PFS events required. In case a lower FPR is desired, a longer follow-up or additional participants may be treated in order to observe additional PFS events.

Treatment Arms and Duration:

- **Treatment Arm A:** Investigator choice of chemotherapy (gemcitabine + /nab-paclitaxel [ABRAXANE®] or 5-FU/leucovorin [calcium folinate]/irinotecan liposome [ONIVYDE®]*).
  *ONIVYDE-based regimen can be substituted with FOLFIRI.
- **Treatment Arm B:** Cabiralizumab administered in combination with nivolumab.

- **Treatment Arm C:** Cabiralizumab administered in combination with nivolumab and gemcitabine + nab-paclitaxel (ABRAXANE®).
- **Treatment Arm D:** Cabiralizumab administered in combination with nivolumab and oxaliplatin/5-FU/leucovorin (calcium folinate; FOLFOX).

Participants will be allowed to continue study treatment until the first occurrence of any of the following situations:

- Progressive disease defined per RECIST v1.1, unless participants meet criteria for treatment beyond progression.
- Clinical deterioration suggesting that no further benefit from treatment is likely.
- Intolerability to therapy.
- Participant meets criteria for discontinuation of study treatment.
- Withdrawal of consent.

Study treatment:

Treatment Arm(s)	Study Treatment	Unit Dose Strength(s)/Dosage Level(s)	Dosage Formulation Frequency of Administration (28-day Cycle)	Route of Administration
A	**Investigator choice of chemotherapy**	As appropriate	As appropriate	As appropriate
B, C, and D	**Cabiralizumab**	4 mg/kg IV	Days 1 and 15	IV Infusion
B, C, and D	**Nivolumab**	480 mg IV	Day 1	IV Infusion
C	**Gemcitabine**	1000 mg/m^2 IV	Days 1, 8, and 15	IV Infusion
C	**Nab-paclitaxel (ABRAXANE®)**	125 mg/m^2 IV	Days 1, 8, and 15	IV Infusion
D	**Oxaliplatin**	85 mg/m^2 IV	Days 1 and 15	IV Infusion
D	**5-FU**	400 mg/m^2 Bolus AND 2400 mg/m^2 IV	Days 1 and 15	Bolus and IV Infusion
D	**Leucovorin (calcium folinate)**	400 mg/m^2 IV	Days 1 and 15	IV Infusion

Abbreviations: 5-FU = 5-fluorouracil; IV = intravenous; Q2W = every 2 weeks; Q4W = every 4 weeks

Data Monitoring Committee: No

[redacted]

[redacted]

2 SCHEDULE OF ACTIVITIES

Study assessments and procedures are presented in Table 2-1 (Screening Procedural Outline), Table 2-2 (On-treatment Procedural Outline), and Table 2-3 (Follow-up Procedural Outline).

In limited circumstances, assessments and procedures may occur outside the indicated timeframes due to scheduling issues, but the Sponsor should be notified accordingly.

Table 2-1: Screening Procedural Outline

Procedure	Screening Visit (Day -30 to Day-1)	Notes
Eligibility Assessments		
Informed Consent	X	A participant is considered enrolled only when a protocol specific informed consent is signed.
IRT Participant Assignment/Treatment Assignment	X	After the participant consents, the site will use the IRT to have the participant number assigned. After the participant has completed all screening procedures, IRT will be used for treatment assignment or discontinuing the participant. Subsequent visits will need to be registered into the IRT system for drug supply.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose.
Medical History	X	Include any toxicities or allergy related to previous treatments, irAEs, cardiac signs/symptoms/disease, and immunization (eg, influenza vaccine).
Prior Systemic Therapies	X	Including radiotherapy, surgery, and systemic therapy.
ECOG Status Assessment	X	See Appendix 6
Archived Tumor Tissue Sample	X	Archival tumor tissue samples, if available, may be provided for participants in all arms as 1 paraffin block or 20 FFPE unstained slides. Samples must be shipped to the central laboratory.
Fresh Pretreatment Tumor Biopsy	X	**All participants require a mandatory pretreatment biopsy[a] during screening** **Biopsy samples must be documented to have adequate tumor content for molecular analyses prior to participant treatment** • Tumor samples must be obtained from a metastatic tumor lesion or from an unresectable primary tumor lesion. • Tumor content may be evaluated either by local pathology H&E or submission to the central laboratory for central assessment of tumor content. • Up to approximately 20% of the cohort will be allowed on treatment with a pretreatment biopsy that does not yield adequate tumor tissue, beyond that, re-biopsy may be performed if the sample has been inadequately prepared or contains insufficient tumor content

Table 2-1: Screening Procedural Outline

Procedure	Screening Visit (Day -30 to Day-1)	Notes
		• If adequate tumor tissue is confirmed from a biopsy done in the preceding 90 days with no intervening therapy and at least 20 unstained slides are available, the sample may replace the mandatory pretreatment biopsy. Residual sample(s) may be retained for additional research.
Safety Assessments		
PE	X	If the screening PE is performed within 24 hours prior to dosing on Day 1, then a single exam may count as both the screening and predose evaluation.
Physical Measurements	X	Includes height and weight.
Vital Signs	X	Includes body temperature, respiratory rate, and seated blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.
Concomitant Medication Use	X	Medications taken within 4 weeks prior to study treatment administration must be recorded on the CRF.
12-lead ECG	X	12-lead ECGs should be recorded after the participant has been supine for at least 5 minutes.
Clinical Complaints	X	Clinical complaints related to the disease under study present 14 days prior to the first dose of study treatment must be collected.
Laboratory Tests		Includes blood and urine samples.
Serology, Hematology, Serum Chemistry, Urinalysis, and Thyroid Panel	X	See Section 9.4.4.
Pregnancy Test (Serum or Urine)	X	For WOCBP only; serum will be collected at **screening and within 24 hours prior to dosing**. The serum pregnancy test may be completed on the first day of treatment provided that the results are available before the start of study treatment. If performed within 24 hours of dosing on Cycle 1 Day 1, then Cycle 1 Day 1 pregnancy test is not required.
Follicle Stimulating Hormone	X	Women only if needed to confirm post-menopausal status. Refer to Appendix 4.
[redacted]		

Table 2-1: Screening Procedural Outline

Procedure	Screening Visit (Day -30 to Day-1)	Notes
[redacted]		
Adverse Event Reporting		
Monitor for Serious Adverse Events	X	All SAEs must be collected from the date of the participant's written consent until 100 days after discontinuation of dosing or the participant's participation in the study if the last scheduled visit occurs at a later time. eSAEs should be approved in the electronic capture system within 5 business days of entry.
Efficacy Assessments		
Disease Assessment	X	Please see inclusion criteria (Section 6.1) for details.
Body Imaging/Baseline Tumor Assessment	X	See Section 9.1.1. Assessed by RECIST v1.1 criteria (see Appendix 5). Must be performed within 30 days prior to first dose
Brain Imaging	X	See Section 9.1.2. MRI of the brain without and with contrast is required for participants with suspected brain metastases.
Other: Bone scan	X	See Section 9.1.2. As clinically indicated per local standards.

Abbreviations: AE = adverse event; BMI = body mass index; CRF = Case Report Form; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eSAE = electronic serious adverse event; FFPE = formalin-fixed paraffin-embedded; HIV = human immunodeficiency virus; irAE = immune-related adverse event; IRT = Interactive Response Technology; MRI = magnetic resonance imaging; PE = physical examination; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SAE = serious adverse event; WOCBP = women of childbearing potential

[a] Samples collected after the last cancer treatment (either systemic or local) will be considered as fresh biopsies.

Table 2-2: On-Treatment Procedural Outline

Procedure	Cycle 1 and Cycle 2					Subsequent Cycles			EOT	Notes
	D1 ± 2 days	D2 ± 2 days	D8 ± 2 days	D15 ± 2 days	D21 ± 2 days	D1 ± 2 days	D8[a] ± 2 days	D15 ± 2 days		
Safety Assessments										
PE	X			X		X		X	X	Predose.
Symptom-directed PE		X	X		X					As needed, if clinically indicated.
ECOG Performance Status	X			X		X		X	X	ECOG score (Appendix 6).
Vital Signs	X			X		X		X	X	See note in screening procedures. Vital Signs to be collected for every treatment arm before infusion of the first drug on Day 1 and Day 15. Approximately the same time as ECG Cycle 1 and Cycle 5 Only. • For cabiralizumab (BMS-986227), vital signs will be obtained before the infusion and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the infusion. • For nivolumab, vital signs will be obtained before the infusion and 10 minutes (± 5 minutes) after completion of the infusion. If any vital sign is abnormal (based on clinician's assessment) at the final check, the participant must be observed for a further period of time, as clinically indicated.

Table 2-2: On-Treatment Procedural Outline

Procedure	Cycle 1 and Cycle 2					Subsequent Cycles			EOT	Notes
	D1 ± 2 days	D2 ± 2 days	D8 ± 2 days	D15 ± 2 days	D21 ± 2 days	D1 ± 2 days	D8[a] ± 2 days	D15 ± 2 days		
ECG	X					X			X	See note in screening procedures. Single Lead ECG tests will be conducted for all participants prior to the start of the infusion of the first drug Initial 6 participants enrolled in Treatment Arms C and D only: 12-lead ECG to be performed at both predose and 4 hours postdose on Cycle 1Day 1 only
Laboratory Tests										See note in screening procedures and Section 9.4.4. Predose on Day 1.
Chemistry, Hematology, Thyroid Panel, and Urinalysis	X		X	X	X	X	X[a]	X	X	
Pregnancy Test	X					X			X	WOCBP: Serum or urine pregnancy test must be performed within 24 hours prior to administration of study treatment and on Day 1 of each cycle.
AE Reporting and Concomitant Medication Assessments										
Concomitant Medication Assessments	X									Review prior to dosing.
Monitor for Non-serious Adverse Events	X									Non-serious AEs will be collected starting with the first dose of study treatment and through 100 days after last dose of study drug.
Monitor for Serious Adverse Events	X									See note in screening procedures.

Table 2-2: On-Treatment Procedural Outline

Procedure	Cycle 1 and Cycle 2					Subsequent Cycles			EOT	Notes
	D1 ± 2 days	D2 ± 2 days	D8 ± 2 days	D15 ± 2 days	D21 ± 2 days	D1 ± 2 days	D8[a] ± 2 days	D15 ± 2 days		
Sample Collections										
[redacted]										

Table 2-2: On-Treatment Procedural Outline

Procedure	Cycle 1 and Cycle 2					Subsequent Cycles			EOT	Notes
	D1 ± 2 days	D2 ± 2 days	D8 ± 2 days	D15 ± 2 days	D21 ± 2 days	D1 ± 2 days	D8[a] ± 2 days	D15 ± 2 days		
Efficacy Assessments										
Body Imaging/Radiographic Tumor Assessments	See Section 9.1.1									Tumor assessments should occur every 8 weeks (starting from first dose ± 7 days) for the first 48 weeks, then every 12 weeks (± 7 days) until withdrawal of consent, death, or initiation of another anti-cancer treatment, whichever occurs first.
Other: Brain Scan / Bone Scan	See Section 9.1.2									As clinically indicated per local standards.
[redacted]										

Table 2-2: On-Treatment Procedural Outline

Procedure	Cycle 1 and Cycle 2					Subsequent Cycles			EOT	Notes
	D1 ± 2 days	D2 ± 2 days	D8 ± 2 days	D15 ± 2 days	D21 ± 2 days	D1 ± 2 days	D8[a] ± 2 days	D15 ± 2 days		
Clinical Drug Supplies										
Randomize										Randomization should occur no more than 3 business days prior to the first day of treatment on Cycle 1 Day 1, unless otherwise agreed upon with the Medical Monitor.
Study Drug Administration	See Table 7.1-1									Dosing calculations for cabiralizumab are based on the body weight assessed at Cycle 1 Day 1. Weight measurements should be repeated prior to each dosing of cabiralizumab.

Abbreviations: [redacted] D = day; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; PE = physical examination; [redacted] RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1; WOCBP = women of childbearing potential

[a] Only for participants treated with gemcitabine and nab-paclitaxel (ABRAXANE).

Table 2-3: Follow-up Procedural Outline

Procedure	Safety Follow-up[a]			Survival/Response Long-term Follow-up	Notes
	FU 1 30 days (± 7 days)	**FU 2 60 days (± 7 days)**	**FU 3 100 days (± 7 days)**	**Begins After Completion of Safety Follow-up Q12W (± 2 weeks) Until 2 Years After Last Dose of Study Treatment**	
Safety Assessments					
System-directed PE	X	X	X		Targeted, system-directed PE only.
Physical Measurements	X	X	X		Weight only
Vital Signs	X	X	X		See note in screening procedures.
ECGs	X	X	X		See note in screening procedures.
ECOG Performance Status	X	X	X		ECOG score (Appendix 6)
Laboratory Tests					See note in screening procedures.
Serum Chemistry, Thyroid Panel, and Hematology	X	X	X		
Urinalysis	As clinically indicated				
Pregnancy Test	X	X	X		
Adverse Event Reporting					
Concomitant Medication Assessments	X	X	X		
Monitor for Non-serious Adverse Events	X	X	X		See note in screening procedures.
Monitor for Serious Adverse Events	X	X	X		See note in screening procedures.

Table 2-3: Follow-up Procedural Outline

Procedure	Safety Follow-up[a]			Survival/Response Long-term Follow-up	Notes
	FU 1 30 days (± 7 days)	**FU 2 60 days (± 7 days)**	**FU 3 100 days (± 7 days)**	**Begins After Completion of Safety Follow-up Q12W (± 2 weeks) Until 2 Years After Last Dose of Study Treatment**	
Efficacy Assessments					
Body Imaging/Radiographic Tumor Assessment	See Section 9.1.1				Tumor assessments should occur every 12 weeks (± 7 days) until withdrawal of consent, death, or initiation of another anti-cancer treatment, whichever occurs first.
Other: Brain Scan / Bone Scans	See Section 9.1.2				As clinically indicated per local standards.
[redacted]					

Abbreviations: ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FU = Follow-up; PE = physical examination; MRI = Magnetic Resonance Imaging; Q12W = every 12 weeks.

[a] Follow-up visits at Days 30, 60, and 100 (± 7 days each) should occur after the last dose or on the date of discontinuation (± 7 days)

In the event that multiple procedures are required at a single time point, the following is a list of procedures from highest to lowest priority:

[redacted]

2) Safety (electrocardiogram [ECG])
3) Clinical laboratory assessments

3 INTRODUCTION

CA025006 is a Phase 2 study of cabiralizumab (a recombinant, humanized immunoglobulin G4 [IgG4] monoclonal antibody [mAb] that binds to human colony-stimulating factor 1 receptor [CSF1R]; BMS-986227 or FPA008) in combination with nivolumab (a programmed cell death-1 [PD-1] receptor blocking mAb) with or without chemotherapy in participants with advanced/metastatic pancreatic cancer who have progressed on or after 1 line of chemotherapy (Second-line [2L] Cohort).

In this study, the efficacy, safety profile, tolerability [redacted] of cabiralizumab administered in combination with nivolumab, with or without chemotherapy, will be evaluated versus standard-of-care chemotherapy.

In the 2L Cohort, cabiralizumab will be administered in combination with nivolumab (Treatment Arm B), nivolumab and gemcitabine + nab-paclitaxel (ABRAXANE®; Treatment Arm C), or nivolumab and oxaliplatin/5-fluorouracil (5-FU)/leucovorin (calcium folinate; FOLFOX; Treatment Arm D), or participants will receive investigator's choice of reference standard-of-care chemotherapy alone (Treatment Arm A).

3.1 Study Rationale

Pancreatic ductal adenocarcinoma (PDAC) remains a dreadful diagnosis due to its often advanced stage at diagnosis and poor sensitivity to chemotherapy. Treatment options for patients with metastatic pancreatic cancer are limited. Gemcitabine combined with nab-paclitaxel (ABRAXANE®) is a United States (US) Food and Drug Administration (FDA) approved 1L treatment for patients with advanced pancreatic cancers. This regimen showed a median progression-free survival (PFS) of 5.5 months and a median overall survival (OS) of 8.5 months and is the predominantly used regimen in metastatic pancreatic cancer.

Immunotherapy has emerged as a therapeutic approach that offers effective and durable treatment options for subsets of patients with various types of cancer. However, these successes have not manifested similar benefits for PDAC patients mostly due to a lack of pre-existing T-cell immunity and/or a highly immunosuppressive tumor microenvironment (TME). [redacted] The addition of chemotherapy could further potentiate the anti-tumor effects of immunotherapy approaches by reducing the tumor burden, exposing antigens and directly affecting the immunosuppressive TME compartment.

To explore the synergy of the proposed combinatorial approach, cabiralizumab in combination with nivolumab with or without chemotherapy will be administered to participants who have progressed on or after 1 line of systemic chemotherapy in the metastatic setting.

3.1.1 Rationale for Selection of Patients with Advanced Pancreatic Cancer

Despite a relatively low incidence projected for 2017 (53,670 new cases), PDAC is expected to be the third leading cause of cancer-related deaths (mortality 43,090) in the US in 2017. In Europe, PDAC was the fourth most fatal cancer in 2014, accounting for 82,300 deaths with a life

expectancy of 5% at 5 years. A similar trend is observed in Japan, where 40,000 new cases of PDAC were expected for 2016 with 33,700 deaths.[1]

The high mortality observed worldwide can be explained by the often advanced stage at diagnosis and the poor responses to conventional chemotherapy treatments.

3.1.1.1 Rationale for the 2L Cohort

In 2015, the FDA granted its first approval for a chemotherapy combination to treat patients with advanced pancreatic cancer that has progressed after gemcitabine-based chemotherapy. Unfortunately, even these new agents can only provide minor improvements in outcomes. The combination of ONIVYDE® (irinotecan liposome injection) with fluorouracil and leucovorin (calcium folinate) resulted in an increase in median OS to 6.1 months compared with 4.2 months with fluorouracil/leucovorin (calcium folinate). In addition, these regimens also have significant toxicity and additional options are clearly needed in advanced pancreatic cancer.

Thus, development of newer and novel agents in the treatment of diseases resistant to chemotherapy such as PDAC is an area of unmet need.

Taken together, these data highlight the refractory nature of the disease to conventional treatment approaches and the need for alternative therapeutic options for patients diagnosed with advanced/metastatic pancreatic cancer that progress after the 1L of chemotherapy.

3.1.2 Rationale for Inhibiting CSF1R in Cancer

Macrophages are myeloid-derived cells that carry out a variety of functions in the human body. They can colonize tissues and tumors through two distinct mechanisms: hematogenous seeding from circulating monocytes or local self-renewal in the form of tissue-resident macrophages.[2] Recent studies have shown that macrophages exert their physiological effect within, and play roles unique to, the tissues in which they are active.[3] Macrophage regulation is complex as these cells actively secrete and respond to multiple cytokine and chemokine gradients within their local environment. Macrophages are among the most abundant immune cell types in the TME. Based on their opposing functions, macrophages can be classified into 2 major phenotypes, M1 and M2. M1 macrophages are immunostimulatory and tumor suppressive, while M2 macrophages are immunosuppressive and tumor promoting. Substantial evidence suggests that TAMs are polarized towards an anti-inflammatory M2 phenotype.[4] Consistent with this, increased levels of TAMs are associated with a poor prognosis in the majority of cancers.[5] Based on their tumor-promoting phenotype, TAMs have become an attractive therapeutic target.

CSF1R signaling plays a fundamental role in the differentiation, maintenance, and function of macrophages.[6] There are 2 ligands for CSF1R: CSF1 and IL34. These agonists bind to overlapping regions of CSF1R with similar affinity.[7] Mice lacking CSF1R, CSF1, or IL34 have deficiencies in macrophages, underscoring the essential role of the CSF1R pathway in the biology of this cell type.[7,8] Pharmacologic treatments that block CSF1R in cancer settings are expected to reduce or reprogram M2 TAMs and reduce immune suppression. Following treatment with anti-CSF1R agents, the remaining macrophage compartment may be repolarized from an M2

immunosuppressive state to an M1 anti-tumor state, which would support T-cell responses. This conversion associated with concurrent treatment modalities, such as anti-PD-1 treatment, could have an increased effect on reduction of tumor growth.[9] Support for targeting CSF1R in cancer comes from animal studies in which antibody or small molecule inhibition of CSF1R decreases M2 TAMs resulting in decreased immune suppression and a more robust cytotoxic T-cell response.[10,11,12] Cabiralizumab is a recombinant, humanized IgG4 mAb that binds to human CSF1R. The interaction of cabiralizumab and CSF1R antagonizes the binding of both CSF1 and IL34 to CSF1R, thereby preventing receptor activation. In vitro, cabiralizumab inhibits CSF1 and IL34-induced proliferation and survival of peripheral blood monocytes. In vivo, cabiralizumab inhibits the survival of subsets of monocytes and macrophages.

