Official Title of Study:

A Phase 1b/2 Study of BMS-813160 in Combination with Chemotherapy or Nivolumab in Patients with Advanced Solid Tumors

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Clinical Protocol CV202103

A Phase 1b/2 Study of BMS-813160 in Combination with Chemotherapy or Nivolumab in Patients with Advanced Solid Tumors

Short Title:

A Study of BMS-813160 in Combination with Chemotherapy or Nivolumab in Patients with Advanced Solid Tumors

Revised Protocol 06
Incorporates Administrative Letter 05

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 06	05-Dec-2019	The following key changes were made: • Closed enrollment in Cohort 4 of Part 2. • Removed stratification from the protocol. • Revised time that women of childbearing potential must follow contraception instructions to duration of study therapy plus 10 months.
Administrative Letter 05	16-Oct-2019	Updated study personnel.
Administrative Letter 04	07-Jun-2019	Updated study personnel.
Revised Protocol 05	12-Dec-2018	Revised protocol incorporates changes described in the table of Summary of Key Changes for Revised Protocol 05.
Revised Protocol 04	12-Jul-2018	Revised protocol incorporates changes described in the table of Summary of Key Changes for Revised Protocol 04.
Administrative Letter 03	27-Jun-2018	Clarify that the peripheral blood mononuclear cells (PBMC) sample collections in Table 9.8-2, Biomarker Sampling Schedule - Part 2, will be whole blood sample collections.
Administrative Letter 02	24-May-2018	Change a typographical error on the title page and page footer throughout the protocol. The Revise Date of the Revised Protocol 03 is 07-May-2018, not 07-May-2017.
Revised Protocol 03	07-May-2018	Revised protocol incorporates changes described in the table of Summary of Key Changes for Revised Protocol 03.
Revised Protocol 02	11-Sep-2017	Revised protocol incorporates changes described in the table of Summary of Key Changes in Appendix 13.
Revised Protocol 01	28-Jun-2017	Revised protocol incorporates changes described in the table of Summary of Key Changes in Appendix 13.
Administrative Letter 01	20-Jun-2017	1. Remove a typographical error in the nivolumab treatment schedule for Day 28 in Table 2-4. 2. Reformat the list of study inclusion criteria. 3. Include serum testing for hepatitis C antibody to the list of clinical laboratory assessments. 4. Remove PBMC sample collections from the biomarker sample schedule. Simplify the biomarker sample schedule by aligning the tumor sample collection with the on-treatment procedural outlines for Arms A, B, C, and D.
Original Protocol	11-May-2017	Not applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 06:

This protocol has been revised to 1) close enrollment in Cohort 4 of Part 2 (BMS 813160 + nivolumab in second line [2L] pancreatic cancer) due to futility based on a predetermined analysis, 2) remove stratification from the randomization process to align with the IRT system, 3) allow biosimilars of bevacizumab to be added to 2L FOLFIRI treatment to align protocol treatment with current standard of care, and 4) increase the duration of contraception following study treatment to align with current BMS and Health Authority guidelines. Additional key changes included in this revised protocol are summarized in the table below.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 06

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 2-2 Baseline for Cross-Over Procedural Outline - Cohort 1c to Cohort 5 - Cohort 3c to Cohort 4 (Closed per Revised Protocol 06) - Part 2 (CV202103); Figure 5.1-2 Study Design Schematic (Part 2) - Combination Therapy Expansion; Section 5.1.3 Treatment Period (Part 2); Section 5.1.4 Treatment Period (Parts 1 and 2); Section 5.1.5.1 Safety Follow-up; Section 5.4.3 Rationale for 2-Stage Design in Cohorts in Arm C; Section 5.4.3.1 Rationale for Closing Cohort 4; Section 6.1 Inclusion Criteria ii) 9); Section 10.1 Sample Size Determination; Table 10.1-1 Example of Design Characteristics	Closed enrollment in Cohort 4 of Part 2 (2L pancreatic cancer; BMS-813160 + nivolumab). Participants in Cohort 3c that progress on treatment can no longer cross over to Cohort 4. Cohort 7 (BMS-813160 monotherapy; 2L pancreatic cancer) will not open for enrollment due to lack of clinical response in Cohort 4.	Following a predetermined analysis at Stage 1 for Part 2 Cohort 4, this BMS-813160 in combination with nivolumab in 2L pancreatic cancer cohort was closed due to futility. Discontinuation is not due to safety concerns. As such, participants who progress on 1L chemotherapy in Part 2 Cohort 3c can no longer cross over to Cohort 4. In addition, Cohort 7 will not open for enrollment because predetermined criteria (ORR ≈ 15% or durable responses) in Cohort 4 were not met.
Table 2-3: On treatment Procedural Outline - BMS-813160/FOLFIRI (Arm A) - Parts 1 and 2 (CV202103); Section 3.1.3 Rationale for the Chemotherapy Regimens in Arms A and B; Section 5.1.3 Treatment Period (Part 2); Section 5.5.3 Rationale for Dose Selection of FOLFIRI; Section 7.1 Treatments Administered	Indicated that biosimilars of bevacizumab can be added to 2L FOLFIRI treatment if appropriate.	Modified to align with current standards of care.
Section 3.2.1.4 Clinical Safety of BMS-813160; Section 3.3 Benefit/Risk Assessment	Updated safety data for Study CV202103.	Updated to align with updated Investigator Brochure (IB).

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 06

Section Number & Title	Description of Change	Brief Rationale
Figure 5.1-1 Study Design Schematic (Part 1); Section 5.5.2 Rationale for Testing Lower Dose of BMS-813160	Indicated for Arm C that the BMS-813160 150-mg and 300-mg QD dose assignments are only allowed for participants with colorectal cancer.	Added to clarify eligibility criteria.
Section 5.4.4 Rationale for Control Arms; Section 7.2 Method of Treatment Assignment; Section 10.3.1 Efficacy Analyses;	Stratification was removed from the protocol.	BMS discovered that the stratification of subjects was not occurring in the IRT system in Study CV202103. The lack of stratification does not have any effect on patient safety. As this study is powered to estimate an efficacy signal with moderate confidence, not to establish efficacy with high precision as in a registrational study, the absence of a single stratification factor per randomization is not expected to affect the scientific value of the study. The appropriate data are being collected and a retrospective analysis of both tumor sidedness and prior therapies will be performed.
Section 6.1 Inclusion Criteria 3)d)i)	Amended criterion to allow up to 15% of treated participants per arm without confirmation of adequate tissue in mandatory pre-treatment biopsy.	Previous version of protocol allowed 5 participants per cohort, which was not practical as randomization occurs after quality control confirmation. 15% per arm is in line with the original intent of the protocol.
Section 6.1 Inclusion Criteria 4)d) Section 6.1 Inclusion Criteria 4)e)	Women of childbearing potential (WOCBP) must follow contraception instructions for duration of study therapy plus 10 months. Males who are sexually active with WOCBP must follow contraception instructions for duration of study therapy plus 7 months.	Updated per BMS guidelines and to align with the new FDA guidelines regarding required contraception duration timeframe for agents with reproductive toxicity in female participants (5 half-lives plus 6 months).
Section 6.2 Exclusion Criteria 4)d); Section 7.7.1 Prohibited and/or Restricted Treatments	Added language clarifying that Class 1A and 1C antiarrhythmics and tricyclic antidepressants are prohibited concomitant therapies, and that caution is warranted with use of Class 1B antiarrhythmics and methadone.	Added to clarify prohibited and restricted medications associated with sodium channel blockade.
Section 7.4.2 Management Algorithms for Immuno-oncology Agents;	Added myocarditis to list of adverse events with management algorithms in Appendix 6-2.	Aligned with contents of Appendix 6-2.
Section 9.2.5 Pregnancy	Extended the duration of contraception.	Updated per BMS protocol standards.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 2 Study Governance Considerations	Updated language around reporting potential serious breaches and added section on Scientific Publications.	Updated per BMS protocol standards
Appendix 4 Women of Childbearing Potential Definitions and Methods of Contraception	Clarified descriptions of contraceptive methods.	Updated per BMS protocol standards.
Appendix 6-2 Management Algorithms	Added management algorithm for myocarditis.	Updated per BMS protocol standards
All	Minor formatting and typographical corrections.	

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: A Phase 1b/2 Study of BMS-813160 in Combination with Chemotherapy or Nivolumab in Patients with Advanced Solid Tumors

Short Title:

A Study of BMS-813160 in Combination with Chemotherapy or Nivolumab in Patients with Advanced Solid Tumors

Study Phase:

Phase 1b/2

Rationale:

This is a Phase 1b/2, first-in-oncology study of BMS-813160, a dual antagonist of cysteine-cysteine (C-C) chemokine receptor 2 (CCR2) and C-C chemokine receptor 5 (CCR5) in participants with advanced colorectal and pancreatic cancers.

Treatment options for patients with metastatic colon or rectal cancer are predominantly 5-fluorouracil (5-FU) and leucovorin containing regimens in combination with either oxaliplatin or irinotecan (FOLFOX or FOLFIRI) with a biologic agent such as bevacizumab. Switching from FOLFOX to FOLFIRI in second-line (2L) and vice versa showed no difference in survival in metastatic colorectal cancer (CRC) with median overall survival (OS) of 21.5 months vs 20.6 months. FOLFIRI is being used in this trial as 2L chemotherapy in CRC to avoid any potential drug-drug interaction (DDI) between BMS-813160 and oxaliplatin. Bevacizumab or its biosimilar can be added to 2L FOLFIRI if it is appropriate and available locally as part of standard of care.

Treatment options for patients with metastatic pancreatic cancer are limited. Gemcitabine (Gem) combined with nab-paclitaxel (ABRAXANE®) is a United States (US) Food and Drug Administration (FDA) approved first-line (1L) treatment for patients with advanced pancreatic cancers. This regimen showed a median progression-free survival (PFS) of 5.5 months and a median OS of 8.5 months and is the predominantly used regimen in metastatic pancreatic cancer.

Patients with advanced pancreatic cancer can be treated with 5-FU/liposomal irinotecan in the 2L setting and patients with advanced CRC are treated with regorafenib or trifluridine/tipiracil in the third-line (3L) setting. However, outcomes with these agents are generally poor with low objective response rate (ORR), a median PFS of only 2 to 3 months, and median OS of 6 to 7 months. These regimens also have significant toxicity and additional options are clearly needed in advanced pancreatic and colorectal cancers. Development of newer and novel agents in the treatment of these diseases resistant to chemotherapy is an area of unmet need.

CCR2 and CCR5 are two chemokine receptors that are expressed on myeloid cell and T-cell infiltrates in the tumor microenvironment (TME). Each receptor has been separately shown to be an important player in multiple models of cancer, including pancreatic cancer and CRC. Therefore, targeting both receptors with a small-molecule dual antagonist is a potential novel treatment for

cancer where compelling evidence supports that myeloid and regulatory T cells (Treg) play a key role in mediating immune suppression within the TME.

Clinical data support targeting CCR2 to reverse the immunosuppressive TME in pancreatic cancer. Similarly, CCR5 has been targeted in the treatment of CRC. Given the clinical data with CCR2 and CCR5 antagonism individually in CRC and pancreatic cancer, the potential exists that dual CCR2/5 targeting in combination with chemotherapy may lead to even greater benefit. Inhibition of the tumor promoting effects of CCR2 and CCR5 signaling in the TME may work synergistically with chemotherapy and the lack of overlapping toxicity with chemotherapy also supports combining chemotherapy with a CCR2/5 inhibitor.

The immune effects seen with targeting the CCR2/5 pathways suggest that combination with other immune agents such as nivolumab, a monoclonal antibody that blocks the programmed death-1 pathway, may provide additional benefit. Thus, this initial cancer trial of BMS-813160 will also study a combination with nivolumab in participants with advanced CRC or pancreatic cancer.