Taken together, these and other emerging data suggest that blocking CSF1R with cabiralizumab treatment may reduce immunosuppression in the tumor environment generated by TAMs and enhance the efficacy of immune-based anti-cancer therapies including nivolumab.

3.1.3 Rationale for Immunotherapy

Antibody-based therapy for cancer has become established in recent years and is now one of the most successful and important strategies for treating patients with hematological malignancies and advanced solid tumors.[13] Aside from targeting antigens that are involved in cancer-cell proliferation and survival, antibodies can also function to either activate or inactivate immunological pathways that are important in cancer immune surveillance.[14] It is now clear that an antigen-specific anti-cancer immune response is the result of a complex dynamic interplay between the T lymphocyte cells (T cells), the TME, and the target cancer cells. The critical balance of T-cell activity that dictates whether endogenous anti-tumor immune responses will be effective are largely understood to be controlled by antigen-specific stimuli sensed by the T-cell receptor and by the combined activity of both positive (co-stimulatory) and negative (co-inhibitory) T-cell surface molecules.[15] Within the past decade, antibodies against these key receptors have been designed and evaluated in the clinic with impressive results, heralding the onset of immunotherapy as a key pillar of anti-cancer therapy.[16]

The most extensively studied immunotherapies in cancer target the negative regulatory receptors cytotoxic T-lymphocyte antigen-4 (CTLA-4) or PD-1.[17] Inhibition of these negative regulatory receptors, referred to as immune checkpoint blockade, results in the enhanced activation of T-cell responses and potent anti-tumor activity in nonclinical models. Studies with CTLA-4 blockade provided the first clinical evidence of improvement in OS with immune modulatory anti-cancer therapy in patients with metastatic melanoma.[18,19] Following that, Topalian et al showed that anti-PD-1 antibody therapy resulted in objective responses in patients with melanoma, non-squamous cell lung cancer (NSCLC), and renal cell carcinoma (RCC).[20]

The TME plays a central role in determining the pro-inflammatory or immunosuppressive nature of the anti-tumor responses. Emerging data on the role of the TAMs and their impact on tumor progression and prognosis supported the development of antibodies that specifically target TAMs, and currently, several antibodies targeting TAMs are being tested in multiple clinical trials.

With recent emerging clinical evidence of significant anti-tumor activity of single-agent immunotherapies, combination therapies are now being explored because they could lead to greater depth of response and OS.

3.1.4 Rationale for Combining Cabiralizumab and Nivolumab

Given the complex nature of an anti-tumor immune response, effective cancer therapy may require combining multiple immunotherapy agents.

In an orthotopic PDAC model, CSF1R pathway blockade selectively decreased immunosuppressive TAMs, reduced immunosuppression, and skewed the remaining macrophage population to a pro-inflammatory state, which increased the anti-tumor $CD8^+$ T-cell response.[11] This, in turn, produced an increased interferon response that upregulated T-cell checkpoint inhibitors, including programmed death-ligand 1 (PD-L1), on tumor cells. This counter-regulation served to limit the anti-tumor T-cell response through engagement of the T-cell inhibitor PD-1. Anti-PD-1 treatment was able to overcome the PD-L1-mediated inhibition. Anti-PD-1 or CSF1R pathway inhibitors as single agents showed limited efficacy in restraining PDAC tumor growth in this model, but combining anti-PD-1 with CSF1R blockade potently elicited tumor regression even in large established tumors.[21]

In a recent clinical study, RG7155 (a CSF1R-targeting antibody) was tested in subjects with solid tumors and was shown to substantially reduce $CSF1R^+$ and $CD163^+$ macrophages in tumors.[11] This reduction in macrophages was associated with a shift toward cytotoxic $CD8^+$ T cells, similar to what was observed in the mouse tumor models. These data suggest that TAMs behave similarly in humans and mice to suppress the anti-tumor immune response.

Preliminary data from FPA008-003 clinical trial showed how the combination of cabiralizumab and nivolumab was able to induce durable partial responses (PR) in a cohort of patients with advanced, metastatic pancreatic cancer (see Section 5.4.2 for details)

The totality of the data suggests that reprogramming the TAM compartment in tumors via cabiralizumab-mediated CSF1R blockade could reduce immunosuppressive TAMs in the TME and increase $CD8^+$ T-cell anti-tumor responses. However, PD-L1 expression in the TME could still be acting to restrain the anti-tumor CD8 response. The addition of an anti-PD-1 agent, such as nivolumab, could remove the negative effect of the PD-L1 upregulation.

3.1.5 Rationale for Combining Immunotherapy and Chemotherapy Regimens

Until recently, chemotherapy was thought to have negative effects on the immune system by reducing the lymphocyte numbers and inhibiting the expansion of activated lymphocytes. In reality, chemotherapy can promote the anti-tumor effects of the immune system by decreasing tumor burden, promoting immunogenic cell death, and interfering with the immunosuppressive TME.[22] The effects of paclitaxel on the microtubule dynamics and the induction of apoptosis are well known. In addition to the cytotoxic effects, paclitaxel can modulate the TME in a variety of ways.[22] Paclitaxel can induce macrophage activation and release of inflammatory cytokines in mouse models[23] and can induce apoptosis on regulatory T cells, thus reducing their

immunosuppressive abilities.[24] Gemcitabine, in addition to the antimetabolite effects on cancer cells, can also promote an immune inflammatory environment by selectively decreasing the infiltration of myeloid suppressor cells in the TME, and cisplatin can stimulate immune responses by activating antigen-presentation capacities of macrophages.[25,26]

On the other hand, immunotherapy can, in addition to the direct effects on the immune system, affect the metabolism and the effects of chemotherapy. TAMs are directly implicated in increasing the resistance to gemcitabine and cisplatin by upregulating cytidine deaminase (CDA) in tumor cells. The CDA is an enzyme that metabolizes gemcitabine and cisplatin into their inactive forms, thus reducing the apoptotic effects of these drugs on cancer cells.[27]

A proof of principle of synergy between chemotherapy and checkpoint inhibitors has been provided by the approval in May 2017 of pembrolizumab in combination with pemetrexed and carboplatin for the treatment of subjects with previously untreated metastatic NSCLC. In this setting, the combination of immunotherapy and chemotherapy showed improvement over chemotherapy in ORR (55% versus 29%, respectively) and PFS (13 months versus 8.9 months, respectively).[28]

Considering the central role of TAMs and T cells in influencing the anti-tumor responses in pancreatic cancer and the role of chemotherapy to target the tumor cells and support the responses of the immune system, the combination of chemotherapy and immunotherapy represents a promising approach to improve the response rate of this otherwise deadly disease.

Despite the increased experience with approaches that combine chemotherapy and immunotherapy, the potential for overlapping toxicities in the setting of combination therapies cannot be excluded. As a consequence, the seriousness, relatedness, frequency, severity and causality of the adverse events (AEs) can be different from what is usually observed after administration of chemotherapy or immunotherapy alone.

[redacted] In addition, all agents that will be used in the proposed combinations have shown well-defined toxicity profiles based on a safety database comprised of participants treated with either monotherapy or combinations across multiple tumor types. The combination of nivolumab with gemcitabine + nab-paclitaxel in 1L pancreatic cancer was shown to be safe in a Phase 1/2 study.[29] Among participants with previously untreated pancreatic cancer treated with nivolumab and gemcitabine + nab-paclitaxel, 1 dose-limiting toxicity (DLT) of Grade 3 non-immune hepatitis was reported and attributed to gemcitabine. The participant with this DLT was able to continue on treatment with nivolumab and nab-paclitaxel without any further episodes of hepatitis. Anemia was the only Grade 3 or higher treatment-emergent AE reported in more than 1 participant in Arm B. Out of the 6 DLT-evaluable participants in Arm B, 3 had PRs and 3 had stable disease (SD). [redacted]

The current protocol was designed to detect and manage AEs as early as possible. To maximize the safety of the participants enrolled in this study and to better characterize the risk for potential overlapping toxicities between immunotherapy and chemotherapy, a preliminary safety cohort was implemented for the 2L Cohort Treatment Arms C and D. Six participants per arm in both Treatment Arms C and D have been treated and monitored for 4 weeks. [redacted]

In addition, across the entire trial, special attention is given to liver enzyme alterations since they can be associated with either cabiralizumab, nivolumab, or chemotherapy. Guidelines for the management of laboratory abnormalities and immune-mediated adverse events (IMAEs) are included in the protocol (Appendix 7 and Appendix 8) as well as guidelines for dose reduction for chemotherapy and immunotherapy (Section 7.4).

Frequent safety assessments will be carried out by the Sponsor/BMS Medical Monitor (or designee) and investigators throughout the study to determine whether dose modification, additional safety measures, or termination of the study treatment combination arm is required at any time. The AEs and serious AEs (SAEs) will be reviewed regularly by the BMS Medical Monitor (or designee) and the Pharmacovigilance group to look for trends and potential safety signals. Treatment of AEs will follow institutional guidelines and recommended management algorithms, as listed in the Investigator Brochures (IB) and prescribing information, as applicable, for each combination agent and contemporaneous control comparator.

3.2 Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of cabiralizumab and nivolumab are provided in the IB for each product.[30,31]

3.2.1 Cabiralizumab

3.2.1.1 Mechanism of Action

The TME, composed of non-cancer cells and stroma, is recognized as a major factor influencing the growth of tumor cells. TAMs are particularly abundant in the TME and are thought to play a key role in promoting tumor growth. Substantial evidence suggests that TAMs are polarized towards an anti-inflammatory phenotype and through the expression of cell surface T-cell inhibitors and immunosuppressive soluble factors play a major role in inhibiting anti-tumor immune responses.[4] In the majority of tumors, TAMs are associated with a poor prognosis,[5] making TAMs an attractive therapeutic target. Because CSF1 is a major survival factor for TAMs, targeting CSF1R with cabiralizumab should reduce TAM-mediated immune suppression.

Cabiralizumab is a recombinant, humanized IgG4 monoclonal antibody that binds to human CSF1R. Cabiralizumab contains a single amino acid substitution in the hinge region to prevent hemi-dimer exchange. Binding of cabiralizumab to CSF1R antagonizes its natural ligands, CSF1 and IL34, thereby preventing activation of CSF1R.

Cabiralizumab inhibits both CSF1- and IL34-induced CSF1R phosphorylation in a cell line engineered to overexpress CSF1R (CHO-CSF1R), demonstrating that cabiralizumab blocks the activation of ligand-induced CSF1R signaling pathways. Cabiralizumab also inhibits CSF1- and IL34-induced proliferation and survival of peripheral blood monocytes in vitro, demonstrating that cabiralizumab inhibits not only the initiation of CSF1 and IL34 signaling pathways but also the subsequent physiologic responses of primary human monocytes to these ligands.

CSF1R is expressed on cells of the monocyte/macrophage lineage, and signaling through CSF1R via its ligands, CSF1 and IL34, supports differentiation, maintenance, and function of monocytes, macrophages, and osteoclasts. TAMs are among the most abundant immune cell types in the TME. Substantial evidence suggests that TAMs are polarized toward an anti-inflammatory phenotype (M2 TAMs) and through both cell surface inhibitors and soluble factors, such as immunosuppressive cytokines, playing a major role in inhibiting anti-tumor immune responses.[4] CSF1 is a major survival factor for TAMs, and targeting CSF1R with cabiralizumab should reduce TAM-mediated immune suppression, resulting in strengthening the anti-tumor response to immunotherapy. Therefore, a drug that inhibits CSF1R should limit the immunosuppressive influence of TAMs on the TME and could be complementary and augment current cancer therapies.

3.2.1.2 Preclinical Summary

The PK profile of cabiralizumab is complex and characterized by nonlinear clearance that is likely mediated by binding to CSF1R on cells. [redacted] As target-mediated clearance becomes saturated at high or repeat doses, cabiralizumab clearance is similar to other human IgG antibodies.

[redacted]

In in vivo toxicology studies in cynomolgus monkeys, cabiralizumab was generally well tolerated. Test article-related findings included clinical observations, hematology and clinical chemistry changes, and histopathological 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 the edema did not show a clear relationship to exposure levels, but edema resolved after systemic clearance of the drug. Periorbital edema is a known side effect of drugs affecting the CSF1 pathway.[10] The main hematologic change was a

reversible decrease [redacted], which was considered a pharmacodynamic effect. [redacted] These laboratory abnormalities were not associated with any histopathological evidence of liver, cardiac, or muscle tissue injury. Additionally, cardiac troponin, skeletal troponin, myoglobin, and aldolase did not show any changes, further confirming the lack of any liver or muscle injury. The increased serum levels are attributed to diminished clearance of ALT, AST, CK, and LDH molecules from serum due to a reduced number of liver Kupffer cells.[32] [redacted]

The no-observable-adverse-effect level (NOAEL) for cabiralizumab was determined to be 100 mg/kg when administered for 13 weekly doses to cynomolgus monkeys, which provided a 32-fold safety factor based on body surface area calculation for the starting dose of 1 mg/kg in humans.

Since cabiralizumab does not cross-react to mouse CSF1R, a surrogate antibody, cmFPA008, was developed that binds and blocks mouse CSF1R with similar potency observed for cabiralizumab against human CSF1R. Binding of cmFPA008 to mouse CSF1R was demonstrated in a direct binding enzyme-linked immunosorbent assay (ELISA), and cmFPA008 inhibitory activity was demonstrated by its ability to inhibit CSF1- and IL34-induced proliferation of a CSF1/IL34-dependent cell line (mNFS60). The EC_{50} value for cmFPA008 binding to mouse CSF1R was 2.4 ng/mL, and the IC_{50} values for inhibition of mouse CSF1- and IL34-induced proliferation/survival of mNFS60 cells were 32.9 and 9.1 ng/mL, respectively. The ability of cmFPA008 to inhibit cancer growth in vivo was studied in an MC38 colon cancer model in immune-competent mice. These mice were selected to allow for the establishment of an intact tumor-immune interaction. [redacted] These data suggest that reduction of immunosuppressive macrophages by cmFPA008 results in a shift toward a greater cytotoxic T-cell response in the tumor.

For more detailed information or background on cabiralizumab, please refer to the cabiralizumab IB.[30]

3.2.1.3 Clinical Summary

The clinical summary of safety and efficacy is based on 4 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 2 or 3 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 in participants with pigmented villonodular synovitis (PVNS). As of 02-Jul-2018, approximately 54 participants have been treated.
3) Study FPA008-003 is evaluating the safety and efficacy of cabiralizumab as monotherapy and in combination with nivolumab in participants with advanced cancers. As of 02-Jul-2018, approximately 312 participants have been treated
4) Study CA025001 is evaluating the safety and efficacy of cabiralizumab as monotherapy and in combination with nivolumab in Japanese participants with cancer. As of 16-Jul-2018, approximately 13 participants have been treated.

Clinical Pharmacology Summary (Pharmacokinetics, Immunogenicity, and Pharmacodynamics)

The available PK, ADA [redacted] status following cabiralizumab treatment with either monotherapy or in combination with nivolumab were characterized in 3 trials: FPA008-001, FPA008-002, and FPA008-003. The PK, ADA [redacted] data from Study FPA008-003 are summarized below; data from Studies FPA008-001 and FPA008-002 are presented in the cabiralizumab IB.[30]

[redacted]

Study FPA008-003 – Advanced Cancer (Cabiralizumab Monotherapy)

In Phase 1a, participants with cancer received cabiralizumab at doses of 2, 4, or 6 mg/kg every 2 weeks (Q2W) as monotherapy or 1, 2, or 4 mg/kg Q2W in combination with nivolumab 3 mg/kg Q2W. There were a total of 25 participants (n = 16 for monotherapy and n = 9 for combination treatment) with PK data as of 15 December 2016. Blood samples for determination of serum cabiralizumab concentration were collected before dosing and at various times throughout the study. Blood samples for determination for anti-cabiralizumab antibodies were collected before dosing and at various time points from Day 15 to the end-of-treatment follow-up.

[redacted]

Assessment [redacted] in Study FPA008-003 has been evaluated in cohorts receiving cabiralizumab 2, 4, or 6 mg/kg monotherapy. In addition, assessment [redacted] has been evaluated in cohorts receiving a combination of cabiralizumab 1, 2, or 4 mg/kg with nivolumab 3 mg/kg. [redacted]

[redacted]

Clinical Safety Summary

Study FPA008-001 – Healthy Volunteers and Rheumatoid Arthritis

Thirty-six healthy volunteers and 18 RA participants received cabiralizumab in Study FPA008-001. No dose-limiting toxicities (DLTs) were reported and no unexpected treatment-related AEs have been reported in RA participants treated with 3 doses up to 6 mg/kg. Details relating to safety are included in the latest version of the cabiralizumab IB.[30]

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.[30]

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

As of 02-Jul-2018, AEs have been experienced by 264 of 265 (99.6%) participants treated with cabiralizumab 4 mg/kg + nivolumab 3 mg/kg Q2W across multiple cohorts, while treatment-related AEs were experienced in 245 of 265 (92.5%) participants treated with cabiralizumab 4 mg/kg + nivolumab 3 mg/kg Q2W.

Treatment-related AEs are summarized in Table 3.2.1.3-1

Table 3.2.1.3-1: FPA008-003: Phase 1a and Phase 1b Combination Therapy (N = 265) Summary of Incidence of Treatment-related Adverse Events Occurring in > 10% of Participants by Preferred Term Dosed with Cabiralizumab 4 mg/kg and Nivolumab 3 mg/kg

	Phase 1a and 1b Combination Therapy Cabiralizumab 4 mg/kg + Nivolumab 3 mg/kg Q2W Cohorts 1aC3, 1b1-1b7, and 1aE2-1aE4 N=265		
Preferred Term	**All Grades N (%)**	**Grade 3/4 N (%)**	**Grade 5 N (%)**
Total subjects with a treatment-related AE	245 (92.5)	135 (50.9)	3 (1.1)
Treatment-related AEs reported in > 10% of subjects			
Blood creatine phosphokinase increased	122 (46.0)	43 (16.2)	0
Periorbital edema	115 (43.4)	4 (1.5)	0
Fatigue	102 (38.5)	15 (5.7)	0
Aspartate aminotransferase increased	100 (37.7)	17 (6.4)	0
Alanine aminotransferase increased	51 (19.2)	3 (1.1)	0
Amylase increased	51 (19.2)	22 (8.3)	0
Rash	50 (18.9)	10 (3.8)	0
Pruritus	47 (17.7)	1 (0.4)	0
Lipase increased	44 (16.6)	20 (7.5)	0
Diarrhea	41 (15.5)	8 (3.0)	0
Nausea	41 (15.5)	1 (0.4)	0
Blood lactate dehydrogenase increased	32 (12.1)	3 (1.1)	0
Anemia	28 (10.6)	9 (3.4)	0

Source: Investigator Brochure for Cabiralizumab.[30]

Notes: All participants received cabiralizumab 4 mg/kg + nivolumab 3 mg/kg Q2W. Cohort 1aC3 is a Phase 1a combination therapy dose escalation part in participants (n=3) with selected advanced cancers. Cohorts 1b1-1b7 are Phase 1b combination therapy dose expansion parts in participants with PD-1 naive NSCLC (1b1; n=30), PD-1 resistant (de novo/acquired) NSCLC (1b2; n=31), SCCHN (1b3; n=30), pancreatic cancer (1b4; n=33), advanced ovarian cancer (1b5; n=31), RCC (1b6; n=30), or malignant glioma (1b7; n=30). Cohorts 1aE2-E4 are Phase 1a dose expansion parts in participants with melanoma (1aE2; n=11), anaplastic thyroid cancer (1aE3; n=1), or pancreatic cancer (1aE4; n=35).