Study Population:

Participants must be at least 18 years old with a histological or cytological confirmed diagnosis of an advanced CRC or pancreatic cancer and measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Objectives and Endpoints:

This study will evaluate the safety profile, tolerability, pharmacokinetics (PK), pharmacodynamics, and preliminary efficacy of BMS-813160 alone or in combination with either chemotherapy or nivolumab or chemotherapy plus nivolumab in participants with metastatic colorectal and pancreatic cancers. The study will be conducted in 2 parts. Part 1 will evaluate safety, tolerability, PK, and pharmacodynamics of 2 different doses of BMS-813160 (ie, 300 mg twice a day [BID] or 600 mg once daily [QD]) in combination with either FOLFIRI (Arm A), Gem/ nab-paclitaxel (ABRAXANE) [Arm B], or nivolumab (Arm C) in participants with advanced colorectal and pancreatic cancers. Part 1 Arm C evaluated the PK and pharmacodynamics of low dose BMS-813160 (300 mg daily and 150 mg daily) in combination with nivolumab in patients with advanced colorectal cancer. Part 2 is a dose expansion study to assess preliminary efficacy of BMS-813160 alone (Arm D) or in combination with either chemotherapy or nivolumab or chemotherapy plus nivolumab in participants with advanced CRC or pancreatic cancer. Arm D (BMS-813160 monotherapy) will only open if participants in Arm C show an ORR of approximately 15% or durable responses are seen with the combination of nivolumab and BMS-813160, and will be important to evaluate the contribution of components.

The objectives and endpoints for the primary, secondary, and exploratory analyses of this study are shown in Table 1-1 (Part 1) and Table 1-2 (Part 2).

Table 1-1: Objectives and Endpoints (Part 1)

Objectives	Endpoints
Primary 1) To assess the safety and tolerability of BMS-813160 in combination with either FOLFIRI (Arm A), Gem + nab-paclitaxel (Arm B), or nivolumab (Arm C) in participants with advanced CRC or pancreatic cancer 2) To assess the pharmacodynamic effects of BMS-813160 in tumor samples	1a) Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and death; Incidence of laboratory abnormalities 1b) Additional safety endpoints: summary measurements of vital signs or ECGs 2) Decrease in Treg or TAM in tumor samples
Secondary 1) To assess the preliminary efficacy of BMS-813160 in combination with either FOLFIRI (Arm A), Gem + nab-paclitaxel (Arm B), or nivolumab (Arm C) in participants with advanced CRC or pancreatic cancer 2) To characterize the PK of BMS-813160 and its metabolite (BMS-939429) when administered alone, and in combination with either Gem + nab-paclitaxel, FOLFIRI or nivolumab 3) To characterize the immunogenicity of nivolumab when administered in combination with BMS-813160	1) ORR, median DOR, and PFS rate at 24 weeks 2a) PK parameters, such as Cmax, Tmax, Ctrough, C24, AUC(0-8), AUC(0-24), CLT/F, AI, CLR, %UR, MR_Cmax, and MR_AUC(0-24), if data permit 2b) Cmax and Ctrough concentrations of BMS-813160 during combination therapy 3) Frequency of positive ADA to nivolumab during combination therapy
Exploratory 1) To characterize the PK of nivolumab when administered in combination with BMS-813160 2) To assess the potential effect of BMS-813160 monotherapy on the CLR of NMN an endogenous biomarker for multidrug and toxin extrusion transporters (MATE1 and MATE2-K) 3) To assess the potential effect of BMS-813160 monotherapy on levels of NMN, an endogenous marker for renal transporters 4) To assess the pharmacodynamic effects of BMS-813160 in peripheral blood 5) To assess OS	1) Concentrations at end of infusion and Ctrough for nivolumab during combination therapy 2,3) Change of NMN in plasma and urine and CL change of creatinine levels in plasma and urine and CLR 4) Change of MCP-1 and CCR2 positive monocyte count in peripheral blood 5) OS rate at 1 year and 2 years

Abbreviations: %UR = percent urinary recovery over dosing interval; ADA = anti-drug antibody; AEs = adverse events; AI = accumulation index; AUC(0-8) = area under the concentration-time curve from time 0 to 8 hours post dose; AUC(0-24) = area under the concentration-time curve from time 0 to 24 hours post dose; C24 = observed plasma concentration at 24 hours post dose (for QD dosing only); CCR2 = cysteine-cysteine chemokine receptor 2; CL = clearance; CLR = renal clearance; CLT/F = apparent total body clearance; Cmax = maximum observed plasma concentration; CRC = colorectal cancer; Ctrough = trough observed plasma concentration; DLT = dose limiting toxicity; DOR = duration of response; ECGs = electrocardiograms; FOLFIRI = FOL (folinic acid [leucovorin]) F (fluorouracil [5-fluorouracil]) IRI (irinotecan [CAMPTOSAR]); Gem = gemcitabine; MATE = multidrug and toxin extrusion protein; MCP-1 = monocyte chemotactic protein-1; MR_AUC(0-24) = ratio of metabolite AUC(0-24) to parent AUC(0-24), corrected for molecular weight; MR_Cmax = ratio of metabolite Cmax to parent Cmax, corrected for molecular weight; NMN = N-methylnicotinamide; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic(s); SAEs = serious adverse events; TAM = tumor-associated macrophages; Tmax = time of maximum observed plasma concentration; Treg = regulatory T cells.

Table 1-2: Objectives and Endpoints (Part 2)

Objectives	Endpoints
Primary	
1) To assess the preliminary efficacy of BMS-813160 in combination with either FOLFIRI (Arm A), Gem + nab-paclitaxel or nivolumab + Gem + nab-paclitaxel (Arm B), or nivolumab (Arm C), and as monotherapy (Arm D) in participants with advanced CRC or pancreatic cancer	1) ORR as assessed by investigator using RECIST v1.1, median DOR, and PFS Rate at 24 weeks
Secondary	
1) To assess the safety and tolerability of BMS-813160 in combination with either FOLFIRI (Arm A), Gem + nab-paclitaxel or nivolumab + Gem + nab-paclitaxel (Arm B), or nivolumab (Arm C), and as monotherapy (Arm D) in participants with advanced CRC or pancreatic cancer 2) To assess the pharmacodynamic effects of BMS-813160 in tumor samples	1a) Incidence of AEs, SAEs, AEs leading to discontinuation, and death; incidence of laboratory abnormalities. 1b) Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria in Cohort 3b 1c) Additional safety endpoints: summary measures of vital signs or ECG 2) Decrease in Treg & TAM in tumor samples
Exploratory	
1) To assess the PK of BMS-813160 when administered as monotherapy and with different chemotherapy or nivolumab combination regimens 2) To characterize the immunogenicity of nivolumab when administered in combination with BMS-813160 or BMS-813160 plus chemotherapies 3) To assess the pharmacodynamic effects of BMS-813160 in peripheral blood 4) To assess the PK of irinotecan and nab-paclitaxel in a subset of participants when combined with BMS-813160 5) To assess OS	1a) Cmax and Ctrough concentrations of BMS-813160 during monotherapy and combination therapy 1b) Concentrations at end of infusion and Ctrough for nivolumab during combination therapy 2) Frequency of positive ADA to nivolumab during combination therapy 3) Change of MCP-1 and CCR2 positive monocyte count in peripheral blood 4) Cmax, Tmax, AUC(0-24), Ctrough of irinotecan, SN-38, and nab-paclitaxel 5) OS rate at 1 year and 2 years

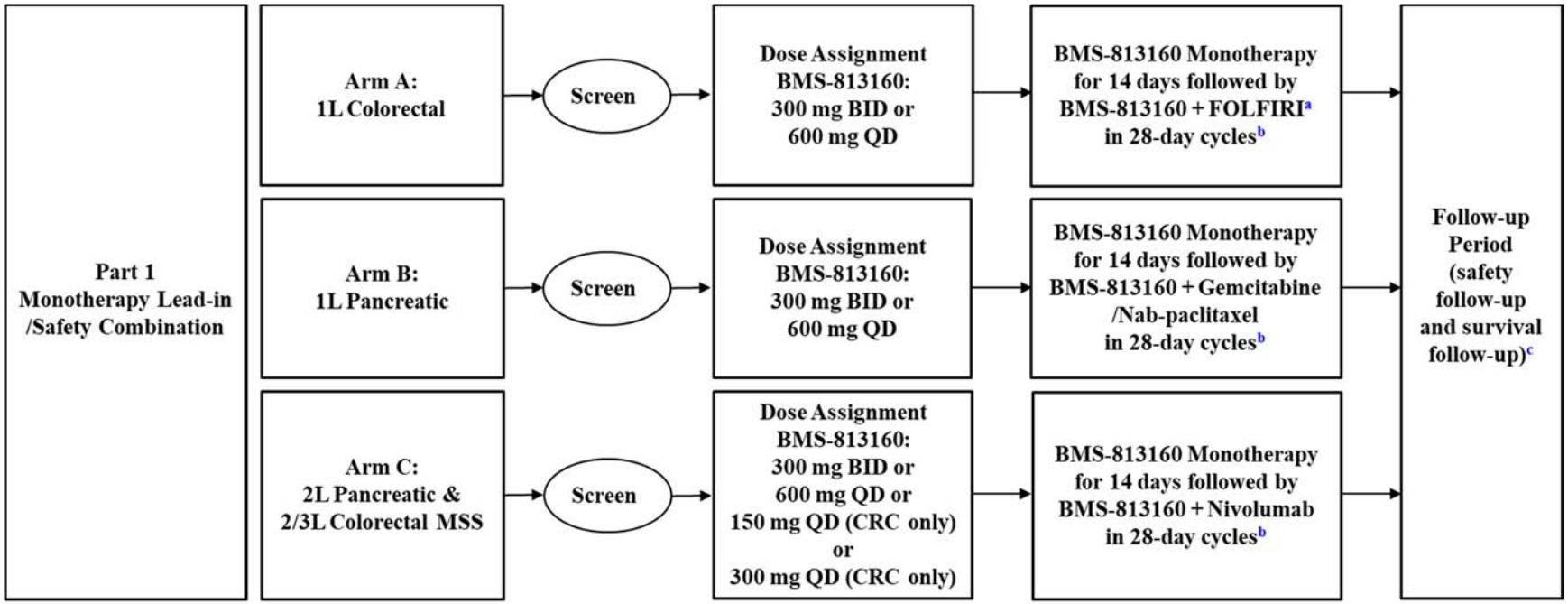
Abbreviations: ADA = anti-drug antibody; AEs = adverse events; AUC(0-24) = area under the concentration-time curve from time 0 to 24 hours post dose; CCR2 = cysteine-cysteine chemokine receptor 2; Cmax = maximum observed plasma concentration; CRC = colorectal cancer; Ctrough = trough observed plasma concentration; DLT = dose-limiting toxicity; ECGs = electrocardiograms; FOLFIRI = FOL (folinic acid [leucovorin]) F (fluorouracil [5-fluorouracil]) IRI (irinotecan [CAMPTOSAR]); Gem = gemcitabine; MCP-1 = monocyte chemotactic protein-1; ORR = objective response rate; OS = overall survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; SAEs = serious adverse events; TAM = tumor-associated macrophages; Tmax = time of maximum observed plasma concentration; Treg = regulatory T cells

Overall Design:

This is a Phase 1b/2, open-label, 2-part, multicenter trial to assess the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and preliminary efficacy of BMS-813160 alone or in combination with either FOLFIRI, gemcitabine (Gem)/nab-paclitaxel (ABRAXANE), nivolumab/Gem/nab-paclitaxel, or nivolumab in participants with advanced CRC or pancreatic cancer.

The study design scheme is presented in Figure 1-1 (Part 1) and Figure 1-2 (Part 2).

Figure 1-1: Study Design Schematic (Part 1)



Note: FOLFIRI (irinotecan 180 mg/m^2 over 90 minutes; leucovorin 400 mg/m^2 over 2 hours [leucovorin may be given concurrently with irinotecan]; 5-FU 400 mg/m^2 bolus followed by 2400 mg/m^2 over 46 hours continuous infusion) on Days 1 and 15 of a 28-day cycle.