Abbreviations: AE = adverse event; NSCLC = non-small cell lung cancer; PD-1 = programmed death-1; RCC = renal cell carcinoma; SCCHN = squamous cell carcinoma of the head and neck.

One hundred thirty-four of 265 participants (50.6%) receiving cabiralizumab 4 mg/kg + nivolumab 3 mg/kg Q2W experienced a treatment-related SAE (cabiralizumab or nivolumab). Related SAEs reported in at least 2 participants included: increased blood creatine kinase and pneumonitis (8 participants each), pneumonitis (5 participants each), colitis (4 participants each), acute respiratory

failure, brain edema, diarrhea, myocarditis, pancreatitis, pleural effusion, and troponin increase (2 participants each). All other treatment-related SAEs were reported in 1 participant each.

A total of 128 of 265 (48.3%) participants receiving cabiralizumab 4 mg/kg + nivolumab 3 mg/kg Q2W died during the course of the study. A total of 17 of 265 (6.4%) participants died due to an AE, and treatment-related Grade 5 AEs were experienced by 3 of 265 (1.1%) participants and included acute respiratory failure (2 [0.8%] participants) and respiratory distress (1 [0.4%] participant).

Overall, the combination of cabiralizumab and nivolumab appears to be manageable with a safety profile consistent with the individual components, and the frequency and types of IMAEs appear to be similar across multiple tumor types.

Details relating to safety are included in the latest version of the cabiralizumab IB.[30]

3.2.2 Nivolumab

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immuno-surveillance and escape effective innate and adaptive immune responses.[33,34,35] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[36] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA.[37] PD-1 signaling has been shown to inhibit CD28-mediated upregulation of IL-2, IL-10, IL-13, interferon-γ (IFN-γ) and Bcl-xL. PD-1 expression has also been noted to inhibit T-cell activation and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[38] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

PD-1 is a 55 kD type I transmembrane protein primarily expressed on activated T cells, B cells, myeloid cells, and antigen-presenting cells (APCs).[39] Binding of PD-1 to PD-L1 and programmed death-ligand 2 (PD-L2) has been shown to down-regulate T-cell activation in both murine and human systems.[27,37,40,41] PD-1/PD-L1 interactions may also indirectly modulate the response to tumor antigens through T-cell/APC interactions. Therefore, PD-1 engagement may represent 1

means by which tumors evade immuno-surveillance and clearance.[42] Blockade of the PD-1 pathway by nivolumab has been studied in a variety of preclinical in vitro assays, and anti-tumor activity using a murine analog of nivolumab has been shown in a number of immunocompetent mouse cancer models. Nivolumab is currently being evaluated extensively across a wide range of solid tumors and hematological malignancies. These findings provided the rationale for expanding the evaluation of PD-1 pathway blockade in combination with novel immunotherapy agents in clinical studies.

Nivolumab (BMS-936558) is a fully human, immunoglobulin G4 (IgG4) [kappa] isotype mAb that binds to PD-1 with nanomolar affinity (dissociation constant [Kd], 3.06 nM) with a high degree of specificity. In vitro, nivolumab binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4, and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction. Using a cytomegalovirus (CMV) re-stimulation assay with human peripheral blood mononuclear cells (PBMC), the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and results in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[43]

The nonclinical safety of nivolumab was evaluated in a comprehensive toxicology program in mice and monkeys and was submitted as part of Biologics License Application 125527.22. Details of the in vitro and in vivo nonclinical pharmacology studies conducted to support the development of nivolumab can be found in Section 4.1 of the Nivolumab IB.[31]

There is a potential for enhanced toxicity when combined with other immunotherapeutic agents. Combination nonclinical toxicology studies with cabiralizumab and nivolumab have not been conducted and are not required by the International Council on Harmonisation S9 Note for Guidance on Nonclinical Evaluation for Anticancer Pharmaceuticals. The safety of the combination will be carefully monitored in the planned clinical trial.

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

For nivolumab monotherapy, the safety profile is similar across tumor types. The only exception is pulmonary inflammation AEs, which may be numerically greater in participants with NSCLC. In NSCLC patients, it can be difficult to distinguish between nivolumab-related and nivolumab-unrelated causes of pulmonary symptoms and radiographic changes. Most AEs were low grade (Grades 1 to 2) with relatively few related high-grade (Grades 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level. These AEs have included pulmonary toxicity, renal toxicity (including acute renal failure), endocrine abnormalities, gastrointestinal (GI) toxicity, dermatologic toxicity (including rash), and hepatotoxicity. A pattern of IMAEs has been defined, for which management algorithms have been developed; these are provided in Appendix 7. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms. There is no relationship between the incidence, severity, or causality of AEs and the nivolumab dose level.

Nivolumab, alone or in combination with chemotherapy, is currently being tested for the treatment of advanced/metastatic PDAC. Preliminary results from Study CA209032 show that nivolumab, administered as monotherapy, was well tolerated in participants with advanced/metastatic PDAC. [redacted] In addition, the combination of nivolumab and gemcitabine + nab-paclitaxel is currently being tested as 1L treatment for participants with advanced/metastatic PDAC (NCT02309177). The combination appears to be well tolerated with a safety profile similar to the individual components. As of February 2017, 20 participants were evaluable for efficacy. The preliminary ORR is 25% (5 out of 20 participants experienced a PR). [redacted]

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

Additional details on the safety profile of nivolumab, including results from other clinical studies, are summarized in the Nivolumab IB.[31]

3.2.3 Clinical Experience Involving Serum Enzyme Elevations

The safety and preliminary efficacy of cabiralizumab is currently being evaluated in 4 clinical trials. A common feature observed across the clinical trials is an elevation of AST, CK, and LDH after the administration of cabiralizumab. These alterations are the consequence of the direct effect of anti-CSF1R antibodies on the Kupffer cell in the liver that results in a depletion of these cells. Depletion of Kupffer cells allows the enzymes, which are released following normally occurring liver cell turnover, to enter circulation (where they are measured by routine laboratory assessment) rather than being absorbed by the Kupffer cells. [redacted] The observed elevations were asymptomatic, not permanent, and not associated with clinical sequelae. Similar effects have been observed across other CSF1R targeted agents (see cabiralizumab IB for additional details). The data with

cabiralizumab and with other agents in the class suggest that the observed serum enzyme elevations do not compromise the safety profile of cabiralizumab and therefore support modification of the safety monitoring criteria.

3.2.3.1 Serum Enzyme Elevations with Cabiralizumab

In Study FPA008-003, 34 participants have been dosed as part of Phase 1a dose escalation (24 in cabiralizumab monotherapy and 10 in cabiralizumab + nivolumab combination therapy) and 195 participants have been dosed as part of Phase 1b dose expansion as of 01-Aug-2017. In Phase 1a, CK was elevated in 11 of 34 participants (32%), and 3 events (9%) were Grade 3 or higher. AST was elevated in 16 of 34 participants (47%), and 10 events (29%) were Grade 3 or higher. ALT was elevated in 4 of 34 participants (17%), and none of these were Grade 3 or higher. In Phase 1b, CK was elevated in 82 of 195 participants (42%), and 29 events (15%) were Grade 3 or higher. AST was elevated in 76 of 195 participants (39%), and 14 events (7%) were Grade 3 or higher. ALT was elevated in 39 of 195 participants (20%), and 5 events (3%) were Grade 3 or higher.

The serum enzyme elevations for Studies FPA008-001 and FPA008-002 follow a similar pattern. Please refer to the cabiralizumab IB for more detailed information about these serum enzyme elevations.

3.2.3.2 Management of Isolated Laboratory Abnormalities

[redacted] To rule out any potential hepatic injury in relation to elevated transaminases, additional monitoring following the Drug-Induced Liver Injury (DILI) Guidance from the FDA[44] will be performed for bilirubin, INR, and ALT/AST. In the case of elevated CK, additional assessments will be performed for CK isoenzymes (CK-MM, CK-MB, and CK-BB) and troponins (I or T). The investigator should notify the Sponsor of increased serum levels above specific cutoffs, but below those that would trigger drug modification or discontinuation. Additional monitoring of clinical signs and symptoms known to be associated with hepatic damage, per the FDA DILI Guidance, is recommended. These additional measures should be followed as per the guidance in Appendix 8.

3.3 Benefit/Risk Assessment

Patients with advanced/metastatic pancreatic cancer have a dismal prognosis due to the often advanced stage at diagnosis (see Section 3.1.1).

Two combination regimens, FOLFIRINOX and gemcitabine + nab-paclitaxel, have gained acceptance as front-line treatments. While these chemotherapy regimens have shown to improve survival of patients with advanced/metastatic pancreatic cancer, more than three-fourths of pancreatic cancer patients progress within 1 year of diagnosis. In addition, for patients that progress after 1L therapies, limited options are available (see Section 3.1.1); therefore, better treatment options are clearly needed for subjects that progress after 1L treatments.

The combination of immunotherapy and chemotherapy has been tested in multiple settings, with a manageable safety profile reported using established safety guidelines.[45,46] The combinations

also yielded substantial clinical efficacy as demonstrated by the combination of pembrolizumab with pemetrexed and carboplatin for the treatment of participants with previously untreated metastatic NSCLC.[28]

The combination of cabiralizumab and nivolumab, as demonstrated in Study FPA008-003, has a manageable safety profile that is minimally overlapping with that of the chemotherapy regimens being evaluated in this study. Preclinical evidence supports the potential advantages of combining immunotherapy and chemotherapy, but overall, the potential benefit of the proposed combination over standard-of-care chemotherapy is not yet known. Nevertheless, the dismal prognosis of patients with advanced pancreatic cancer and the lack of curative options support the need for novel combinatorial approaches.

The safety profile of cabiralizumab and nivolumab has been tested in > 250 participants. The frequency and types of immune-mediated adverse reactions are similar across multiple types of tumors and are described in the Reference Safety Information in the current cabiralizumab IB.[30] Management algorithms for IMAEs involving gastrointestinal, renal, pulmonary, hepatic, endocrine, skin, and neurologic systems are included in the protocol. The safety of the chemotherapy combinations with cabiralizumab and nivolumab will be carefully monitored. A preliminary safety cohort was planned and has been completed in the 2L Cohort Treatment Arms C and D of the current study. Six participants per arm in both Treatment Arms C and D were treated and monitored for 4 weeks. [redacted]

The mandated biopsies pose limited risk to the participant, which includes discomfort, pain, and bleeding. Because of the need to understand the effect of cabiralizumab and nivolumab with or without chemotherapy on the TME [redacted] the limited risk of a research biopsy is considered appropriate in an early-phase clinical trial research setting.

Continuous safety assessments will be utilized by the Investigators and BMS to determine whether dose modification, additional safety measures, or termination of the study is required at any time. In addition, AEs and SAEs will be reviewed on an ongoing basis by the BMS Medical Monitor and Global Pharmacovigilance and Epidemiology representatives to monitor for any safety signals or trends. As the combination of cabiralizumab and nivolumab with or without chemotherapy is an experimental treatment, it is possible that unforeseen, unknown, or unanticipated reactions may occur. The protocol was developed carefully balancing risks and benefits of treatment of a novel therapy in this patient population with an unmet medical need.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the PFS of cabiralizumab administered in combination with nivolumab with and without chemotherapy relative to investigator's choice of chemotherapy in participants with advanced/metastatic pancreatic cancer who progressed on or after the first line of chemotherapy (either gemcitabine-based or 5-FU-based chemotherapy).	• PFS per RECIST v1.1 by BICR
Secondary	
• To evaluate the anti-tumor activity of cabiralizumab administered in combination with nivolumab with or without chemotherapy relative to investigator's choice of chemotherapy in participants with advanced/metastatic pancreatic cancer who progressed on or after the first line of chemotherapy (either gemcitabine-based or 5-FU-based chemotherapy) using RECIST v1.1.	• PFS per RECIST v1.1 by investigator assessment; ORR, DOR, and PFSR at 6, 9, and 12 months per RECIST v1.1 by BICR and investigator assessment
• To assess OS.	• OS and OSR at 6 months, 1 year, and 2 years
• To assess the safety of cabiralizumab administered in combination with nivolumab with or without chemotherapy in participants with advanced/metastatic pancreatic cancer who progressed on or after the first line of chemotherapy (either gemcitabine-based or 5-FU-based chemotherapy).	• Incidence of AEs, SAEs, AEs leading to discontinuation, death, and laboratory abnormalities
[redacted]	
[redacted]	

[redacted]

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
[redacted]	

Abbreviations: 5-FU = 5-fluorouracil; [redacted] AE = adverse event; BICR = blinded independent central review; [redacted] ORR = objective response rate; OS = overall survival; OSR = overall survival rate; PFS = progression-free survival; PFSR = progression-free survival rate; [redacted] RECIST = Response Evaluation Criteria In Solid Tumors; SAE = serious adverse event; [redacted]

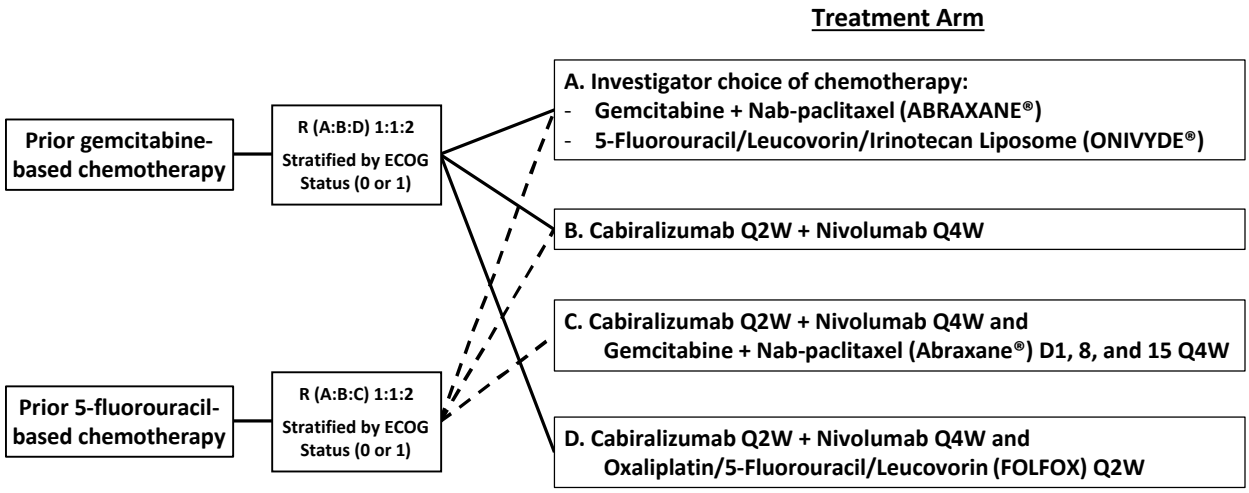
5 STUDY DESIGN

5.1 Overall Design

This is a Phase 2, open-label, randomized study to evaluate the efficacy, safety, tolerability [redacted] of cabiralizumab in combination with nivolumab with or without gemcitabine + nab-paclitaxel or oxaliplatin, 5-FU, and leucovorin (calcium folinate; FOLFOX), or an alternative choice of chemotherapy, in participants with locally advanced/metastatic pancreatic tumors who have progressed during or after no more than 1 line of systemic chemotherapy (either gemcitabine-based or 5-FU-based) in the metastatic setting.

The study design schematic for the study is presented in Figure 5.1-1.

Figure 5.1-1: Study Design Schematic



Note: ONIVYDE-based regimen can be substituted with FOLFIRI.

Abbreviations: ECOG = Eastern Cooperative Oncology Group; Q2W = every 2 weeks; Q4W = every 4 weeks; R = randomized.

The study will consist of 3 periods: Screening, Treatment, and Safety/Survival Follow-up. The study will end after the last participant completes the last visit.

5.1.1 Screening Period

The screening period will last for up to 30 days. The screening period begins by establishing the participant's initial eligibility and signing of the informed consent form (ICF). The screening assessments are shown in Table 2-1. If a participant surpasses the 30-day window during the screening period due to a study-related procedure (eg, scheduling of a tumor biopsy or waiting time for a study-related laboratory value), the participant must be re-consented but does not need to be assigned a new participant identification (PID) number. In this situation, the least amount of repeat procedures from the initial screening to qualify the participant, while maintaining safety and eligibility under the discretion of the BMS Medical Monitor and investigator, may be done to reduce any undue burden of procedures in this participant population. Participants will be randomized and treated in 1 of 4 arms as described in Section 5.1.2 based on their 1L treatment for pancreatic cancer. Allocation will be based on availability of slots in each of the arms and participants meeting cohort-specific eligibility criteria.

Tumor tissue from a biopsy obtained during screening, or from a sample collected within 3 months prior to treatment, is required for enrollment. If the tumor sample is from a prior collection, participants should not have received any systemic anticancer therapy between collection and enrollment in the current study. Tumor samples must be obtained from a metastatic tumor lesion or from an unresectable primary tumor lesion. Tumor samples may be obtained from a core biopsy, excisional biopsy, or surgical specimen; formalin-fixed paraffin-embedded (FFPE) blocks or a minimum of 20 slides are required. Participants with lesions in a previously irradiated field as the sole site of measurable disease will be permitted to enroll, provided the lesion(s) has demonstrated

clear progression and can be measured. Adequate tumor content must be documented by hematoxylin and eosin (H&E) stain, performed either locally or on samples submitted to the central laboratory, for participants to receive treatment. Local H&E or central laboratory results must be provided to the Interactive Response Technology (IRT) prior to randomization/treatment assignment.

5.1.2 Treatment Period

The randomization call is made into the IRT no more than 3 business days prior to the first day of treatment on Cycle 1 Day 1, unless otherwise agreed upon with the Medical Monitor. The participant will be randomly assigned to the open-label cohort dependent on their initial chemotherapy treatment (gemcitabine-based or 5-FU-based). Participants will not receive the same therapeutic combination that they received in the 1L setting.

Participants who have previously received gemcitabine-based chemotherapy will be stratified according to Eastern Cooperative Oncology Group (ECOG) status (0 or 1) and randomly assigned in a 1:1:2 ratio to 1 of the 3 following treatment options:

- **Treatment Arm A:** Investigator choice of chemotherapy (gemcitabine + nab-paclitaxel [ABRAXANE®]; 5-FU/leucovorin [calcium folinate]/irinotecan liposome [ONIVYDE®]*);
- **Treatment Arm B:** Cabiralizumab and nivolumab in combination;
- **Treatment Arm D:** Cabiralizumab and nivolumab in combination with oxaliplatin/5-FU/leucovorin (calcium folinate; FOLFOX).

*ONIVYDE-based regimen can be substituted with FOLFIRI (irinotecan/leucovorin/5-FU)

Participants who have previously received 5-FU-based chemotherapy will be stratified according to ECOG status (0 or 1) and randomly assigned in a 1:1:2 ratio to 1 of the 3 following treatment options:

- **Treatment Arm A:** Investigator choice of chemotherapy (gemcitabine + nab-paclitaxel [ABRAXANE®]; 5-FU/leucovorin [calcium folinate]/irinotecan liposome [ONIVYDE®]*);
- **Treatment Arm B:** Cabiralizumab and nivolumab in combination;
- **Treatment Arm C:** Cabiralizumab and nivolumab in combination with gemcitabine + nab-paclitaxel (ABRAXANE®).

*ONIVYDE-based regimen can be substituted with FOLFIRI

A total of 6 participants per arm were included in a preliminary safety cohort in Treatment Arms C and D. After the first 3 participants were treated with the combination of immunotherapy and chemotherapy, using an interval of 5 days between each participant, the subsequent 3 participants were enrolled competitively. The 6 participants were monitored for up to 4 weeks before additional participants were treated in the same arm. [redacted]

[redacted]

Blood, urine, tumor biopsy, fecal samples, and electrocardiograms (ECGs) will be collected and participants will receive study treatments as per the Schedule of Activities (Table 2-2). Participants will have baseline imaging within approximately 30 days before the start of the study and then every 8 weeks after starting combination treatment for reassessment. Tumor progression or response endpoints will be assessed using RECIST v1.1 for solid tumors. Participants will continue on treatment until withdrawal of consent, death, or initiation of another anti-cancer treatment. Participants who discontinue treatment will be followed for safety assessments and survival status as described in Section 5.1.4 and Table 2-3.