Note: The recommended dose of nab-paclitaxel (ABRAXANE) is 125 mg/m^2 administered as an intravenous 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.

Note: Nivolumab 480 mg administered as an intravenous infusion over 30 minutes every 4 weeks.

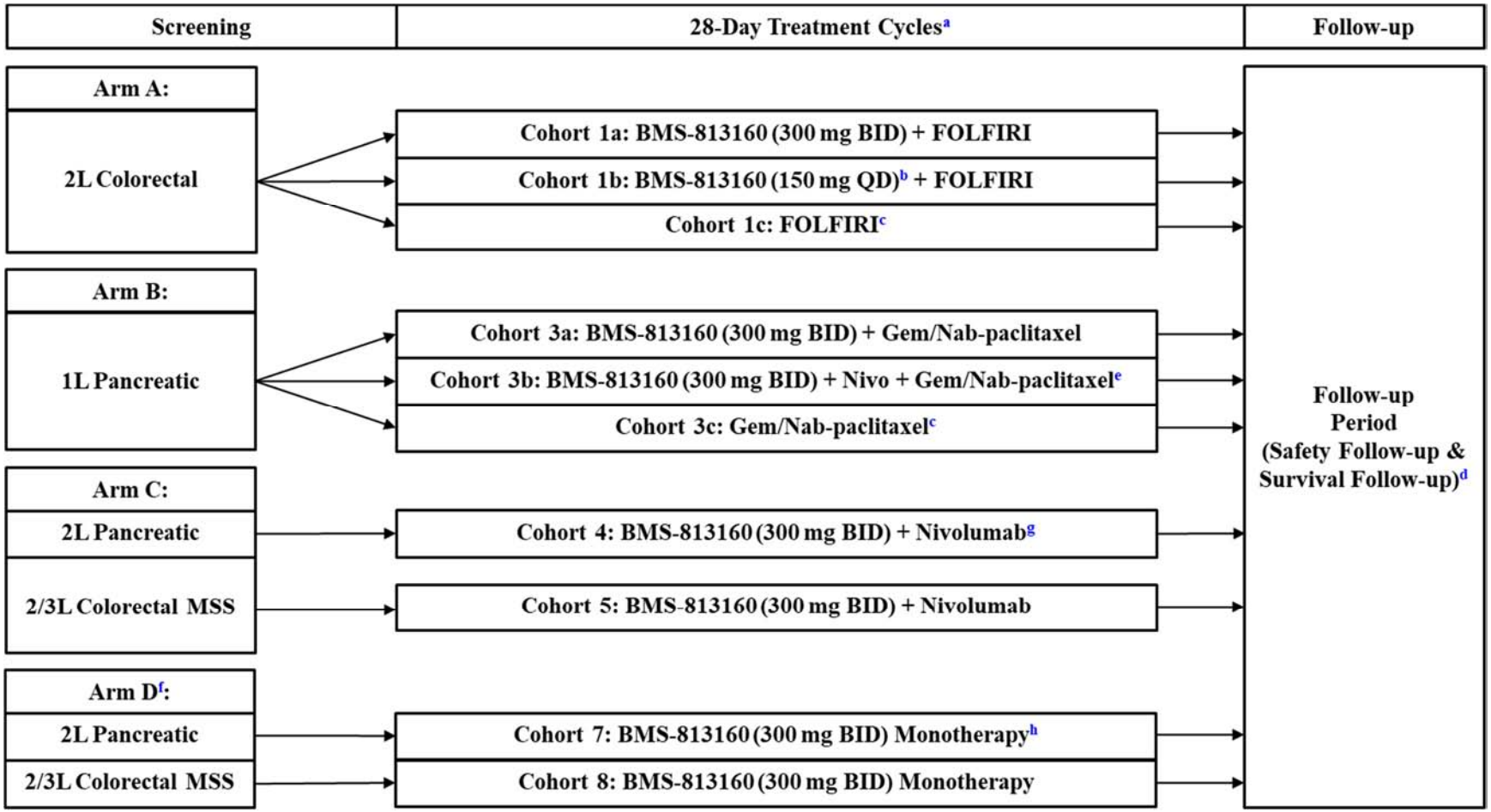
Abbreviations: 1L = first-line; 2L = second-line; 3L =third-line; 5-FU = 5-fluorouracil; BID = twice a day; CRC = colorectal cancer; FOLFIRI = FOL (folinic acid [leucovorin]) F (fluorouracil [5-fluorouracil]) IRI (irinotecan [CAMPTOSAR]); m^2 = square meter; mg = milligram; MSS = microsatellite stable; QD = once daily.

[a] Bevacizumab, cetuximab, or panitumumab can be added to 1L FOLFIRI if appropriate.

[b] Participants will continue on the combination until disease progression , intolerance to treatment, meeting discontinuation criteria, or withdrawal of consent.

[c] Safety follow-up: 30 days for Arms A and B and 100 days for Arm C. Survival follow up to begin after completion of safety follow-up every 12 weeks (± 2 weeks) until 2 years after last dose of study treatment.

Figure 1-2: Study Design Schematic (Part 2) - Combination Therapy Expansion



Note 1: FOLFIRI (irinotecan 180 mg/m^2 over 90 minutes; leucovorin 400 mg/m^2 over 2 hours [leucovorin may be given concurrently with irinotecan]; 5-FU 400 mg/m^2 bolus followed by 2400 mg/m^2 over 46 hours continuous infusion) on Days 1 and 15 of a 28-day cycle.

Note 2: The recommended dose of nab-paclitaxel (ABRAXANE) is 125 mg/m^2 administered as an intravenous 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.

Note 3: Nivolumab 480 mg administered as an intravenous infusion over 30 minutes every 4 weeks. In Cohort 3b, administer nivolumab followed by chemotherapy 30 minutes later.

Abbreviations: 1L = first-line; 2L = second-line; 3L =third-line; 5-FU = 5-fluorouracil; BID = twice a day; FOLFIRI = FOL (folinic acid [leucovorin]) F (fluorouracil [5-fluorouracil]) IRI (irinotecan [CAMPTOSAR]); Gem = gemcitabine; m^2 = square meter; mg = milligram; MSS = microsatellite stable; Nivo = nivolumab; ORR = objective response rate; PD = progressive disease; QD = once daily.

[a] Participants will continue on the combination until disease progression , intolerance to treatment, meeting discontinuation criteria, or withdrawal of consent.

[b] Lower dose: BMS-813160 150 mg QD.

[c] Participants in Cohort 1c will be allowed to cross over to Cohort 5 at the time of PD if it's felt to be in their best interest by their treating physician and participants meet all eligibility criteria to enroll in Arm C. Participants will have to meet all eligibility criteria to re-enter the study, undergo baseline assessment (Table 2-2) and need a 28-day washout period prior to first dose of study treatment in the new arm.

[d] Safety follow-up: 30 days for Arms A, B (Cohorts 3a and 3c), and D; 100 days for Arm C and Cohort 3b. Survival follow up to begin after completion of safety follow-up every 12 weeks (± 2 weeks) until 2 years after last dose of study treatment.

[e] The Gem/nab-paclitaxel in combination with nivolumab and BMS-813160 cohort had a safety lead-in of approximately 6 participants who were treated with BMS-813160 300 mg BID and monitored for 4 weeks before additional participants are added to the cohort. In addition a staggered dosing (sentinel participant) approach was used for the first three participants. The first participant to be dosed was observed for 5 days, before additional participants (ie, participant 2 and 3) received study treatments.

[f] Arm D (BMS-813160 monotherapy) will only open if participants in Arm C show an ORR of approximately 15% or durable responses are seen with the combination of nivolumab and BMS-813160.

[g] Cohort 4 was closed per Revised Protocol 06. Participants in Cohort 3c can no longer crossover to Cohort 4 per Revised Protocol 06.

[h] Cohort 7 will not open for enrollment due to Cohort 4 being closed due to futility per Revised Protocol 06.

The study is divided into 3 periods: Screening, Treatment (Part 1 and Part 2), and Follow-up (Safety and Survival Phases).

Screening Period:

- The Screening Period will last for up to 28 days.
- The Screening Period begins by establishing the participant's initial eligibility upon signing of the informed consent form.
- Participants will be enrolled using the Interactive Response Technologies or Interactive Web Response Systems.

Treatment Period (Part 1):

- The Treatment Period (Part 1) will have a 2-week monotherapy lead-in with BMS-813160 prior to combination with either FOLFIRI (Arm A) in 1L CRC, Gem/nab-paclitaxel (Arm B) in 1L pancreatic, or nivolumab (Arm C) in 2L pancreatic or 2/3L CRC. Participants will continue on the combination until disease progression, intolerance to treatment, meeting discontinuation criteria, or withdrawal of consent.
- All 3 arms will enroll participants in parallel. Participants will be assigned to the BMS-813160 300 mg BID or 600 mg QD cohort in each arm of the study. In Arm C, participants with 2/3L CRC can also be assigned to receive 150 mg QD or 300 mg QD. The BMS-813160 monotherapy lead-in serves the purpose of establishing the safety and tolerability of BMS-813160 in oncology patients and facilitating the characterization of the added or synergistic toxicity of the subsequent combination regimens. The monotherapy lead-in also enables a biopsy at 2 weeks to characterize pharmacodynamic effects of BMS-813160.
- Approximately 6 evaluable participants will be treated at each BMS-813160 dose (ie, 300 mg BID or 600 mg QD) for a total of 12 participants per arm (6 participants per dose per treatment arm or per lower doses [150 mg QD and 300 mg QD] of BMS-813160 in combination with nivolumab). Up to 6 additional participants may be added to a dose cohort to better characterize the safety, PK, or pharmacodynamic profile and inform Part 2 dose selection of BMS-813160 if needed after discussion with the Sponsor and investigators.
- After 2 weeks of BMS-813160 monotherapy, participants will have a mandatory biopsy and will then start the combination phase with FOLFIRI, Gem/nab-paclitaxel, or nivolumab along with continued treatment with BMS-813160. Participants will continue on the combination until disease progression, intolerance to treatment, meeting discontinuation criteria, or withdrawal of consent.
- Tumor progression or response endpoints will be assessed using RECIST v1.1 for solid tumors. Participants with a response of stable disease (SD), partial response (PR), or complete response (CR) will continue to the next treatment cycle.

Treatment Period (Part 2):

- The doses of BMS-813160 in Part 2 were chosen based on safety, PK, and pharmacodynamic data available from Part 1 of the study. Based on these considerations, the BMS-813160 300 mg BID dosing regimen was selected for primary investigation in this study. A regimen of BMS-813160 150 mg QD in combination with FOLFIRI also will be evaluated in Arm A.
- The Treatment Period (Part 2) will explore the preliminary signals of efficacy of BMS-813160 in combination with FOLFIRI (Arm A) in 2L CRC, Gem/nab-paclitaxel or nivolumab/Gem/nab-paclitaxel (Arm B) in 1L pancreatic cancer, or nivolumab (Arm C) in 2L pancreatic (**closed per Revised Protocol 06**) and 2/3L CRC microsatellite stable (MSS), and as monotherapy (Arm D) in 2L pancreatic and 2/3L CRC: 10 disease-specific cohorts in total, 31 to 35 evaluable participants in each cohort (Arms A, B, and C) and 18 per cohort (Arm D).
- An additional arm (Arm D) with BMS-813160 monotherapy will only open if participants in Arm C show an ORR of approximately 15% or durable responses are seen with the combination of nivolumab and BMS-813160.
- Participants in Cohort 1c will be allowed to cross over to Cohort 5 at the time of disease progression if felt to be in their best interest by their treating physician and participants meet all eligibility criteria to enroll in Arm C. Participants will have to meet all eligibility criteria to re-enter the study and need a 28-day washout period prior to treatment in the new arm. Participants in Cohort 3c will not be allowed to cross over to Cohort 4 at the time of disease progression since Cohort 4 was closed per Revised Protocol 06
- Tumor progression or response endpoints will be assessed using RECIST v1.1 for solid tumors. Participants with a response of SD, PR, or CR will continue to the next treatment cycle.