Physical examinations, vital sign measurements, 12-lead ECG and clinical laboratory evaluations will be performed at selected times throughout the dosing interval. In the event that multiple procedures are required at a single time point, the following is a list of procedures from highest to lowest priority: [redacted] ECG and vital signs, and laboratory tests. Participants will be closely monitored for AEs throughout the study. Blood samples will be collected at baseline and after study treatment administration for [redacted] analyses according to the schedules outlined in Section 9.5.

Participants with a response of SD, PR, or complete response (CR) at the end of a given cycle will continue to the next treatment cycle. Participants will generally be allowed to continue study treatment until the first occurrence of either 1) progressive disease, 2) clinical deterioration suggesting that no further benefit from treatment is likely, 3) intolerability to therapy, 4) the participant meets criteria for discontinuation of study treatment as outlined in Section 7.4.4, or 5) withdrawal of consent.

Treatment beyond disease progression will be allowed in participants with initial RECIST v1.1-defined progressive disease in Treatment Arms B, C, and D, as described in Section 5.1.3.

Participants who experience toxicities confirmed to be related to 1 of the study drugs in a combination therapy can continue treatment with the other drug(s) of the combination per protocol (see Section 7.4).

5.1.3 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of patients treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease per RECIST v1.1.

Participants treated with cabiralizumab and nivolumab combination therapy in Treatment Arms B, C, and D will be permitted to continue cabiralizumab and nivolumab treatment beyond initial RECIST v1.1-defined progressive disease, as assessed by the investigator, as long as the following criteria are met:

- Investigator-assessed clinical benefit and no rapid disease progression;
- Participant is tolerating study treatment;

- Stable performance status;
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Participants provides written informed consent prior to receiving additional study treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options;

The decision to continue treatment beyond initial investigator-assessed progression should be discussed with the BMS Medical Monitor and documented in the study records. A radiographic assessment/scan should be performed approximately 4 weeks (±7 days) after initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued progressive disease. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with cabiralizumab and nivolumab.

If the investigator feels that any participant receiving cabiralizumab and nivolumab will obtain clinical benefit by continuing treatment, the participant may remain on the trial and continue to receive monitoring according to the time and event schedules as per the protocol.

For participants who continue cabiralizumab and nivolumab study therapy beyond progression, confirmation of progression will be assessed based on 1) at least 5 mm of further increase in target or new target lesion burden, 2) further increase in the size of non-target lesion(s), 3) appearance of new lesion or additional new lesions in the next consecutive assessment. If complete or partial response, or stable disease criteria are met at the next assessment, then initial progression status is reset. Cabiralizumab and nivolumab treatment should be discontinued permanently upon documentation of confirmed progression.

5.1.4 Follow-up Period

5.1.4.1 Safety Follow-up Period

Once the decision is made to discontinue the participant from treatment, that is, at end of treatment (EOT), all participants will enter a Safety Follow-up Period.

For participants who will not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data) and will not need to be repeated. Accordingly, for these participants, this visit will be considered the start of the safety follow-up period.

After the EOT visit, all participants will be evaluated for any new AEs for at least 100 days after the last dose of study treatment. Follow-up visits should occur at Days 30, 60, and 100 (± 7 days for all study visits) after the last dose or at the date of discontinuation (± 7 days). All participants should complete the 3 clinical safety follow-up visits regardless of whether new anti-cancer therapy is started, except those participants who will withdraw consent for study participation.

5.1.4.2 Imaging Follow-up Period

At the time of study treatment discontinuation, participants will continue to have radiologic and clinical tumor assessments every 12 weeks (± 7 days) until withdrawal of consent, death, or initiation of another anti-cancer treatment, whichever occurs first. Radiological assessments for participants who have ongoing clinical benefit may continue to be collected after participants complete the Survival Follow-up Period of the study. Participants who have disease progression after an initial course of study therapy will be evaluated beyond the EOT visit and will be allowed to receive other tumor-directed therapy as required.

5.1.4.3 Survival Follow-up Period

In parallel with the safety follow-up period, all participants will start the survival follow-up period. Participants will be followed-up by telephone every 12 weeks (after completion of Safety Follow-up Visit 3) for 2 years or until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first. Participants with SD, PR, or CR will have both the safety follow-up period and survival follow-up period occur simultaneously during the 2-year follow-up period. 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 period.

5.1.5 Data Monitoring Committee and Other External Committees

Based on the key points listed and the comprehensive safety monitoring plan outlined below, BMS has elected to not use a Data Monitoring Committee (DMC) for this study.

- This is an open label study.
- The eligibility criteria exclude participants with disease characteristics that could predispose them to a higher risk of morbidity (eg, history of interstitial lung disease, recent history of thrombosis)
- Exclusion of participants with known autoimmunity also applies as they could be at risk for exacerbation of their condition by the administration of therapies that relieve immune suppression such as nivolumab.
- Participants will be observed frequently for clinical evaluation and blood counts.
- Well-defined discontinuation criteria are established in the protocol for individual participants for both safety and treatment futility with clear criteria for treatment discontinuation, dose delay, and toxicity management.

[redacted]

[redacted]

5.2 Number of Participants

Approximately 160 participants will be treated (approximately 40 participants in each treatment arm). Six participants from each of Treatment Arms C and D were evaluated for safety prior to continuation of enrollment in these treatment arms. The first 3 participants in the preliminary safety cohort were treated at intervals of at least 5 days; the enrollment for the additional 3 participants was competitive. [redacted]

Study enrollment is now open competitively. Refer to Section 10.1 for details regarding the sample size determination.

5.3 End of Study Definition

The start of the trial is defined as the first visit for the first participant screened. End of trial is defined as the last visit or scheduled procedure shown in the Schedule of Activities for the last participant. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

5.4 Scientific Rationale for Study Design

Cabiralizumab is being investigated in combination with nivolumab in subjects with advanced solid tumors. The study design includes the following:

[redacted]

- 30-day screening period
- Treatment period
- Safety/survival follow-up period

The rationale for the individual elements of the study design is provided below.

5.4.1 Rationale for Chemotherapy-only Regimens

Evaluating efficacy of a combination in a single arm study can be difficult due to many uncertainties, particularly if part of the combination has known anti-tumor activity. In addition, historical controls may not be fully representative of the patient population in this study. Therefore, stratified randomization is being used to avoid possible bias in treatment assignment and potential imbalance of baseline characteristics.

5.4.1.1 Treatment Arm A

Treatment options for patients with PDAC are usually very limited beyond 1L treatment. For patients with distant metastases who have received systemic chemotherapy and maintain an adequate performance status and comorbidity profile, a switch to an alternative regimen is considered reasonable. Patients who received a 5-FU-based chemotherapy regimen as 1L therapy are usually treated with a gemcitabine-based chemotherapy regimen as 2L; in contrast, patients who received a gemcitabine-based chemotherapy regimen are usually treated with a combination of fluorouracil/leucovorin (calcium folinate) and ONIVYDE after progression.

To align with the standard approach currently taken to treat patients that progress after initial chemotherapy, both gemcitabine + nab-paclitaxel and fluorouracil/leucovorin (calcium folinate) and ONIVYDE have been offered as treatment options in the 2L Cohort Treatment Arm A. Sites may substitute the ONIVYDE-based regimen with FOLFIRI if ONIVYDE is not available, per country/institution guidelines.

5.4.2 Rationale for Cabiralizumab and Nivolumab Combination Therapy

Please also refer to Section 3.2.1.3 and Section 3.1.4.

As of 02-Jul-2018, 32 participants with advanced/metastatic PDAC treated with cabiralizumab 4 mg/kg + nivolumab 3 mg/kg Q2W in Cohort 1b4 of study FPA008-003 were evaluable for efficacy.[30] Based on investigator-assessed responses, durable clinical benefit (PR + stable disease) was observed in 5 of 32 (15.6%) evaluable participants, with an ORR of 9.4% (with 3 of 32 participants experiencing prolonged, sustained PR per investigator assessment). The duration of response for the 3 subjects with PR was: 14.1+, 9.3, and 8.4 months.

The initial blinded independent central review (BICR), as of 30-Oct-2017, showed an ORR of 13%, with 4 of 31 participants experiencing prolonged PR. The updated BICR was available as of 02-Sep-2018. Due to the need to change the team of readers, the scans of all active participants were re-analyzed. The most recent BICR assessment is now aligned with the investigator assessment, reporting an ORR of 9.4%, with 3 of 32 participants experiencing a durable PR.

Of note, all 3 PRs occurred in participants with microsatellite stable and low tumor mutational burden tumors. In addition, preliminary orthogonal immunohistochemistry (IHC) and transcriptome-wide analyses demonstrated that cabiralizumab induces CSF1R blockade in the periphery and tumor microenvironment in participants with advanced cancer.

In addition to the 32 participants treated in Cohort 1b4, additional participants with PDAC have been treated with the combination of cabiralizumab and nivolumab in study FPA008-003.[30] Preliminary analysis of the data is available for the 34 participants with PDAC who were evaluated for response in Cohort 1aE4 (cabiralizumab 4 mg/kg + nivolumab 3 mg/kg Q2W) and showed 6 (17.6%) participants with stable disease. Preliminary analysis of the data is also available for the 6 participants with PDAC who were evaluated for response in Cohort 1aC4 (cabiralizumab 6 mg/kg + nivolumab 3 mg/kg Q2W) and showed 1 (16.7%) participant with a confirmed PR and 3 (50.0%) participants with stable disease. Further follow up will reveal a more mature efficacy assessment with BICR confirmation.

These data support the need for further analysis of the combination of cabiralizumab and nivolumab for patients with metastatic PDAC.

5.4.3 Rationale for Cabiralizumab in Combination with Nivolumab and Gemicitabine + Nab-paclitaxel or FOLFOX

Please also refer to Section 3.1.5 above.

Gemcitabine + nab-paclitaxel is a global standard treatment for newly diagnosed PDAC.

In consideration of the potential synergy between gemcitabine and cabiralizumab + nivolumab, this combination has been included in Treatment Arm C of this protocol.

Historically, patients that received gemcitabine + nab-paclitaxel as their 1L of treatment have been treated with a 5-FU-based chemotherapy in 2L, while patients treated with a 5-FU-based chemotherapy in 1L have been treated with gemcitabine + nab-paclitaxel in 2L.

In light of the activity of platinum-based chemotherapies and gemcitabine on macrophages, and considering the need to provide a different chemotherapy based on the initial treatment received by the patient, both gemcitabine + nab-paclitaxel and FOLFOX regimens have been included in this protocol in combination with immunotherapy.

5.5 Justification for Cabiralizumab Dose

A cabiralizumab dose of 4 mg/kg has been tested in combination with nivolumab in 195 participants across a number of tumors in Part 1b of Study FPA008-003. The safety profile of this dose is described in Section 3.2.1.3. The dose of 4 mg/kg was selected in this trial based on [redacted] a tolerable safety profile.

Consistent with healthy subjects and RA and PVNS trials, a dose-dependent reduction [redacted] after cabiralizumab administration was observed in subjects with cancer in Study FPA008-003. [redacted]

the 4 mg/kg Q2W dose was associated with [redacted] consistent suppression [redacted] after dosing (Cabiralizumab IB[30] Sections 6.1 and 6.2), as well as preliminary response signal in pancreatic cancer (see Section 5.4.1).

5.6 Justification for Nivolumab Dose

The nivolumab flat dose of 480 mg Q4W is approved in the US as monotherapy for unresectable or metastatic melanoma, metastatic NSCLC, advanced RCC, locally advanced or metastatic urothelial carcinoma, hepatocellular carcinoma, and as maintenance therapy for unresectable or metastatic melanoma after induction therapy with nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for 4 doses. In addition, nivolumab 480 mg Q4W monotherapy is approved in the EU for the treatment of unresectable or metastatic melanoma and advanced RCC. Flat dosing of nivolumab was supported using modeling and simulation approaches using population PK (PPK) and exposure-response (ER) analyses examining relationships between nivolumab exposures and efficacy (eg, OS, OR) and safety responses, using data from studies in multiple tumor types (melanoma, NSCLC, and RCC) with body weight-normalized dosing (mg/kg). The PPK analyses have shown that exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered Q2W, and no clinically meaningful differences in PK across ethnicities and tumor types were observed. Nivolumab clearance and volume of distribution were found to increase as body weight increases but less than proportionally with increasing weight, indicating that milligram-per-kilogram dosing represents an over-adjustment for the effect of body weight on nivolumab PK.

Using the PPK and ER models, nivolumab exposures and probabilities of efficacy responses and risks of AEs were predicted following nivolumab 480 mg Q4W and compared to those following nivolumab 3 mg/kg Q2W. The overall distributions of average nivolumab steady-state exposures (Cssavg) are comparable following administration with either nivolumab 3 mg/kg Q2W or nivolumab 480 mg Q4W. While nivolumab 480 mg Q4W is predicted to result in approximately 43% greater steady-state peak concentrations (Cmaxss) compared to nivolumab 3 mg/kg Q2W, these exposures are predicted to be lower than the exposure ranges observed at doses up to nivolumab 10 mg/kg Q2W used in the nivolumab clinical program; the predicted Cmaxss following nivolumab 480 mg Q4W is well below the median Cmaxss achieved following administration of nivolumab 10 mg/kg Q2W, a safe and tolerable dose level.

Exposure-safety analysis demonstrated that the exposure margins for safety are maintained following nivolumab 480 mg Q4W. Safety analyses using available data following nivolumab 3 mg/kg Q2W and 10 mg/kg Q2W administration indicated that there were no differences in AE profiles across body weight groups. Finally, initial evidence demonstrates that, following administration of nivolumab 480 mg Q4W, nivolumab is well tolerated.

Nivolumab 480 mg Q4W is predicted to be approximately 16% lower steady-state trough concentrations (Cminss) compared to nivolumab 3 mg/kg Q2W. While these exposures are predicted to be lower, they are on the flat part of the exposure-response curves and are not predicted to affect efficacy. Exposure-efficacy analyses of multiple PK measures and efficacy endpoints (eg, OS, OR) indicated that, following administration of nivolumab 480 mg Q4W, efficacy is

predicted to be similar to that following administration of nivolumab 3 mg/kg Q2W across multiple tumor types. Based on these data, nivolumab 480 mg Q4W is expected to have similar efficacy and safety profiles to nivolumab 3 mg/kg Q2W, which has been studied in combination with cabiralizumab 4 mg/kg.

The doses for the additional investigational products (gemcitabine, nab-paclitaxel [ABRAXANE] and oxaliplatin/5-FU/leucovorin [calcium folinate; FOLFOX]) are in accordance with the Summary of Product Characteristics for these products.

5.6.1 Rationale for Infusion Times for Cabiralizumab and Nivolumab

Administration of nivolumab using a 30-minute infusion time has been evaluated in participants with cancer. Previous clinical studies of nivolumab monotherapy for the treatment of cancer have used a 60-minute infusion duration wherein nivolumab has been safely administered up to 10 mg/kg over long treatment periods. Infusion reactions including high-grade hypersensitivity reactions have been uncommon across the nivolumab clinical program. In Study CA209010, a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg, and 18.5% at 10 mg/kg). All the events were Grades 1 or 2 and were manageable. An infusion duration of 30 minutes for nivolumab 3 mg/kg (30% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared to the prior experience at nivolumab 10 mg/kg infused over a 60-minute duration. The safety of nivolumab 3 mg/kg administered as a 30-minute infusion was assessed in Study CA209153 in patients with previously treated advanced NSCLC (see Nivolumab IB[31] Section 5.5.1.2). Overall, there were no clinically meaningful differences in the frequency of hypersensitivity/infusion-related reactions (of any cause or treatment-related) in cancer patients administered nivolumab over a 30-minute infusion compared with that reported for patients treated with the 60-minute infusion. Thus, it was shown that nivolumab can be safely infused over 30 minutes in subjects with cancer.

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

6 STUDY POPULATION

For entry into the study, the following criteria MUST be met.

6.1 Inclusion Criteria

1. Signed Written Informed Consent

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

b) Consent for fresh pre-treatment, on-treatment, and upon progression biopsy samples at acceptable clinical risk, as judged by the investigator.

c) Participants must be willing and able to comply with scheduled visits, treatment schedule, and laboratory testing.

2) Type of Participant and Target Disease Characteristics

a) Participants must be at least 18 years old.

b) Participants must have histological or cytological confirmed diagnosis of locally advanced or metastatic adenocarcinoma of the pancreas, which has progressed during or after no more than 1 line of systemic chemotherapy in the metastatic setting (gemcitabine or 5-FU-based regimens).

i) If a participant received adjuvant/neoadjuvant systemic therapy, and progressed within 6 months, the adjuvant/neoadjuvant treatment will be considered as 1 line of systemic treatment.

c) In general, discontinuation of 1 drug in a multi-drug regimen and continuation of other drug(s), is considered part of the same line of treatment. Restarting the same regimen after a drug holiday or maintenance chemotherapy can also be considered part of the same line of treatment. Switching from IV (5-FU) to an oral formulation (capecitabine) of the same drug is also considered part of the same line of treatment.

d) Minimum time from first systemic therapy for recurrent/metastatic adenocarcinoma of pancreas to progression should be at least 3 months.

3) General Inclusion Criteria

a) Participants must have measurable disease by RECIST v1.1 (Appendix 5) and have at least 1 lesion accessible for biopsy in addition to the target lesion.

i) Participants with lesions in a previously irradiated field as the sole site of measurable disease will be permitted to enroll provided the lesion(s) have demonstrated clear progression and can be measured.

b) Prior palliative radiotherapy must have been completed at least 2 weeks prior to the first dose of the study treatment. Participants with symptomatic tumor lesions at baseline that may require palliative radiotherapy within 4 weeks of the first dose of study treatment are strongly encouraged to receive palliative radiotherapy prior to enrollment.

c) ECOG performance status of ≤ 1

d) All participants will be required to undergo mandatory pre- and on-treatment biopsies.

i) An archival sample is acceptable only if there is no systemic therapy administered after the archival sample is collected.

ii) Participants whose pretreatment biopsy yields inadequate tissue quantity or quality that do not have an appropriate archival sample will not be eligible (exception: Up to approximately 20% of the cohort will be allowed on treatment with a pre-treatment biopsy that does not yield adequate tissue quantity/quality).

iii) If a participant had a biopsy in the preceding 90 days with no intervening anti-cancer therapy, participants can be enrolled without needing a repeat biopsy after discussion with the BMS Medical Monitor and availability of FFPE blocks or unstained slides as delineated below. Participants will however be required to undergo on-treatment and

upon progression biopsies at acceptable clinical risk as judged by the investigator in all arms.

iv) Pretreatment tumor tissue will be assessed for adequate tumor content prior to participants receiving study treatment. Pretreatment tissue must be collected and confirmed for adequate tissue quantity (20 slides) and quality (100 viable tumor cells and 20% tumor content) during the screening period prior to first dose of study treatment. Participants who had a biopsy after signing consent which confirmed diagnosis but did not yield sufficient tissue for all correlative studies may be allowed after discussion with the BMS Medical Monitor.

[redacted]

vi) Where possible, the biopsied lesion should be distinct from target lesions being evaluated for radiologic response, and the same lesion should be used for both the baseline and on-treatment sampling.

e) Adequate marrow function as defined by the following:

i) White blood cell (WBC) ≥ 2000/μL (stable off any growth factor within 4 weeks of first study treatment administration);

ii) Neutrophils ≥ 1500/μL (stable off any growth factor within 4 weeks of first study treatment administration);

iii) Platelets ≥ 100×10^3/μL (transfusion to achieve this level is not permitted within 2 weeks of first study treatment administration);

iv) Hemoglobin ≥ 8.5 g/dL (transfusion to achieve this level is not permitted within 2 weeks of first study treatment administration).

f) Adequate other organ functions as defined by the following:

i) ALT and (AST) ≤ 2× institutional ULN

ii) Total bilirubin ≤ 1.5× institutional ULN (except participants with Gilbert's Syndrome who must have normal direct bilirubin)

iii) Serum creatinine ≤ 1.5× ULN or creatinine clearance (CLcr) ≥ 40 mL/min (measured using the Cockcroft-Gault formula below):

$$\text{Female CLcr} = \frac{(140 - \textit{age in years}) \times \textit{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\text{Male CLcr} = \frac{(140 - \textit{age in years}) \times \textit{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

g) Ability to comply with study visits, treatment, procedures [redacted] and required study follow-up.