Follow-up Period:

- Safety Follow-up Phase (Parts 1 and 2):
  - Participants on Arms A, B (Cohorts 3a and 3c), and D must be followed for at least 30 days after the last dose of study treatment to monitor for adverse events (AEs).
  - Participants on Arm C and Cohort 3b (Arm B, Part 2) will be followed for at least 100 days after the last dose of study treatment to monitor for AEs to account for the long half-life of nivolumab.
  - All participants, except those participants who withdraw consent for study participation, will be required to complete Clinical/Safety Follow-up visits as above (per Table 2-7 in Schedule of Activities) after the last dose of study treatment, regardless of whether they start a new anti-cancer therapy.
- Survival Follow-up Phase:
  - After completion of the Safety Follow-up Phase, all participants will enter the Survival Follow-up Phase. Participants will be followed up (by telephone or clinic visit) every 12 weeks (Q12W) [± 2 weeks], from the last dose of study treatment for 2 years or until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first.

- The duration of this phase is up to 2 years following the last dose of study treatment, although a longer follow-up phase could be considered in selected cases if an efficacy signal is apparent.
- Data from imaging assessments for participants who have ongoing clinical benefit may continue to be collected while participants complete the survival phase of the study.

Treatment Beyond Progression (Arm C only): Participants will be permitted to continue on study treatment beyond initial RECIST v1.1-defined progressive disease as long as they meet the criteria. The decision to continue study treatment beyond initial investigator-assessed progression should be discussed with the BMS Medical Monitor (or designee) and documented in the study records.

Number of Participants:

Approximately 54 evaluable participants (6 to 9 participants per dose per treatment arm) may be treated in Part 1 (monotherapy lead-in/combination safety). If additional participants are enrolled (as indicated in Section 5.1.2), approximately 48 additional participants could be enrolled in Part 1 (6 participants per dose per treatment arm or per lower doses [150 mg QD and 300 mg QD] of BMS-813160 in combination with nivolumab). Approximately 308 evaluable participants may be treated in Part 2, Cohorts 1a to 8 (efficacy expansion) [approximately 35 evaluable participants per tumor indication per treatment in Arms A and B and approximately 31 evaluable participants per tumor indication per treatment in Arm C]. For each of the pancreatic and CRC MSS cohorts, approximately 18 additional evaluable participants will be treated in a treatment Arm D (BMS-813160 monotherapy) [opens if ORR of approximately 15% or durable responses are seen in Arm C]. The number of participants will be continuously monitored such that the number of evaluable participants in Part 2 will not exceed 40 in any cohort. If the study is expanded further to add more participants, a protocol amendment will be submitted justifying the sample size.

Treatment Arms and Duration:

Study Treatment:

The study treatment is presented in Table 1-3.

Table 1-3: Study Treatment for CV202103

Medication	Potency	IP/Non-IMP[a]
BMS-813160 Capsule	150 mg	IP
BMS-813160 Film Coated Tablet	300 mg	IP
BMS-813160 Film Coated Tablet	75 mg	IP
Nivolumab Injection[b]	100 mg/vial (10 mg/mL)	IP
Nivolumab Injection[b]	40 mg/vial (10 mg/mL)	IP
Gemcitabine Injection[c]	1000 mg/vial and various strengths	IP
Nab-paclitaxel (ABRAXANE)[c]	100 mg/vial and various strengths	IP
5-FU[c]	Various strengths	IP
Leucovorin[c]	Various strengths	IP
Irinotecan[c]	Various strengths	IP

Abbreviations: 5-FU = 5-fluorouracil; IP = investigational product; Non-IMP = non-investigational medicinal product.

[a] Where allowed by local regulations, chemotherapy treatments may be considered Non-IMP.

[b] Nivolumab (BMS-936558) will be supplied as a 240 mg kit - each kit containing (2) 100 mg vials and (1) 40 mg vial.

[c] These products will be obtained as local commercial product in countries if allowed by local regulations or through investigating site's standard prescribing procedures, otherwise the Sponsor will supply these products.

The selection and timing of dose for each participant is presented in Table 1-4.

Table 1-4: Selection and Timing of Dose

Study Treatment	Dosage level(s)	Frequency of Administration	Route of Administration
BMS-813160 (150 mg capsule or 300 mg tablet)	300 mg	BID	PO
BMS-813160 (150 mg capsule or 300 mg tablet)	600 mg	QD	PO
BMS-813160 (150 mg capsule or 75 mg tablet)	150 mg	QD	PO
BMS-813160 (150 mg capsule or 300 mg tablet)	300 mg	QD	PO
Nivolumab	480 mg IV	Q4W	IV infusion
5-FU	400 mg/m^2 Bolus AND 2400 mg/m^2 IV	Day 1, 15: Q4W	Bolus and IV infusion
Leucovorin	400 mg/m^2 IV	Day 1, 15: Q4W	IV infusion
Irinotecan	180 mg/m^2 IV	Day 1, 15: Q4W	IV infusion
Gemcitabine	1000 mg/m^2 IV	Day 1, 8, 15: Q4W	IV infusion
Nab-paclitaxel (ABRAXANE)	125 mg/m^2 IV	Day 1, 8, 15: Q4W	IV infusion

Abbreviations: 5-FU = 5-fluorouracil; BID = twice a day; IV = intravenous; PO = per os (by mouth [orally]); Q4W = every 4 weeks; QD = once daily.

FOLFIRI (irinotecan 180 mg/m^2 over 90 minutes; leucovorin 400 mg/m^2 over 2 hours [leucovorin may be given concurrently with irinotecan]; 5-FU 400 mg/m^2 bolus followed by 2400 mg/m^2 over 46 hours continuous infusion) on Days 1 and 15 of a 28-day cycle. Bevacizumab or its biosimilar can be added to 2L FOLFIRI if appropriate, and will be administered in accordance with local Health Authority approved labeling for these agents. Levoleucovorin can be substituted for leucovorin as per site's standard practice.