4) Age and Reproductive Status

a) Males and females, ages 18 or age of majority or older.

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

c) Women must not be breastfeeding.

d) 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 6 months posttreatment completion for participants who received nab-paclitaxel (ABRAXANE®), and 5 months posttreatment for participants who received any other study treatment(s).

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with study treatment(s) and for a total of 7 months posttreatment completion. In addition, male participants must be willing to refrain from sperm donation during this time.

f) Azoospermic males are required to use a condom for the duration of the study.

Investigators shall counsel WOCBP and male participants who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception (Appendix 4) which have a failure rate of < 1% when used consistently and correctly.

6.2 Exclusion Criteria

1) Target Disease Exclusions

a) Suspected or known CNS metastases (imaging required only if participants are symptomatic).

2) Medical History and Concurrent Disease

a) 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 BMS Medical Monitor.

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

Note: Treatment with a short course of steroids (< 5 days) for up to 7 days prior to initiating study treatment is permitted.

c) Interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected treatment-related pulmonary toxicity.

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

e) Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:

i) Myocardial infarction or stroke/transient ischemic attack within the past 6 months
ii) Uncontrolled angina within the past 3 months
iii) Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes)
iv) History of other clinically significant heart disease (eg, cardiomyopathy, congestive heart failure with New York Heart Association functional classification III to IV, pericarditis, significant pericardial effusion, or myocarditis)
v) Cardiovascular disease-related requirement for daily supplemental oxygen therapy.

f) History of any chronic hepatitis as evidenced by the following:
i) Positive test for hepatitis B surface antigen
ii) Positive test for qualitative hepatitis C viral load (by polymerase chain reaction [PCR]).

Note: *Participants with positive hepatitis C antibody and negative quantitative hepatitis C by PCR are eligible. History of resolved hepatitis A virus infection is not an exclusion criterion.*

g) Previous malignancies (except non-melanoma skin cancers, and in situ bladder, gastric, colorectal, endometrial, cervical/dysplasia, melanoma, or breast cancers) unless complete remission was achieved at least 2 years prior to study entry and no additional therapy is required during the study period.
h) Prior organ allograft or allogeneic bone marrow transplantation.
i) Any major surgery within 4 weeks of study treatment. Participants must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study treatment.
j) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.03) or baseline before administration of study treatment. Participants with toxicities attributed to prior anti-cancer therapy that are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum-based therapy, are permitted to enroll.
k) Evidence of uncontrolled, active infection, requiring parenteral anti-bacterial, anti-viral or anti-fungal therapy ≤ 7 days prior to administration of study medication.
l) Any uncontrolled inflammatory GI disease including Crohn's Disease and ulcerative colitis.
m) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (Testing for HIV must be performed at sites mandated by local requirements.)
n) Any uncontrolled medical condition or psychiatric disorder which, in the opinion of the Investigator, would pose a risk to participant safety or interfere with study participation or interpretation of individual participant results.
o) Not Applicable as per Revised Protocol 02 - Current or recent (within 3 months of study drug administration) gastrointestinal disease that could impact upon the absorption of study drug.
p) Transfusion completed within 72 hours prior to first dose of study drug administration

q) Not Applicable as per Revised Protocol 01 - Any GI surgery that could impact upon the absorption of study drug.

r) Not Applicable as per Revised Protocol 01 - Inability to tolerate oral medication.

s) Inability to be venipunctured and/or tolerate venous access.

t) Positive test for latent tuberculosis (TB) at screening (eg, T-SPOT or Quantiferon test) or evidence of active TB.

3) Prior Therapies

a) Prior exposure to anti-CSF1R, anti-PD-1, anti-PD-L1, anti PD-L2, or anti-CTLA-4.

b) For any anti-cancer therapy (eg, chemotherapy, biologics, vaccines, or hormonal treatment), including investigational drugs, 4 weeks or 5 half-lives (whichever is shorter) must have elapsed between last dose and first treatment with any study treatments; if 5 half-lives are shorter than 4 weeks, agreement with the Medical Monitor must be obtained.

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

d) Prior exposure to gemcitabine and 5-FU or gemcitabine and oxaliplatin co-administered as 1L treatment.

4) Restricted Concomitant Therapies

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

b) Receipt of a live/attenuated vaccine within 30 days of first treatment. The inactivated seasonal influenza vaccine can be given to participants before treatment and while on therapy without restriction.

5) Physical and Laboratories Test Findings

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

b) Evidence of coagulopathy or bleeding diathesis

c) Ascites needing paracentesis or medical management

d) Peripheral Neuropathy greater than Grade 1

e) Albumin less than 3 g/dL

f) Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG, or clinical laboratory determinations beyond what is consistent with the target population

6) Allergies and Adverse Drug Reactions

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

b) History of allergy to study treatments or any of their components

7) Other Exclusion Criteria

a) Not applicable per Revised Protocol 02 - Consumption of non-pasteurized milk while on study drug and for 30 days after discontinuing study drug

b) Pregnant or breastfeeding

c) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included as a participant. Strict conditions apply and BMS approval is required.

d) Participants who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and that the results of the study can be used. It is imperative that participants fully meet all eligibility criteria.

6.3 Lifestyle Restrictions

Participants should abstain from consumption of alcoholic beverages while on study.

Male participants receiving gemcitabine, ABRAXANE, and fluorouracil should seek advice regarding cryoconservation of sperm prior to treatment because of the possibility of infertility.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently randomized in the study/included in the analysis population. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, as applicable, and to respond to queries from regulatory authorities.

6.4.1 Retesting During Screening

Participant Re-enrollment: This study permits the re-enrollment of a participant that has discontinued the study as a pretreatment failure (ie, participant has not been randomized / has not been treated). If re-enrolled, the participant must be re-consented.

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

The most current result prior to Randomization is the value by which study inclusion will be assessed, as it represents the participant's most current, clinical state.

Laboratory parameters and/or assessments that are included in Table 2-1, Screening Procedural Outline may be repeated in an effort to find all possible well-qualified participants. Consultation with the BMS Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

7 TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device intended to be administered to a study participant according to the study randomization or treatment allocation.

Study treatment includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical study.
- Study required premedication
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy and rescue medications)

An IP, also known as IMP in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-IP.

In this protocol, IPs are the following:

- Cabiralizumab
- Nivolumab

In this protocol, non-IPs are the following:

- Gemcitabine
- Irinotecan
- Nab-paclitaxel
- Oxaliplatin
- 5-FU
- Leucovorin

Study treatment descriptions including dosage form, potency, IP/non-IMP, and storage conditions are presented in Table 7-1.

Table 7-1: Study treatments for CA025006

Product Description / Class and Dosage Form	Potency	IP/Non-IP[a]	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Cabiralizumab (BMS-986227) Solution for Injection	100 mg/vial (20 mg/mL)	IP	Open Label	Vial	Refer to the label on container and/or pharmacy manual
Cabiralizumab (BMS-986227) Solution for Injection	140 mg/vial (20 mg/mL)	IP	Open Label	Vial	Refer to the label on container and/or pharmacy manual
Nivolumab Solution for Injection	100 mg/vial and 40 mg/vial (10 mg/mL)	IP	Open Label	Vial	Refer to the label on container and/or pharmacy manual
Gemcitabine Powder for Concentrate for Solution for Infusion[a]	1000 mg/vial and various strengths	Non-IP	Open Label	Vial and various packaging configurations	Refer to the label on container or package insert / summary of product characteristics
Irinotecan Liposome Solution (ONIVYDE®) for Concentrate for Solution for Infusion[a]	Various strengths	Non-IP	Open Label	Vial and various packaging configurations	Refer to the label on container or package insert / summary of product characteristics
Irinotecan Hydrochloride Solution for Injection[a]	Various strengths	Non-IP	Open Label	Vial and various packaging configurations	Refer to the label on container or package insert / summary of product characteristics
Nab-paclitaxel (ABRAXANE®) Powder for Suspension for Infusion[a]	Various strengths	Non-IP	Open Label	Vial and various packaging configurations	Refer to the label on container or package insert / summary of product characteristics
Oxaliplatin Concentrate for Solution for Infusion[a]	Various strengths	Non-IP	Open Label	Vial and various packaging configurations	Refer to the label on container or package insert / summary of product characteristics
5-Fluorouracil Solution for Injection[a]	Various strengths	Non-IP	Open Label	Vial and various packaging configurations	Refer to the label on container or package insert / summary of product characteristics
Leucovorin (calcium folinate) Solution for Infusion[a]	Various strengths	Non-IP	Open Label	Vial and various packaging configurations	Refer to the label on container or package insert / summary of product characteristics

[a] These products may be supplied by BMS centrally or through investigating site's standard prescribing procedures.

7.1 Treatments Administered

The selection and timing of dose for each participant are as follows:

Table 7.1-1: Selection and Timing of Dose

Treatment Arm(s)	Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage Formulation Frequency of Administration (28-day Cycle)	Route of Administration
A	**Investigator choice of chemotherapy** (see Section 5.1.2) **(see description in text following this table)**	As appropriate **(see description in text following this table)**	As appropriate **(see description in text following this table)**	As appropriate **(see description in text following this table)**
B, C, and D	**Cabiralizumab**	4 mg/kg IV	Days 1 and 15	IV Infusion
B, C, and D	**Nivolumab**	480 mg IV	Day 1	IV Infusion
C	**Gemcitabine**	1000 mg/m^2 IV	Days 1, 8, and 15	IV Infusion
C	**Nab-paclitaxel (ABRAXANE®)**	125 mg/m^2 IV	Days 1, 8, and 15	IV Infusion
D	**Oxaliplatin**	85 mg/m^2 IV	Days 1 and 15	IV Infusion
D	**5-FU**	400 mg/m^2 Bolus AND 2400 mg/m^2 IV	Days 1 and 15	Bolus and IV Infusion
D	**Leucovorin (calcium folinate)**	400 mg/m^2 IV	Days 1 and 15	IV Infusion

Abbreviations: 5-FU = 5-fluorouracil; IV = intravenous.

For the combination arms, cabiralizumab 4 mg/kg and nivolumab 480 mg will be given on Day 1 and cabiralizumab 4 mg/kg will be given alone on Day 15 (± 2 days) of each 28-day treatment cycle until progression of disease, discontinuation due to toxicity, withdrawal of consent, or study closure. Nivolumab will be administered as an IV infusion over 30 (± 5) minutes, and then, after a 30 minute rest period, cabiralizumab will be administered as an IV infusion over 30 (± 5) minutes. Premedication for chemotherapy (based on standard-of-care and local institutional standards) and chemotherapy will then be administered after a further 30 minute rest period.

The dosing regimen for irinotecan liposome injection (ONIVYDE) with 5-FU and leucovorin (calcium folinate) is irinotecan liposome injection 70 mg/m^2 over 90 minutes, followed by leucovorin (calcium folinate) 400 mg/m^2 over 30 minutes, and 5-FU 2400 mg/m^2 over 46 hours on Days 1 and 15 Q4W. The recommended starting dose of ONIVYDE in patients known to be homozygous for the UGT1A1*28 allele is 50 mg/m^2 administered by intravenous infusion over 90 minutes. Increase the dose of ONIVYDE to 70 mg/m^2 as tolerated in subsequent cycles. Sites may substitute the ONIVYDE-based regimen with FOLFIRI if ONIVYDE is not available, per

country/institution guidelines. Each site will use either ONIVYDE or FOLFIRI, but not both. The dose regimen for FOLFIRI is: irinotecan hydrochloride 180 mg/m^2 over 90 minutes on Days 1 and 15 of a 28-day cycle; leucovorin (calcium folinate) 400 mg/m^2 over 90 to 120 minutes on Days 1 and 15 of a 28-day cycle (leucovorin may be given concurrently with irinotecan hydrochloride); 5-FU 400 mg/m^2 bolus on Days 1 and 15, followed by 2400 mg/m^2 over 46 hours (continuous infusion) on Days 1 and 15 of a 28-day cycle.

The recommended dose of nab-paclitaxel (ABRAXANE) is 125 mg/m^2 administered as an IV infusion over 30 to 40 minutes on Days 1, 8, and 15 of each 28-day cycle. Administer gemcitabine 1000 mg/m^2 over 30 to 40 minutes immediately after nab-paclitaxel on Days 1, 8, and 15 of each 28-day cycle.

FOLFOX (oxaliplatin 85 mg/m^2 over 2 hours on Day 1 and Day 15 of a 28-day cycle; leucovorin [calcium folinate] 400 mg/m^2 over 2 hours on Day 1 and Day 15 of a 28-day cycle [leucovorin (calcium folinate) may be given concurrently with oxaliplatin]; 5-FU 400 mg/m^2 bolus on Day 1 and Day 15, followed by 2400 mg/m^2 over 46 hours continuous infusion) will be administered on Days 1 and 15 of a 28-day cycle.

7.2 Method of Treatment Assignment

All participants will be centrally randomized using an IRT. Before the study is initiated, each user will receive log-in information and directions on how to access the IRT.

Study treatment will be dispensed at the study visits as described in Section 7.1.

Enrolled participants, including those not dosed, will be assigned PID numbers comprised of the site number and participant number. For example, the first participant screened (ie, enrolled) at site number [redacted], will have a participant number of [redacted]. Those enrolled participants meeting inclusion and exclusion criteria will be eligible to be dosed.

Participants will not be replaced if they are discontinued from the study.

7.3 Blinding

This is an open-label study; blinding procedures are not applicable.

7.4 Dosage Modification

7.4.1 Dose Delay for Cabiralizumab and Nivolumab

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

- Any Grade 3 fatigue which does not resolve to Grade 1 or baseline before the next treatment visit;
- Any drug-related laboratory abnormalities would not require a dose delay unless clinically indicated or specified in the protocol or abnormal laboratory management table (Appendix 8). Please discuss with the BMS Medical Monitor or designee as needed;
- For dose delays or modifications for all other AEs, please refer to the AE management table in Appendix 7.

- If symptoms or signs of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) appear, nivolumab should be withheld and the patient referred for specialized care for assessment and treatment

Participants who require a dose delay of cabiralizumab or 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 participant experiences an infusion reaction to cabiralizumab or nivolumab, or both study drugs, the infusion reaction should be treated following the infusion reaction treatment guidelines in Section 7.4.7 and Appendix 7. 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 participant.

7.4.2 Management Algorithms for Immuno-oncology Agents

Immuno-oncology (IO) agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab and cabiralizumab are considered IO agents in this protocol. Early recognition and management of AEs associated with IO 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 IMAEs:

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

Specific algorithms for the management of IMAEs are provided in Appendix 7 and are applicable to IMAEs for all IO study treatment combinations.

7.4.3 Dose Reduction for Cabiralizumab and Nivolumab

Dose reduction for cabiralizumab and nivolumab are not permitted.

7.4.4 Dose Discontinuation Criteria for Cabiralizumab and Nivolumab

For comprehensive discontinuation rules, refer to Appendix 7 (AE management) and Appendix 8 (laboratory abnormalities).

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

- Any Grade 3 or higher uveitis ***or*** any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 within the second re-treatment period ***or*** that requires systemic treatment
- Any Grade 3 or higher infusion-related reactions and hypersensitivity requiring discontinuation. Any re-initiation of therapy in this circumstance would require consultation with the Sponsor's Medical Monitor or designee.
- Any Grade 3 non-skin, drug-related AE lasting > 7 days, or recurrences including drug-related uveitis, pneumonitis, hypoxia, bronchospasm, and endocrinopathies with the following exceptions:
  - Grade 3 drug-related diarrhea, colitis, neurologic toxicity, uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with Grade ≥ 2 bleeding requires discontinuation
- Any drug-related liver function test abnormality that meets any one of the following criteria requires discontinuation:
  - ALT or AST > 3× ULN and total bilirubin > 2× ULN or INR > 1.5× ULN (in the absence of anticoagulation).
    - See Appendix 7 and Appendix 8 for guidelines and possibility of restarting therapy
  - ALT or AST > 20× ULN (with or without concurrent liver metastases)
  - Total bilirubin > 3× ULN (> 5× ULN with concurrent liver metastases)
- Any Grade 4 drug-related AE or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia < 7 days
  - Grade 4 lymphopenia or leukopenia < 7 days
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. The Sponsor's Medical Monitor or designee should be consulted for Grade 4 amylase or lipase abnormalities.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy AEs, such as adrenal insufficiency, adrenocorticotropic hormone deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Sponsor's Medical Monitor or designee.

  - Grade 4 CK up to 20× ULN (in the absence of clinical sequelae)
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to manage drug-related AEs are allowed. Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks from the previous dose, the Sponsor's Medical Monitor or designee must be consulted. Tumor assessments should continue as per-protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue per protocol, or more frequently if clinically indicated during such dosing delays or per the Investigator's discretion.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Sponsor's Medical Monitor or designee. Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks, the Sponsor's Medical Monitor must be consulted. Tumor assessments should continue per-protocol every 8 weeks (± 7 days) even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue per-protocol or more frequently if clinically indicated during such dosing delays or per the investigator's discretion.
- Any AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, presents a substantial clinical risk to the participant with continued cabiralizumab and/or nivolumab dosing
- Any drug-related Grade 3 or higher neurological toxicity
- Any Grade 3 or higher periorbital edema and persistent Grade 2 periorbital edema requiring 2 missed doses unless approved by Sponsor's Medical Monitor
- Any Grade 4 skin toxicity
- Any Grade 4 renal toxicity
- Any drug-related Grade 3 or higher pulmonary toxicity
- Confirmed Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) will result in permanent discontinuation of nivolumab.
- Any Grade 3 or higher myocarditis will result in permanent discontinuation of nivolumab.

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

- Timely resolution of the AE based on the treatment modification table
- Clinical benefit is shown by the participant based on investigator assessment.

7.4.5 Criteria to Resume Treatment with Cabiralizumab and Nivolumab

Participants may resume treatment with cabiralizumab and/or nivolumab when the drug-related AE resolves as noted in the AE management tables in Appendix 7 or the abnormal laboratory management table in Appendix 8. The BMS Medical Monitor or designee can be contacted at any time if further clarification is needed.

7.4.6 Dose Modification for Chemotherapy

Since FOLFOX and gemcitabine + nab-paclitaxel are standard therapies for pancreatic cancers, sites may use their discretion for dosing these regimens based on a participant's tolerability. Any laboratory-only abnormalities without clinical manifestations or electrolyte abnormalities that may be managed with supplementation also do not automatically need dose modification. In addition, if participants experience tolerability issues for 5-FU / leucovorin and ONIVYDE, and FOLFIRI, dose modifications for these 2 regimens should be performed according to their respective SmPCs and institutional guidelines.

7.4.6.1 Dose Modification for Gemcitabine + Nab-paclitaxel

Suggested dose modification will be performed according to the nab-paclitaxel (ABRAXANE) package insert (Table 7.4.6.1-1, Table 7.4.6.1-2, and Table 7.4.6.1-3).

If the causality of the AE requiring drug hold is confirmed to be due to 1 of the drugs in the chemotherapy regimen, the other drugs may be continued as per protocol schedule.

Table 7.4.6.1-1: Dose Level Reductions for Participants with Adenocarcinoma of the Pancreas

Dose Level	Nab-paclitaxel (mg/m^2)	Gemcitabine (mg/m^2)
Full Dose	125	1000
1st dose reduction	100	800
2nd dose reduction	75	600

Source: Modified from Table 3 of nab-paclitaxel (ABRAXANE) US Package Insert[47]

Table 7.4.6.1-2: Dose Recommendation and Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or within a Cycle for Participants with Adenocarcinoma of the Pancreas

Cycle Day	ANC (cells/mm3)		Platelet Count (cells/mm3)	Nab-paclitaxel / Gemcitabine
Day 1	< 1500	OR	< 100,000	Delay doses until recovery
Day 8	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level
	< 500	OR	< 50,000	Withhold doses
Day 15: IF Day 8 doses were reduced or given without modification:				
	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level from Day 8
	< 500	OR	< 50,000	Withhold doses
Day 15: IF Day 8 doses were withheld:				
	≥ 1000	OR	≥ 75,000	Reduce 1 dose level from Day 1
	500 to < 1000	OR	50,000 to < 75,000	Reduce 2 dose levels from Day 1
	< 500	OR	< 50,000	Withhold doses

Source: Table 4 of nab-paclitaxel (ABRAXANE) US Package Insert[47]

Abbreviations: ANC = absolute neutrophil count

Table 7.4.6.1-3: Dose Modifications for Other Adverse Drug Reactions in Participants with Adenocarcinoma of the Pancreas

Adverse Drug Reaction	Nab-paclitaxel	Gemcitabine
Febrile Neutropenia: Grade 3 or 4	Withhold until fever resolves and ANC ≥ 1500; resume at next lower dose level	
Peripheral Neuropathy: Grade 3 or 4	Withhold until improves to ≤ Grade 1; resume at next lower dose level	No dose reduction
Cutaneous Toxicity: Grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists	
Gastrointestinal Toxicity: Grade 3 mucositis or diarrhea	Withhold until improves to ≤ Grade 1; resume at next lower dose level	

Source: Table 5 of nab-paclitaxel (ABRAXANE) US Package Insert[47]

Abbreviations: ANC = absolute neutrophil count.

7.4.6.2 Dose Modification for FOLFOX

Suggested dose modifications of FOLFOX are provided in Table 7.4.6.2-1 and Table 7.4.6.2-2.

If the causality of the AE requiring drug hold is confirmed to be due to 1 of the drugs in the chemotherapy regimen, the other drugs may be continued per protocol schedule.

Table 7.4.6.2-1: Recommended Dose Modifications of FOLFOX

Drug	Starting Dose	Dose Modification	
		Dose Level - 1	Dose Level - 2
Oxaliplatin	85 mg/m^2	70 mg/m^2	50 mg/m^2
5-FU	Bolus 5-FU: 400 mg/m^2 Leucovorin (calcium folinate): 400 mg/m^2 Infusion 5-FU: 2400 mg/m^2/46 hours	Bolus 5-FU: 300 mg/m^2 Leucovorin (calcium folinate): 300 mg/m^2 Infusion 5-FU: 2000 mg/m^2/46 hours	Bolus 5-FU: 200 mg/m^2 Leucovorin (calcium folinate): 200 mg/m^2 Infusion 5-FU: 1600 mg/m^2/46 hours

Abbreviations: 5-FU = 5-fluorouracil

Table 7.4.6.2-2: Dose Modifications of FOLFOX

Toxicity	Definition	During a course of therapy	Dose adjustment for next treatments
Neutropenia	Grade 3 or greater	Interrupt until resolved to Grade 2	Dose level -1 *If treatment delayed for 4 consecutive weeks, discontinue all treatment
Thrombocytopenia	Grade 2	Interrupt until resolved to Grade 1	Dose level -1 *If Grade 2 persists > 7 days, oxaliplatin reduced by 2 dose levels when platelets improve to Grade 1
	Grade 3	Interrupt until resolved to Grade 1	Dose level -1 *If Grade 3 persists > 7 days, oxaliplatin reduced by 2 dose levels when platelets improve to Grade 1
	Grade 4	Interrupt until resolved to Grade 1	Dose level -2 *If Grade 4 persists > 7 days, oxaliplatin reduced by 2 dose levels when platelets improve to Grade 1
Neurologic toxicity	Grade 2 peripheral sensory neuropathy	Interrupt oxaliplatin until resolved to Grade 1 or management as per institutional standard	Oxaliplatin dose -1 Continue 5-FU and leucovorin (calcium folinate) *If oxaliplatin delayed for neurologic toxicity for 4 consecutive weeks, discontinue oxaliplatin, continue 5-FU and leucovorin (calcium folinate)

Table 7.4.6.2-2: Dose Modifications of FOLFOX

Toxicity	Definition	During a course of therapy	Dose adjustment for next treatments
	Grade 3 or greater peripheral sensory neuropathy	Discontinue oxaliplatin	Continue 5-FU and leucovorin (calcium folinate)
Gastrointestinal toxicities	Grade 2 or greater diarrhea	Interrupt until resolved to Grade 1	Dose level -1 If dose delayed for diarrhea for 4 consecutive weeks, discontinue all treatment

Abbreviations: 5-FU = 5-fluorouracil.

For toxicities not listed above, dose modifications are permitted per local standards.

Participants may also discontinue oxaliplatin following multiple cycles if, in the investigator's judgment, cumulative toxicity is likely to increase over time.

7.4.7 Treatment of Cabiralizumab and Nivolumab-Related 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 v4.03 guidelines. Any Grade 3 or Grade 4 infusion reaction should be reported within 24 hours to the BMS Medical Monitor or designee, and reported as an SAE if it meets the criteria.

The nivolumab 30 (± 5) minute infusion will be administered first, with a 30 minute rest, followed by the cabiralizumab 30 (± 5) minute infusion. It may be unclear if an infusion reaction is due to cabiralizumab, nivolumab, or to both study drugs. Therefore, 1 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 participant'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 participant 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 participant 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 ≤ 24 hours.

- Interrupt the study drug infusion.
- Begin an IV infusion of normal saline and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol (acetaminophen) 325 mg to 1000 mg.
- Remain at bedside and monitor the participant'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 participant 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 participant until resolution of symptoms.
- If a participant 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 participant 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 case report form (CRF).
- Begin an IV infusion of normal saline and treat the participant 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 participant's vital signs until recovery from symptoms.
- The participant 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).

7.5 Preparation/Handling/Storage/Accountability

For nivolumab and cabiralizumab, please refer to the current version of the Investigator's Brochures[30,31] and/or pharmacy manual for complete storage, handling, dispensing, and infusion information. All other agents provided by BMS should be prepared/stored/administered in accordance with the package insert or summary of product characteristics. The IP should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that the IP must only be dispensed to study participants. The IP 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.

Study treatment not supplied by BMS will be stored in accordance with the package insert.

IP documentation (whether supplied by BMS or not) 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).

Further guidance and information for final disposition of unused study treatment are provided in Appendix 2.

7.5.1 Dosing of Cabiralizumab and Nivolumab

For the combination therapy, nivolumab should always be administered first as a 30-minute (± 5 minutes) IV infusion followed by 30-minute (± 5 minutes) IV infusion of cabiralizumab. The time in between infusions is expected to be approximately 30 minutes but can be more or less depending on the situation. Cabiralizumab will be administered Q2W (± 2days) and nivolumab will be administered Q4W (± 2 days). Participants may be dosed with cabiralizumab no less than 12 days from the previous dose and with nivolumab no less than 24 days from the previous dose.

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

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

7.5.2 Retained Samples for Bioavailability/Bioequivalence/Biocomparability

Not applicable.

7.6 Concomitant Therapy

7.6.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to study drug administration in the study are as follows (unless utilized to treat a drug-related AE or specified in Section 6):

- Immunosuppressive agents;
- Immunosuppressive doses of systemic corticosteroids;
- Any live/attenuated vaccine (eg varicella, zoster, yellow fever, rotavirus, oral polio, and measles, mumps, rubella) during treatment and until 100 days post last dose;
- Statins for treatment of hypercholesterolemia. Statins will be allowed only if the participant is on a stable dose for over 3 months prior to the study and is in a stable status without any CK elevations;
- Other anti-neoplastic therapies including biologic, immunotherapy, extensive non-palliative radiation therapy, standard treatments, or investigational agents or devices.

No concomitant medications (prescription, over-the-counter, or herbal) are to be administered during study unless they are prescribed for treatment of specific clinical events. Any concomitant therapies taken within 4 weeks prior to study drug administration must be recorded on the CRF.

7.6.2 Other Restrictions and Precautions

Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of treatment

assignment are excluded. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease.

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

Concomitant palliative and supportive care for disease-related symptoms, including bisphosphonates and RANK-L inhibitors, is allowed if initiated prior to the first dose of study drug administration. Transfusions are permitted as needed.

The inactivated seasonal influenza vaccine can be given to participants while on therapy without restriction.

Concomitant use of statins will be allowed only if the participant is on a stable dose for over 3 months prior to the study and is in a stable status without any CK elevations.

No routine premedication will be administered for initial cabiralizumab and nivolumab doses. If a participant develops nausea, vomiting, or other infusion-related AEs, the participant may be premedicated with anti-emetics, steroids, or antihistamines prior to subsequent infusions of study drugs at the discretion of the investigator. The treatment will be administered according to the institution's standard practice, and should be captured on the participant's CRF.

7.6.2.1 Imaging Restrictions and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen for each participant. Imaging contraindications and contrast risks should be considered in this assessment. Participants with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to magnetic resonance imaging (MRI), participants with severe renal insufficiency (ie, estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this participant population. In addition, participants are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. The ultimate decision to perform MRI in an individual participant in this study rests with the site radiologist, the investigator, and the standard set by the local ethics committee.

7.7 Treatment After the End of the Study

At the end of the study, BMS will not continue to provide BMS supplied study treatment to participants/investigators unless BMS chooses to extend the study. The investigator should ensure that the participant receives appropriate standard of care to treat the condition under study.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

Participants MUST discontinue IP (and non-IP at the discretion of the investigator) for any of the following reasons:

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information
- Any clinical AE, laboratory abnormality, or intercurrent illness which in the opinion of the investigator indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- Documented disease progression or clinical deterioration while receiving active study therapy with exception as described in Section 5.1.3.
- Pregnancy
- Participants who are required to have prohibited concomitant medications
- Inability to comply with the protocol

Refer to the Schedule of Activities for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

In the case of pregnancy, the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the BMS Medical Monitor/designee of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Refer to Section 9.2.5.

All participants who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 5.1.4. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records and entered on the appropriate CRF page.

8.1.1 Follow-up after Conclusion of Study Treatment

In this study, safety and tolerability information are key endpoints of the study. Post study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

8.2 Discontinuation from the Study

Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study treatment only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-Up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of three documented phone calls, faxes, or emails as well as lack of response by the participant to one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain the date and cause of death.
- If the investigator's use of any third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining the participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.

- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities (Section 2).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities (Section 2).

9.1 Efficacy Assessments

Only data for the procedures and assessments specified in this protocol should be submitted to BMS on a CRF. Additional procedures and assessments may be performed as part of standard of care; however, data for these assessments should remain in the participant's medical record and should not be provided to BMS, unless specifically requested.

9.1.1 Imaging Assessment for the Study

Images will be acquired up to 30 days prior to first dose, every 8 weeks (starting from first dose ± 7 days) for the first 48 weeks, then every 12 weeks (± 7 days) until withdrawal of consent, death, or initiation of another anti-cancer treatment. These will be submitted to an imaging core laboratory for BICR. Sites should be trained prior to scanning the first study participant. Image acquisition guidelines and submission process will be outlined in the CA025006 Imaging Manual to be provided by the core lab.

Efficacy assessments for the anti-tumor activity of cabiralizumab in combination with nivolumab with and without chemotherapy will be based on tumor measurements, using RECIST v1.1 per BICR and investigator assessment. Efficacy evaluation [redacted] will be performed for each experimental arm.

Screening images should be acquired as outlined in Table 2-1. On-study images should be acquired as outlined in Table 2-2 and Table 2-3 from the date of first dose until subsequent therapy is started, withdrawn consent, lost to follow-up, or death, whichever occurs first.

9.1.2 Methods of Measurement

Contrast-enhanced CT of the chest, abdomen, pelvis, and all other known/suspected sites of disease should be performed for tumor assessments. Images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging time points. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Change in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the investigator.

Should a participant have contraindication for CT intravenous contrast, a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

Should a participant have contraindication for both MRI and CT intravenous contrasts, a non-contrast CT of the chest and a non-contrast MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

Should a participant have contraindication for MRI (eg, incompatible pacemaker) in addition to contraindication to CT intravenous contrast, a non-contrast CT of the chest, abdomen, pelvis, and other known/suspected sites of disease is acceptable.

Use of the CT component of a PET/CT scanner: Combined modality scanning such as with FDG-PET/CT is increasingly used in clinical care and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT are of limited use in anatomically-based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically-based RECIST measurements. However, if a site can document that the CT performed as part of a FDG-PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the FDG-PET/CT can be used for RECIST v1.1 measurements. Note, however, that the FDG-PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Bone scan or PET scan is not adequate for assessment of RECIST v1.1 response in target lesions. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

Brain and/or bone scans may be collected per local standards, as clinically indicated.

Screening assessments are to be performed within 30 days prior to first dose. In addition to the chest, abdomen, pelvis, and brain (to rule out brain metastases), all known sites of disease should

be assessed at baseline. Subsequent assessments should include chest, abdomen, pelvis, and all known sites of disease using the same imaging method and technique as was used at baseline.

In addition, participants receiving cabiralizumab and nivolumab treatment beyond progression must continue tumor assessments until such treatment has been discontinued. Treatment beyond disease progression with cabiralizumab and nivolumab in participants with solid tumors is reported in Section 5.1.3.

[redacted]

9.2 Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

[redacted]

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue before completing the study.

IMAEs are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's CRF.

Contacts for SAE reporting are specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment until 100 days after discontinuation of dosing or until starting a new anti-neoplastic therapy (whichever occurs first) at the time points specified in the Schedule of Activities (Section 2). Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participants.

Sections 5.6.1 and 5.6.2 in the Investigator's Brochure (IB) for nivolumab,[31] Section 6.4.1 of the cabiralizumab IB,[30] and Section 4.8 of the SmPCs for gemcitabine,[49] irinotecan (ONIVYDE®),[50] paclitaxel (ABRAXANE®),[51] oxaliplatin,[52] 5-FU,[53] and leucovorin[54] represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting. Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs that occur during the screening period and within 100 days after discontinuation of dosing must be collected except in cases where a study participant has started a new anti-neoplastic therapy. Any SAE occurring after the start of a new treatment that is suspected to be related to study treatment by the investigator will be reported. If applicable, SAEs that relate to any later protocol-specified procedure (eg, a follow-up biopsy) must be collected.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

- Medical occurrences that begin before the start of study treatment but occurred after obtaining informed consent will be recorded on the appropriate section of the electronic CRF.
- All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of this data being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant

has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

The method of evaluating and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 3.

9.2.2 Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AE and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known adverse events, when appropriate for the program or protocol.

9.2.3 Follow-up of AEs and SAEs

- Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment, as appropriate.
- All identified non-serious AEs must be recorded and described on the nonserious AE page of the CRF. Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

Further information on follow-up procedures is given in Appendix 3.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Sponsor or designee will be reporting AEs to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

If following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least

5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, or re-initiation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur. If, for whatever reason, pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended), following approvals of participant/sponsor/IRB/EC, as applicable.

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

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the Sponsor or designee. In order for the 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. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the non-serious AE CRF page or electronic SAE Report Form, as appropriate (paper forms are only intended as a back-up option when the electronic system is not functioning):

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

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

9.2.7 Potential Drug-Induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.2 and Appendix 3 for reporting details).

Potential drug induced liver injury is defined as:

1) Aminotransferase (AT) (ALT or AST) elevation > 3× ULN

AND

2) Total bilirubin > 2× ULN, without initial findings of cholestasis (elevated serum ALP)

AND

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

9.2.8 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a non-serious or SAE, as appropriate, and reported accordingly.

9.3 Overdose

For this study, any dose of cabiralizumab and/or nivolumab greater than the assigned dose and considered excessive and medically important by the investigator will be considered an overdose.

In the event of an overdose, the investigator should:

1) Contact the BMS Medical Monitor immediately
2) Closely monitor the participant for AEs/SAEs and laboratory abnormalities until cabiralizumab and/or nivolumab can no longer be detected systemically (at least 5 days)
3) Obtain a plasma sample [redacted] within 5 days from the date of the last dose of study treatment if requested by the BMS Medical Monitor (determined on a case-by-case basis)
4) Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the BMS Medical Monitor based on the clinical evaluation of the participant.

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities.

Only data for the procedures and assessments specified in this protocol should be submitted to BMS on a CRF. Additional procedures and assessments may be performed as part of standard of care; however, data for these assessments should remain in the participant's medical record and should not be provided to BMS, unless specifically requested.

9.4.1 Physical Examinations

Refer to Schedule of Activities. Standard physical examination will be performed as determined by the investigator, particularly to follow physical findings to resolution. Targeted physical exams should be conducted at any time to follow-up on AE reports.

9.4.2 Vital signs

Refer to Schedule of Activities. Vital signs include respiratory, heart rate, blood pressure, and temperature in the resting position for at least 5 minutes (sitting or supine). Vital signs to be measured for every treatment arm before infusion of the first study drug on Days 1 and 15 of each cycle at approximately the same time as the ECG is obtained. For cabiralizumab administration and nivolumab administration on Cycles 1 and 5, measure vital signs prior to dose and after completion of each IV infusion at the following time points: 15 (± 5) minutes, 30 (± 10) minutes, 45 (± 10) minutes, 60 (± 15) minutes and 360 hours (± 24 hours) [Day 1 and Day 15] post-cabiralizumab administration; 10 (± 5) minutes post-nivolumab administration. If any vital sign is abnormal (based on clinician's assessment) at the final check, the participant must be observed for a further period of time, as clinically indicated.

9.4.3 Electrocardiograms

Refer to Schedule of Activities. A 12-lead ECG will be obtained at screening for all participants. 12-lead ECGs will also be obtained for the initial 6 participants in Treatment Arms C and D, at predose and approximately 4 hours postdose of cabiralizumab and nivolumab (within 4 hours of completion of cabiralizumab) on Cycle 1 Day 1. Subsequent ECGs for these participants will be single-lead ECGs. Single-lead ECG tests will be obtained for all other participants prior to the start of the infusion of the first drug on Day 1 of each cycle. If clinically indicated, additional ECGs may be obtained during the study. To minimize variability, it is important that participants be in a resting position for at least 5 minutes prior to each ECG evaluation.

9.4.4 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- A local laboratory will perform the analyses and will provide reference ranges for these tests.
- Results of clinical laboratory tests performed at Day 1, Day 8 (as appropriate), and Day 15 on each cycle for each treatment arm must be available prior to dosing to allow for dose modifications, if needed (unless obtaining assessment results are not possible due to local laboratory feasibility).

A local laboratory will perform the analyses and will provide reference ranges for these tests.

Results of clinical laboratory tests performed on Day 1 must be available prior to dosing.

Table 9.4.4-1: Clinical Laboratory Tests

Hematology	
Hemoglobin	
Hematocrit	
CBC, including differential	
Platelet count	
Serum Chemistry	
AST	Total protein
ALT	Albumin
Total bilirubin	Sodium
Direct bilirubin	Potassium
ALP	Chloride
LDH	Calcium
Creatinine	Phosphorus
BUN	Magnesium
Uric acid	Creatine kinase
Glucose	Creatinine clearance (CLcr)- screening only
Thyroid Panel (Includes TSH, Free T3 and Free T4)	
Urinalysis	
Protein	
Glucose	
Blood	
Leukocyte esterase	
Specific gravity	
pH	
Serology	
Serum for hepatitis C antibody, hepatitis B surface antigen, HBc antibody, interferon-gamma release assays for tuberculosis (eg, Quantiferon test), and HIV-1 and HIV-2 antibody (screening only)	
Other Analyses	
Pregnancy test (WOCBP only: screening, predose, discharge, and monthly during treatment and safety follow-up periods).	
FSH (screening only for women)	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CLcr = creatine clearance; FSH = follicle-stimulating hormone; Hbc = hepatitis B core; HIV; human immunodeficiency; LDH = lactate dehydrogenase; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

If CK elevation is clinically significant, obtain troponins (cardiac), CK isoenzymes, aldolase, and ECG; repeat CK and these additional tests within 24 hours or other interval, as clinically indicated, until resolved or stable. If either AST or ALT is elevated, obtain total serum bilirubin and ALP; repeat within 24 hours or other interval, as clinically indicated, until resolved or stable. Additional tests may be obtained at any time, if clinically indicated. If a participant is being followed for a tumor marker (eg, CA-19-9 or others), a sample for the tumor marker should be obtained at screening and at every cycle, or if clinically indicated during the study.

9.4.5 Imaging Safety Assessment

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the study investigator as per standard medical/clinical judgment.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

One purpose of the 2L Cohort is to evaluate the preliminary efficacy of cabiralizumab (BMS-986227) in combination with nivolumab with or without chemotherapy compared with the investigator's choice of standard-of-care chemotherapy in participants with advanced or metastatic pancreatic cancer who progressed after the 1L of chemotherapy (gemcitabine-based or 5-FU-based); additional rationale for the 2L Cohort can be found in Section 3.1.1.1 and Section 5.4. Participants who progressed after the 1L gemcitabine-based chemotherapy will be randomized in a 1:1:2 ratio to receive investigator's choice of chemotherapy (Treatment Arm A), cabiralizumab in combination with nivolumab (Treatment Arm B), or cabiralizumab in combination with nivolumab and FOLFOX (Treatment Arm D). Participants who progressed after the 1L 5-FU-based chemotherapy will be randomized in a 1:1:2 ratio to receive investigator's choice of chemotherapy (Treatment Arm A), cabiralizumab in combination with nivolumab (Treatment Arm B), or cabiralizumab in combination with nivolumab and gemcitabine + nab-paclitaxel (Treatment Arm C).

Randomization is used to avoid potential imbalance of baseline characteristics and will be stratified according to ECOG status (0 or 1) prior to treatment. There will be no formal statistical hypothesis testing and no multiplicity adjustment. Evaluation of efficacy will be based primarily on the PFS together with ORR, duration of response (DOR), time to response, depth of response, PFS rate (PFSR), and other aspects of effectiveness.

[redacted]

The sample size consideration is based on the following assumptions:

The false positive rate (FPR) is set at approximately 20%, and the false negative rate (FNR) is set at approximately 10%. The median PFS is assumed as 3.1 months in Treatment Arm A based on the NAPOLI-1 study[55] and 5.4 months in Treatment Arms C and D by combining cabiralizumab and nivolumab with chemotherapy. In this setting, it will be required to observe at least 59 PFS events (see Note below). When the assessment of endpoint is "time-to-event" such as PFS, the number of participants needed to have the required number of PFS events depends on the accrual rate of participants. For example, assuming a fixed accrual rate of 16 participants per month with equal distribution across 4 treatment arms, a total of approximately 80 participants are needed to be treated for Treatment Arms A and C (or D) in order to achieve the 59 PFS events required. The enrollment will take approximately 10 months, and the duration of the study is estimated to be approximately 14 months. If enrollment rate is slower, for example, a fixed accrual rate is 8 participants per month with equal distribution across 4 treatment arms, then a total of 70 participants are needed for Treatment Arms A and C (or D) in order to have 59 PFS events. The accrual duration will be 17.5 months and the maximum duration of the study will be approximately 22 months. Overall, approximately 40 participants in each treatment arm will be treated and followed until 59 PFS events are observed in Treatment Arms A and C combined, as well as in Treatment Arms A and D combined. In case a lower FPR is desired, a longer follow-up may be allowed or additional participants may be treated in order to observe additional PFS events.

NOTE: This sample size calculation is under the assumption that PFS follows an exponential distribution.

10.2 Populations for Analyses

For the purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent and are registered into the IRT.
Randomized	All participants who are randomized to any treatment arm.
Treated	All participants who take at least one dose of study drug and will be analyzed as treated.
Efficacy	Randomized population with at least one dose of study drug and will be analyzed as randomized.
Response-evaluable	Efficacy population with measurable disease at baseline and one of the following: (a) at least 1 post baseline tumor assessment, (b) clinical progression, (c) death.

[redacted]

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Below is a summary of planned statistical analyses of the primary and secondary endpoints.

A description of the participant population will be included in a statistical output report, including subgroups of age, gender, and race.

10.3.1 Efficacy Analyses

Efficacy analyses for the primary and secondary endpoints (Table 10.3.1-1) will be performed on the efficacy population for the final analysis. Efficacy analyses based on the response-evaluable population may be performed for interim analyses when the minimum follow-up period is less than sufficient to warrant adequate interpretation of the result. Details of the censoring scheme on time-to-event endpoints such as DOR, PFSR, and OSR will be described in the Statistical Analysis Plan.

Table 10.3.1-1: Efficacy - Statistical Analyses

Endpoint	Statistical Analysis Methods
PFS and PFSR at 6, 9, and 12 months will be assessed per RECIST v1.1 by BICR and investigator assessment. PFS for a participant is defined as the time from randomization date to the date of first objectively documented disease progression by BICR or investigator per RECIST v1.1 or death due to any cause, whichever occurs first.	PFS curves for each randomized arm will be estimated and plotted using the K-M product limit method. Median PFS along with 95% CI will be constructed based on a log-log transformed CI for PFS. In addition, the hazard ratio and the corresponding 1-sided 80% CI for the HR (each experimental group versus combined chemotherapy) will be estimated in a Cox proportional hazards model.
ORR is defined as the proportion of participants whose BOR is either CR or PR per RECIST v1.1 in the population of interest. BOR for a participant will be assessed per RECIST v1.1 by BICR and investigator assessment.	Estimate of ORR and corresponding 2-sided exact 95% CI using the Clopper-Pearson method.
OS and OSR at 6 months, 1 year, and 2 years OS is defined as the time from randomization to the date of death to any cause.	Estimate by the Kaplan-Meier method and corresponding 2-sided 95% CI using Brookmeyer and Crowley methodology (using log-log transformation) for the median and Greenwood formula for the rate.
DOR will be assessed per RECIST v1.1 by BICR and investigator assessment. DOR for a participant with a BOR of CR or PR is defined as the time between the date of first response and the date of the first objectively documented tumor progression by BICR or investigator per RECIST v1.1 or death, whichever occurs first.	Estimate by the Kaplan-Meier method and corresponding 2-sided 95% CI using Brookmeyer and Crowley methodology (using log-log transformation).

Abbreviations: BICR = blinded independent central review; BOR = best overall response; CI = confidence interval; CR = complete response; DOR = duration of response; ORR = objective response rate; OSR = overall survival rate; PFS = progression-free survival; PFSR = PFS rate; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

10.3.2 Safety Analyses

All safety analyses will be performed on the treated population.

Table 10.3.2-1: Safety - Statistical Analyses

Endpoint	Statistical Analysis Methods
Incidence of AEs, SAEs, and AEs leading to discontinuation, and death AEs will be graded according to CTCAE v4.03.	Frequency distribution of treated participants with AE using the worst CTC grade. Participants will only be counted (1) once at the PT level, (2) once at the SOC level, and (3) once in the "Total subject" row at their worst CTC grade, regardless of SOC or PT.
Laboratory abnormalities Laboratory values will be graded according to CTCAE v4.03.	Laboratory shift table using the worst CTC grade on treatment per participant.

Abbreviations: AE = adverse event; CTC = common terminology criteria; CTCAE = common terminology criteria for adverse events; PT = preferred term; SAE = serious adverse event; SOC = system organ class.

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10.3.7 Interim Analyses

Interim analyses will be performed for administrative purposes or publications. No formal inferences requiring any adjustment to statistical significance level will be performed.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
1L	first line
5-FU	5-fluorouracil
ADA	anti-drug antibody
AE(s)	adverse event(s)
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APC	antigen-presenting cells
AST	aspartate aminotransferase
[redacted]	[redacted]
BICR	Blinded Independent Central Review
BMI	body mass index
BMS	Bristol-Myers Squibb
BOR	best observed response
BUN	blood urea nitrogen
CBC	complete blood count
CDA	cytidine deaminase
[redacted]	[redacted]
CFR	Code of Federal Regulations
CK	creatinine kinase
CI	confidence interval
CLcr	creatinine clearance
[redacted]	[redacted]
Cmaxss	steady-state peak concentration
[redacted]	[redacted]
Cminss	steady-state trough concentration
CMV	cytomegalovirus
CNS	central nervous system

Term	Definition
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRF	Case Report Form, paper or electronic
CSF1R	colony-stimulating factor 1 receptor
[redacted]	[redacted]
CT	computerized tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte antigen-4
[redacted]	[redacted]
[redacted]	[redacted]
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	data monitoring committee
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
ELISA	enzyme-linked immunosorbent assay
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose positron emission tomography
FFPE	formalin-fixed paraffin-embedded
FNR	false negative rate
FOLFIRI	irinotecan/leucovorin/5-fluoruracil
FOLFIRINOX	folinic acid/5-fluoruracil/irinotecan/oxaliplatin
FOLFOX	oxaliplatin, 5-fluorouracil, and leucovorin
FPR	false positive rate

Term	Definition
FSH	follicle stimulating hormone
GFR	glomerular filtration rate
GI	gastrointestinal
[redacted]	[redacted]
H&E	hematoxylin and eosin
HCG	beta-human chorionic gonadotrophin
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
IEC	Independent Ethics Committee
IFN-γ	interferon-γ
IgG4	immunoglobulin G4
IHC	immunohistochemistry
[redacted]	[redacted]
IMP	investigational medicinal product
INR	international normalized ratio
IO	immuno-oncology
IP	investigational product
IRB	Institutional Review Board
[redacted]	[redacted]
IRT	Interactive Response Technology
IV	intravenous
Kd	dissociation constant
LDH	lactate dehydrogenase
mAb	monoclonal antibody
mmHg	millimeters of mercury
MRI	magnetic resonance imaging
[redacted]	[redacted]
N	number of subjects or observations

Term	Definition
NCI	National Cancer Institute
NOAEL	no-observed adverse effect level
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
OSR	overall survival rate
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD-1	programmed cell death-1
PDAC	pancreatic ductal adenocarcinoma
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PET	positron emission tomography
PFS	progression-free survival
PFSR	progression-free survival rate
PID	participant identification
PK	pharmacokinetics
PPK	population pharmacokinetics
PR	partial response
[redacted]	[redacted]
PT	preferred term
PVNS	pigmented villonodular synovitis
Q2W	every 2 weeks
Q4W	every 4 weeks
[redacted]	[redacted]
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SCCHN	squamous cell carcinoma of the head and neck

Term	Definition
SD	stable disease
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
[redacted]	[redacted]
TAM	tumor-associated macrophages
TB	tuberculosis
TME	tumor microenvironment
ULN	upper limit of normal
US	United States
[redacted]	[redacted]
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The term 'Participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'Subject' used in the case report form (CRF) is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines Good Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent form will receive approval/favorable opinion by the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation, etc) that is likely to affect, to a significant degree 1 or more of the following: (1) the physical, safety, or mental integrity of 1 or more subjects/participants; (2) the scientific value of the trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP Regulation(s) or Trial protocol(s).

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, participant recruitment materials (eg, advertisements), and any other written information to be provided to subjects/participants. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects/participants and any updates.

The investigator, Sponsor, or designee should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and, if applicable, also by the local health authority) except where necessary to eliminate any immediate hazard(s) to study subjects/participants.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s), the deviation or change will be submitted, as soon as possible to:

- IRB/IEC
- Regulatory Authority(ies), if applicable by local regulations (per national requirements).

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and, if applicable, also by the local health authority must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects/participants currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects/participants prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

FINANCIAL DISCLOSURE

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

Investigators must ensure that subjects/participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given by subjects/participants, investigators must ensure that their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the participant volunteers to participate.

Sponsor or designee will provide the investigator with an appropriate (ie, global or local) sample informed consent form, which will include all elements required by ICH, GCP, and other applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for a participant, or a participant's legally acceptable representative, to inquire about the details of the study.
- Obtain an informed consent form signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects/participants, prior to the beginning of the study and after any revisions are completed for new information.

If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant, or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue his or her participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects/participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects'/participants' signed ICF, and, in the US, the subjects'/participants' signed HIPAA authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to participant records.

The rights, safety, and well-being of the study subjects/participants are the most important considerations and should prevail over interests of science and society.

SOURCE DOCUMENTS

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original, and attributable, whether the data are handwritten on paper or entered

electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic health/medical records (EHRs/EMRs), adverse event (AE) tracking/reporting, protocol-required assessments, and/or drug accountability records).

When paper records from such systems are used in place of an electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

STUDY TREATMENT RECORDS

Records for study treatments (whether supplied by BMS, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a health authority.

If	Then
Supplied by BMS (including its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • non-study disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence/biocomparability, if applicable • dates and initials of person responsible for investigational product (IP) dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP	The investigator or designee accepts responsibility for documenting traceability and study treatment

If	Then
sourced from the sites stock or commercial supply or a specialty pharmacy)	integrity in accordance with requirements applicable under law and the standard operating procedures (SOPs)/standards of the sourcing pharmacy.

BMS or designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

CASE REPORT FORMS

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the case report form (CRF) must be consistent with the source documents, or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor or designee electronic data capture (EDC) tool, eCRFs will be prepared for all data collection fields except for fields specific to serious adverse events (SAEs) and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If an electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor or designee.

The confidentiality of records that could identify subjects/participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF and SAE/pregnancy CRFs must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. Sub-investigators in Japan may not be delegated the CRF approval task. For eCRFs, review and approval/signature is completed electronically through the BMS EDC tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing eCRFs must meet Sponsor or designee training requirements and must only access the BMS EDC tool using the unique user account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals

MONITORING

Sponsor or designee representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site, they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents.

In addition, the study may be evaluated by Sponsor or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

If the investigator withdraws from the study (eg, due to relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, study site, IRB). Notice of such transfer will be given in writing to BMS or designee.

RETURN OF STUDY TREATMENT

For this study, study treatments (those supplied by BMS or a vendor or sourced by the investigator) such as partially used study treatment containers, vials, and syringes may be destroyed on site.

If	Then
Study treatments supplied by BMS (including its vendors)	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor, unless study treatment containers must be immediately destroyed as required to meet safety and local regulations (eg, cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS or its vendors (examples include study	It is the investigator's or designee's responsibility to dispose of all containers

treatments sourced from the sites stock or commercial supply or a specialty pharmacy)	according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal of study treatments, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the study treatment.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs, and a copy must be provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor, must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Study Monitor to review throughout the clinical trial period.

It is the investigator's or designee's responsibility to arrange for disposal of all empty study treatment containers.

If conditions for destruction cannot be met, the responsible Study Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of non-study treatments sourced by the site, not supplied by BMS, are solely the responsibility of the investigator or designee.

CLINICAL STUDY REPORT

A Signatory Investigator must be selected to sign the clinical study report.

For each CSR related to this protocol, the following criteria will be used to select the signatory investigator:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in the trial design
- Regional representation (eg, among the top quartile of enrollers from a specified region or country)

SCIENTIFIC PUBLICATIONS

The data collected during this study are confidential and proprietary to Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing study site participation in the study. These requirements include, but are not limited to, submitting proposed publications to Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

Scientific Publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any principal investigator, sub-investigator or any other member of the study staff without the prior written consent of the Sponsor. Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable subjects with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who make the most significant contributions, as defined above, will be considered by BMS for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.

An AE can, therefore, be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis..
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term.

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

SERIOUS ADVERSE EVENTS

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery planned prior to signing consent • admission as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy) • medical/surgical admission other than to remedy ill health and planned prior to entry into the study (appropriate documentation is required in these cases) • admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, or administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect

Is an important medical event (defined as a medical event[s] that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., medical, surgical] to prevent 1 of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug-induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

Pregnancy and potential drug induced liver injury (DILI) must follow the same transmission timing and processes to BMS as used for SAEs (see Section 9.2.5 for reporting pregnancies).

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

EVALUATING AEs AND SAEs

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor. • The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term[s] initially reported.) If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs must be followed to resolution or stabilization.

REPORTING OF SERIOUS ADVERSE EVENTS TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the eCRF.
  - The paper SAE Report Form is only intended as a backup option when the electronic data capture (EDC) system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile (fax) transmission
    - When paper forms are used, the original paper forms are to remain on site.
- Pregnancies must be recorded on a Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission.

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause.

Note: Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout periods below are suggested guidelines, and the investigators should use their judgement in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (eg, rings, creams, gels)
- 4 weeks minimum for transdermal products
- 8 weeks minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal.

End of Relevant Systemic Exposure

- End of relevant systemic exposure is the time point where the investigational medicinal product (IMP), or any active major metabolites, has decreased to a concentration that is no longer

considered to be relevant for human teratogenicity or fetotoxicity. This should be evaluated in the context of safety margins from the no-observed adverse effect level (NOAEL) or the time required for 5 half-lives of the IMP to pass.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 6 months after the end of nab-paclitaxel (ABRAXANE®) study treatment, and 5 months after the end of any other study treatment(s).

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Intrauterine device (IUD)[c] • Intrauterine hormone-releasing system (IUS)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

• It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence.
NOTES: [a] Typical-use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] IUDs and IHSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from IUDs do not alter contraception effectiveness.

Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of >1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, postovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • Lactation amenorrhea method

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.

- Male participants are required to use a condom for study duration and until the end of relevant systemic exposure, defined as 7 months after the end of treatment.
- Female partners of male participants to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment of the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of treatment.
- Refrain from donating sperm for the duration of the study treatment and for 7 months after the end of treatment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of pregnancy information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and the Appendix for Adverse Events and Serious Adverse Events Definitions and Procedures for Evaluating, Follow-up, and Reporting.

APPENDIX 5 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) WITH BMS MODIFICATIONS

1 EVALUATION OF LESIONS

Solid tumors will be evaluated using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1) guidelines with BMS modifications.[1]

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

1.1 Measurable

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

10 mm by computerized tomography (CT)/magnetic resonance imaging (MRI) scan (scan slice thickness no greater than 5 mm, or ≥ 2x slice thickness if greater than 5mm).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT/MRI scan (scan slice thickness recommended to be no greater than 5 mm).

Lymph nodes merit special mention since they are normal anatomical structures, which may be visible by imaging even if not involved by a tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT/MRI scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by a solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measurements is the short axis. For example, an abdominal node that is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with a short axis of ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered nonpathological and should not be recorded or followed.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.2 Non-Measurable

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

Note: Lesions on X-Ray are not to be selected as target or non-target lesions.

1.3 Special Considerations Regarding Lesion Measurability

1.3.1 Bone Lesions

- Bone scan, positron emission tomography (PET) scan, and plain films are ***not*** considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

1.4 Baseline Documentation of 'Target' and 'Non-Target' Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only 1 or 2 organ sites involved, a maximum of 2 and 4 lesions, respectively, will be recorded).

Note: A maximum of 2 lesions can be selected per organ system. For example, a maximum of 2 lung lesions can be selected (from 1 lung or 1 lesion from each lung). A maximum of 2 lymph nodes can be selected at baseline, as the lymphatic system is considered as 1 organ.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition, should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

A sum of the diameters (longest axis for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis will be added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum during the study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- **Not Evaluable (NE):** If 1 or more target lesions cannot be measured or adequately assessed as either fully resolved or are too small to measure (due to missing or poor-quality images), and the sum of diameters of the remaining measured target lesions (if any) has not increased sufficiently to meet PD as defined above.

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be 0 even if the complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may, therefore, be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

2.1.1.2 Target lesions that become 'too small to measure'

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when measured to be very small (eg, 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan, such that the radiologist may not feel comfortable assigning an exact measurement and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned as the reference diameter. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is

faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well.) This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5 mm.

2.1.1.3 Lesions that split or coalesce on treatment

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.2 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- **Complete Response (CR):** Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- **Non-CR/Non-PD:** Persistence of 1 or more non-target lesion(s).
- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions.

2.2.1 Special Notes on Assessment of Progression of Non-Target Disease

The concept of progression of non-target disease requires additional explanation as follows:

2.2.1.1 When the patient also has measurable disease

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Pleural effusions, pericardial effusions, and ascites will not be followed as target or non-target lesions and will not contribute to response or progression. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will, therefore, be extremely rare.

2.2.1.2 When the patient only has non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable

disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is will be employed to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in lymphangitic disease from localized to widespread, or which be described as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

2.2.2 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

NOTE: Fluid collections (pleural effusions, pericardial effusions, and ascites) will not be considered new lesions and will not contribute to response or progression. In the event that a new fluid collection is seen on a post-baseline imaging exam, a comment may be made, but the appearance of a new fluid collection alone should not result in an assessment of PD. A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is a patient who has visceral disease at baseline and while on study has a CT or MRI scan of the brain ordered that reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have a brain imaging done at baseline. A lesion identified on chest X-Ray that was not present in a prior CT scan can be considered a new lesion and will result in PD.

If a new lesion is equivocal, for example, because of its small size, continued follow-up evaluation will clarify if it truly represents a new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan. While fluorodeoxyglucose PET (FDG-PET) response assessments need additional study, it is sometimes reasonable to incorporate the use of a FDG-PET scan to complement the CT scan in assessment of progression (particularly of a possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

2. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is considered as PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this is not considered as PD.

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until disease progression or the last response recorded, taking into account any requirement for confirmation and censoring rules regarding subsequent therapy. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require a confirmatory measurement.

2.3.2 Time Point Response

At each protocol-specified time point, a response assessment occurs. Table 2.3.2-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore, non-target) disease only, Table 2.3.2-2 is to be used.

Table 2.3.2-1: Time Point Response: Patients with Target (± Non-Target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluated; PD = progressive disease; PR = partial response; SD = stable disease

Table 2.3.2-2: Time Point Response: Patients with Non-Target Disease Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response; NE = not evaluated; PD = progressive disease		

[a] Non-CR/non-PD is preferred over SD for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials, hence it is not advisable to assign this category when no lesions can be measured.

2.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks (28 days) later. In this circumstance, the best overall response can be interpreted as in Table 2.3.3-1. When SD is believed to be the best response, it must meet the protocol-specified minimum time from the date of first treatment or randomization date.

For example, if the first scheduled follow-up imaging visit is Week 6 (± 7 days) for a particular protocol, a best response of SD can only be made after the subject is on-study for a minimum of 6 weeks (42 days) minus 7 days, for an absolute minimum time on-study of 35 days from the reference start date (reference date is considered Day 1 on study). If the subject is not on-study for at least this amount of time, any tumor assessment indicating SD before this time period will have a best response of NE unless PD is identified.

Special note on response assessment: When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate a progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of '0' on the case report form (CRF).

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided that minimum criteria for SD duration are met; otherwise, PD

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	PD	SD provided that minimum criteria for SD duration are met; otherwise, PD
CR	NE	SD provided that minimum criteria for SD duration are met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided that minimum criteria for SD duration are met; otherwise, PD
PR	NE	SD provided that minimum criteria for SD duration are met; otherwise, NE
NE	NE	NE
CR = complete response; NE = not evaluated; PD = progressive disease; PR = partial response, SD = stable disease		

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

2.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive or subsequent repeat assessments that should be performed no less than 28 days after the criteria for response are first met. Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE or PR (eg, CR NE CR or CR PR CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (eg, PR NE PR or PR SD PR). However, only 1 intervening time point will be allowed between PR/CRs for confirmation.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered to not have PD.

[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-47.

APPENDIX 6 ECOG PERFORMANCE STATUS

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

[a] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655.

APPENDIX 7 ADVERSE EVENT MANAGEMENT FOR CABIRALIZUMAB AND NIVOLUMAB COMBINATION THERAPY ARMS

Gastrointestinal Adverse Event Management		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue study drugs. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.		
Grade of Diarrhea/Colitis (NCI CTCAE v4.03)	**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 3/4
Grade 2: Diarrhea: 4-6 stools/day over baseline; IV fluids indicated <24 hours; not interfering with ADL; Colitis: abdominal pain; blood in stool	– Delay cabiralizumab and nivolumab per protocol[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 ≥24 hours; interfering with ADL; Colitis (G3): Severe abdominal pain, medical intervention indicated, and peritoneal signs Grade 4: Life-threatening perforation	– 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 **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 study drugs.		
Grade of Creatinine Elevation (NCI CTCAE v 4.03)	**Management**	**Follow-Up**
Grade 1: Creatinine > ULN and > baseline but ≤ 1.5x baseline	– 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:** – Treated as Grade 2 or Grade 3/4
Grade 2-3: Creatinine >1.5x ≤ 6x 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 >7 days or worsen:** – Treat as Grade 4
Grade 4: Creatinine >6.0x ULN	– Discontinue cabiralizumab and nivolumab therapy per protocol [c] – Monitor creatinine daily – 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

[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 study drugs. Evaluate with imaging and pulmonary consultation.		
Grade of Pneumonitis (NCI CTCAE v 4.03)	**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)

[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 Without Liver Metastasis		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue study drugs. Consider imaging for obstruction.		
Grade of Liver Test Elevation	**Management**	**Follow-Up**
AST or ALT >3.0x ULN ***and*** Total bilirubin >2x ULN **or** INR > 1.5	– Discontinue cabiralizumab and nivolumab per protocol – Start steroids	– Continue LFT monitoring per protocol until resolution. – Continue monitoring for and other associated clinical signs or symptoms – Contact the Sponsor Medical Monitor – 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 Sponsor/MM and the investigator if receiving additional treatment with cabiralizumab and nivolumab is in the best interest of the patient (eg, if the subject has demonstrated a response to therapy)
AST or ALT >5 to ≤12 xULN ***and*** Total bilirubin ≤2x ULN	– Continue cabiralizumab and nivolumab therapy if there are no clinical signs of significant muscle or hepatic damage – Increase frequency of monitoring of AST, ALT, bilirubin, alkaline phosphatase, and INR (every 48-72 hours or more frequently, as clinically indicated) – Monitor for other clinical symptoms (fatigue, nausea, vomiting, abdominal pain, fever, rash, and/or eosinophilia)	– Contact the Medical Monitor if there are clinical signs of muscle or hepatic injury or other clinical symptoms – Contact the Medical Monitor if there is a concurrent increase of bilirubin, AST, ALT, or alkaline phosphatase – Notify the Medical Monitor if there is an AST or ALT increase >5x ULN – Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic – Consider gastroenterology or hepatology referral
AST or ALT > 12 to ≤ 20 xULN ***and*** Total bilirubin ≤ 2 xULN ***or*** Isolated total bilirubin > 2 to ≤ 3 xULN	– Delay cabiralizumab and nivolumab therapy per protocol[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 phosphatase along with ALT, start steroids immediately	**If AST/ALT return to ≤12x ULN within ≤7 days:** – Resume routine monitoring – Resume cabiralizumab and nivolumab therapy at same dose level per protocol **If elevations persist and remain at the same level >7 days but ≤28 days:** – Start steroids immediately and discontinue further dosing – Continue monitoring and consider dosing the subject with nivolumab therapy at the same dose level – Consider tapering steroids over at least 1 month **If elevations persist at the same level >28 days or worsen:** – Discontinue cabiralizumab and nivolumab 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 – Consider prophylactic antibiotics for opportunistic infections – Discuss with Medical Monitor

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

[a] 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.

Hepatic Adverse Event Management with Liver Metastasis		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue study drugs. Consider imaging for obstruction.		
Grade of Liver Test Elevation	**Management**	**Follow-Up**
AST or ALT >3.0x ULN ***and*** Total bilirubin >2x ULN **or** INR > 1.5	– Discontinue cabiralizumab and nivolumab therapy per protocol – Start steroids	– Continue LFT monitoring per protocol until resolution. – Continue monitoring for and other associated clinical signs or symptoms – Contact the Medical Monitor – Evaluate for non-drug-related causes of the laboratory abnormalities (e.g. obstruction, viral infection, Gilbert's disease, etc) – Under selected circumstances (e.g alternative etiology is identified), the patient may receive additional therapy only after consultation and agreement between the Sponsor/MM and the investigator if receiving additional treatment with cabiralizumab and nivolumab is in the best interest of the patient (e.g if the subject has demonstrated a response to therapy)
AST or ALT > 5 to ≤ 12 xULN ***and*** Total bilirubin ≤ 2 xULN	– Continue cabiralizumab and nivolumab therapy if there are no clinical signs of significant muscle or hepatic damage – Increase frequency of monitoring of AST, ALT, bilirubin, alkaline phosphatase and INR (every 48-72 hours or more frequently, as clinically indicated) – Monitor for other clinical symptoms (fatigue, nausea, vomiting, abdominal pain, fever, rash, and/or eosinophilia)	– Contact the Medical Monitor if there are clinical signs of muscle or hepatic injury or other clinical symptoms – Contact the Medical Monitor if there is a concurrent increase of bilirubin, AST, ALT, or alkaline phosphatase – Notify the Medical Monitor if there is an AST or ALT increase > 5 xULN – Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic. – Consider gastroenterology or hepatology referral
AST or ALT > 12 to ≤ 20 xULN ***and*** Total bilirubin ≤ 2 xULN ***or*** Isolated total bilirubin > 3.0 to ≤ 5 xULN	– 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 AST/ALT return to ≤ 12 xULN within ≤ 7 days:** – Resume routine monitoring, resume cabiralizumab and nivolumab therapy at same dose level per protocol **If elevations persist and remain at the same level > 7 days but ≤ 28 days:** – Start steroids immediately and discontinue further dosing – Continue monitoring and consider dosing the subject with nivolumab therapy at the same dose level – Consider tapering steroids over at least 1 month **If elevations persist at the same level >28 days or worsen:**

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

[a] 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 study drugs. 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 Medical Monitor 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 study drugs.		
Grade of Rash (NCI CTCAE v 4.03)	**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 4.03 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 4.03)	**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 or 3-4
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[b] methylprednisolone IV or PO	**If improves to baseline within 28 days:** – Resume cabiralizumab and nivolumab therapy at same dose level per protocol when improved to baseline **If worsens or persists after 28 days:** – Treat as Grade 3-4
Grade 3–4: Severe symptoms; limiting self-care ADL; life-threatening	– Discontinue cabiralizumab and nivolumab therapy[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 4.03)	**Management**	**Follow-Up**
Grade 1	– Continue cabiralizumab and nivolumab therapy per protocol – Monitor edema weekly	**If worsens:** – Follow as stated below
Grade 2	– Delay cabiralizumab and nivolumab therapy per protocol[a] – Start systemic treatment including steroids, eye drops, or analgesics as needed[b]	**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 4.03)	**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 Medical Monitor 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 v4.03)	**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.

APPENDIX 8 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) Notify the BMS Medical Monitor	**If CK or LDH returns to ≤ 15 xULN within ≤ 28 days:** Resume routine monitoring, resume cabiralizumab and nivolumab therapy at same dose level as per protocol If CK isoenzyme panel is normal continue monitoring the subject. If CK isoenzyme panel is abnormal then consider measuring troponins. If troponins are abnormal, contact 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 Discuss with Medical Monitor
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 9 TNM STAGING

Because only a few patients with pancreatic cancer undergo surgical resection of the pancreas (and adjacent lymph nodes), a single TNM classification must apply to both clinical and pathologic staging.

Table 1: American Joint Committee on Cancer TNM Staging of Pancreatic Cancer (2010)

Primary Tumor (T)		**Regional Lymph Nodes (N)**	
TX	Primary tumor cannot be assessed	NX	Regional lymph nodes cannot be assessed
T0	No evidence of primary tumor	N0	No regional lymph node metastasis
Tis	Carcinoma in situ*	N1	Regional lymph node metastasis
T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension	**Distant Metastases (M)**	
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension	M0	No distant metastases
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery	M1	Distant metastases
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)	**Stage Grouping**	

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
	T1	N1	M0
Stage IIB	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

*This also includes the “PanInIII” classification.

APPENDIX 10 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 03, 24-Apr-2018

Some key changes to Revised Protocol 02 were not included in the final published document. These changes are applied to Revised Protocol 03. Minor clarifications have also been applied.

Summary of key changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-1 Screening Procedural Outline	Addition of language to clarify the pretreatment tumor biopsy	Clarification of pretreatment tumor biopsy to ensure no participants are unnecessarily screen failed
Table 2-2 On-Treatment Procedural Outline	Addition of the collection of Chemistry, Hematology and Urinalysis on D8 for participants receiving Gemcitabine and Nab-Paclitaxel (ABRAXANE) in subsequent cycles.	Omission of safety laboratories for participants receiving Gemcitabine and Nab-Paclitaxel (ABRAXANE)
Table 2-2 On-Treatment Procedural Outline	Update to the notes section for collection of Vital signs	Clarifying Vital Signs collection.
Table 2-2 On-Treatment Procedural Outline	Update to the notes section for collection of ECGs	Clarifying ECG collection.
Table 2-2 On-Treatment Procedural Outline	Inclusion of notes to describe the collection of optional on treatment tumor biopsy and the collection of On Progression tumor biopsy	Clarification to the collection requirements of on treatment and on progression tumor biopsies
[redacted]		
Section 3.1.4 Rationale for Combining Cabiralizumab and Nivolumab, Section 5.4.2 Rationale for Combining Cabiralizumab and Nivolumab Therapy	Addition of data to support the combination of cabiralizumab and nivolumab	To confirm the rationale for combining cabiralizumab and nivolumab.
Table 7-1 Study Treatments for CA025006	Minor updates to the dosage form of some products	
Section 7.4.8, Crossover Post Disease Progression for Participants Treatment with Chemotherapy Only.	Removed Section 7.4.8 and updated Section 5.1.2 Treatment period to reflect the change.	The population eligible for crossover will not meet the eligibility criteria for prior lines of treatment.
Section 9.4.2 Vital Signs	Updated to reflect Table 2-2	Clarifying Vital Sign collection
Section 9.4.3 Electrocardiograms	Updated to reflect Table 2-2	Clarifying ECG collection

Summary of key changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Throughout protocol	Adding a ±5 minute window for infusion period for cabiralizumab and nivolumab	Window period was added to provide some logistical flexibility to the infusion period of cabiralizumab and nivolumab
Section 10.1 Sample Size Determination	Addition wording about the sample size calculation and the assumption of PFS value	Clarification on the PFS assumption used.
Throughout protocol	Minor corrections to add clarity as needed	

Overall Rationale for the Revised Protocol 02, 09-Mar-2018

Changes were made to the protocol based on data collected from the preliminary safety cohort.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3, Introduction; Section 4, Objectives and Endpoints; Section 5.1, Overall Design; Figure 5.1-1, Study Design Schematic; Section 6.1, Inclusion Criteria "2.b"; Section 6.2, Exclusion Criteria "3.d"	Eligible participants include those that have progressed after only 1 line of chemotherapy.	Changed to increase homogeneity of the treated population.
Section 5.1.2, Treatment Period; Section 10.1, Sample Size Determination	Participants will be stratified by ECOG status (0 or 1).	Changed to ensure similar distribution across cohorts and increase homogeneity of the treated population.
Table 2-1, Screening Procedural Outline; Section 5.1.1, Screening Period; Section 5.1.2, Treatment Period; Section 5.4, Scientific Rationale for Study Design; Section 9.1.1, Imaging Assessment for the Study	Screening window updated from 28 to 30 days.	Screening window was increased to provide more time to evaluate the participant without the need to repeat laboratory assessments and scans.
Table 2-1, Screening Procedural Outline; Section 5.1.1, Screening Period; Section 6.1, Inclusion Criteria "3.d.ii"	All participants must have fresh tumor biopsy taken during screening. Up to approximately 8 participants/cohort (~20%) will be allowed on treatment with	To minimize the number of participants that are deemed ineligible based on the absence of adequate tumor sample after

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	pretreatment biopsies that do not yield adequate tumor tissue.	already having undergone the procedure.
Section 7.1, Treatments Administered	For combination cohorts, cabiralizumab will be given on Day 1 and Day 15 of each 28-day treatment cycle.	Corrected typographical error.
Table 2-1, Screening Procedural Outline; Table 9.4.4-1, Clinical Laboratory Tests	Removed fasting requirement for laboratory tests.	Removed, as study treatment is not expected to have a major influence on blood sugar.
Table 2-2, On-treatment Procedural Outline; Section 9.4.2, Vital Signs; Section 9.4.3, Electrocardiograms	Study assessments separated into Cycles 1 and 2 and subsequent cycles.	Edited to streamline the number of visits for the participants.
[redacted]		
Section 5.1.2, Treatment Period; Section 5.4.1, Rationale for Chemotherapy Regimes in Treatment Arm A; Table 7-1, Study Treatments for CA025006; Section 7.1, Treatments Administered	ONIVYDE-based treatment regimens may be substituted with FOLFIRI.	To provide an alternative treatment option for sites where ONIVYDE is not commonly used.
Section 4, Objectives and Endpoints; Section 9.1, Efficacy Assessments	Edited and added to primary, secondary, [redacted] endpoints.	Edited to streamline the endpoints.
Section 5.1.3.1, Safety Follow-up Period; Section 5.1.3.2, Imaging Follow-up Period	Follow-up text edited to match current BMS programs.	Edited to align with BMS processes.
Section 6.1, Inclusion Criteria "3.f.i"	Adequate organ function is defined as ALT and AST ≤ 2 × ULN.	Decreased to minimize the number of participants that may need to hold/discontinue study treatments due to pre-existing liver alterations.
Section 6.1, Inclusion Criteria; Section 6.2, Exclusion Criteria; Section 6.3, Lifestyle Restrictions; Section 7.4.4, Dose Discontinuation Criteria for Cabiralizumab and	Changes to study restrictions based on current study data: • Upon progression biopsy added	Study restrictions were updated based on current safety information.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Nivolumab; Section 7.4.6.1, Gemcitabine + Nab-paclitaxel; Section 7.4.6.2, Dose Modification for FOLFOX; Section 7.6.1, Prohibited and/or Restricted Treatments; Section 9.4.4, Clinical Safety Laboratory Assessments; Section 9.8.1, Tumor Tissue Specimens	• Clarified that participants may only have 1 previous line of therapy • Progressive CNS metastases not excluded • Removed exclusion of participants with current or recent gastrointestinal disease • Added exclusion of participants with prior exposure to gemcitabine and 5-FU or gemcitabine and oxaliplatin co-administered as first line treatment • Removed restriction of consumption of non-pasteurized milk while on study • Added restriction of alcoholic beverage consumption while on study	
Table 7.4.6.2-1, Recommended Dose Modifications of FOLFOX	5-FU infusions updated to 46 hours at all dose levels.	Aligned to standard of care guidelines.
Section 7.4.7, Treatment Beyond Disease Progression	Imaging language updated.	Aligned to BMS standards.
Section 7.4.8, Crossover Post-Disease Progression for Participants Treatment with Chemotherapy Only	Removed section.	The population eligible for crossover will not meet the eligibility criteria for prior lines of treatment.
Appendix 9	TNM Staging added.	Added to better characterize the baseline characteristic of the treated population.
Throughout	Instances of “leucovorin” updated to “leucovorin (calcium folinate)”.	Clarified for generic drug naming conventions.
Throughout	General edits for clarity.	Corrected errors

Overall Rationale for the Revised Protocol 01, 28-Nov-2017

Changes were made to the protocol based on data collected from the preliminary safety cohort.

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1 Synopsis	Revision to Objectives	Revision to Objectives align with protocol body
Section 2 Schedule of Activities	Added Hematology and urinalysis in Laboratory Tests; Added Fresh On-Treatment Tumor Biopsy	Added to correct omission
Section 3.1.5 Rationale for Combining Immunotherapy and Chemotherapy Regimens	Expanded rationale for combining immunotherapy and chemotherapy agents	Added [redacted]
Section 6.2 Exclusion Criteria	Removed criteria excluding participants who had any GI surgery and an inability to tolerate oral medication	Removed [redacted]
Section 7.4.4 Dose Discontinuation Criteria for Cabiralizumab and Nivolumab	Added criteria for permanent dose discontinuation and exceptions	Added [redacted]
Section 7.4.8 Treatment Beyond Disease Progression with Chemotherapy in Subjects with Solid Tumors	Correction to re-assignment of treatment to participants receiving platinum-based chemotherapy	Correction of error
Section 9.4.2 Vital Signs	Added description of vital sign time points	Clarified vital sign time points in the Preliminary Safety Cohorts
[redacted]		