The recommended dose of nab-paclitaxel (ABRAXANE) is 125 mg/m^2 administered as an intravenous 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.

Nivolumab 480 mg administered as an intravenous infusion over 30 minutes every 4 weeks.

Treatment Duration: Participants will be treated until disease progression, intolerance to treatment, meeting discontinuation criteria, or withdrawal of consent. Participants in Arm C may be treated beyond progression as long as they meet the criteria. Participants who discontinue chemotherapy in part or whole due to intolerance can continue BMS-813160 or BMS-813160 and nivolumab (Cohort 3b) on study after investigator's discussion with the medical monitor or Sponsor designee. Participants will continue to get all study evaluations as per the Schedule of Activities.

Data Monitoring Committee: No

BMS has developed a multi-layered process to ensure safety monitoring through close collaboration of study site investigators, the BMS study team, and the BMS Global Pharmacovigilance and Epidemiology (GPVE) led Safety Management Team (SMT). This collaborative process constitutes the safety monitoring plan for the study. To support safety oversight, BMS has established ongoing processes for collection, review, analysis, and submission of individual AE reports and their aggregate analyses. Because this is an open-label study, GPVE, the BMS medical monitor, and the investigators will have access to all data necessary for safety evaluation.

BMS GPVE is an internal group that operates independently from the clinical team to monitor safety across all BMS protocols, and analyze all data in an unblinded fashion. Within BMS, an SMT is established for investigational therapies under clinical development, and a member of GPVE chairs this team. In addition, signal detection is performed at least monthly and ad hoc throughout the study by the SMT composed, at a minimum, of the GPVE medical safety assessment physician (Chairman of the SMT) and GPVE single case review physician, the study medical monitor, the study biostatistician, and epidemiologist; all of whom, analyze the data in an unblinded fashion. Furthermore, the SMT routinely monitors for actual or potential issues related to participant safety that could result in a change in the medical risk-benefit balance associated with the use of study treatment(s).

2 SCHEDULE OF ACTIVITIES

Study assessments and procedures are presented in the following tables:

- Table 2-1: Screening Procedural Outline
- Table 2-2: Baseline for Cross-Over Procedural Outline - Cohort 1c to Cohort 5 - Cohort 3c to Cohort 4 (Closed per Revised Protocol 06) - Part 2
- Table 2-3: On-treatment Procedural Outline - Arm A - Parts 1 and 2
- Table 2-4: On-treatment Procedural Outline - Arm B - Parts 1 and 2
- Table 2-5: On-treatment Procedural Outline - Arm C - Parts 1 and 2 (Including Cross Over)
- Table 2-6: On-treatment Procedural Outline - Arm D - Monotherapy Alone
- Table 2-7: 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.

Table 2-1: Screening Procedural Outline - Parts 1 and 2 (CV202103)

Procedure	Day -28 to Day -1	Notes
Eligibility Assessments		
Informed Consent	X	A participant is considered enrolled only when a protocol specific informed consent is signed. Obtain patient identification number via IRT after signing of the written informed consent.
Utilize IRT	X	To obtain patient identification number. After completing all screening procedures, utilize IRT to either screen fail or obtain assignment information, as applicable. Assignment/Randomization can occur up to 5 days prior to first dose.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose.
Medical History	X	Includes prior conditions and any toxicities or allergy related to previous treatments and any known mutation status.
Prior Anti-cancer Therapy	X	Prior anti-cancer therapy including radiotherapy, surgery, and systemic therapy.
ECOG Status Assessment	X	See Appendix 7.
Safety Assessments		
Physical Examination (PE)	X	If the screening PE is performed within 24 hours prior to first dose, then a single exam may count as both the screening and pre-dose evaluation.
Physical Measurements	X	Includes height, weight, and BMI.
Vital Signs	X	Includes body temperature, respiratory rate, pulse oximetry, 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	Includes medications taken within 4 weeks prior to treatment.
Electrocardiogram (ECG)	X	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		
Serology, Hematology, Serum Chemistry, Thyroid Panel, and Urinalysis	X	See Section 9.4.4
Pregnancy Test (Serum or Urine)	X	For WOCBP only. Serum or urine within 24 hours prior to first dose of assigned study treatment. See Section 6.1.

Table 2-1: Screening Procedural Outline - Parts 1 and 2 (CV202103)

Procedure	Day -28 to Day -1	Notes
Follicle Stimulating Hormone (FSH)	X	Only women not considered WOCBP. Refer to Appendix 4 for definitions and guidelines.
Disease Assessment	X	MSS status for CRC patients in Arm C and D. Please see inclusion criteria (Section 6.1) for details. Document MSI status for Arm A and B participants if results are available.
Baseline Tumor Assessment	X	Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease within 28 days prior to date of first dose. Participants with symptoms or history of brain metastasis should have a MRI of the brain without and with contrast. CT of the brain without and with contrast can be performed if MRI is contraindicated. Bone scans should be performed as clinically indicated per local standards.
Mandatory Pre-Treatment Biopsy	X	Biopsy must be performed during the Screening Phase in all participants prior to first dose of assigned treatment unless adequate tumor tissue is confirmed from a biopsy done in the preceding 90 days with no intervening therapy. Please see lab manual for details on biopsy collection. Residual sample(s) may be retained for additional research. Sufficient tumor tissue must be obtained and centrally or locally confirmed before start of study treatment (3 to 4 blocks or minimum of 30 slides), obtained by a core needle biopsy, incisional biopsy, or excisional biopsy.
Archival Tumor Tissue Block	X	See Section 6.1. Residual samples may be retained for additional research.
Biomarker Sample Collection	X	See Section 9.8 (Table 9.8-1 and Table 9.8-2). Residual samples may be retained for additional research. Genotyping sample will be collected.
Adverse Event Reporting		
Monitor for Serious Adverse Events	X	All SAEs must be collected from the date of participant's written consent until 30 days (100 days for Arm C and Cohort 3b [Arm B, Part 2]) after discontinuation of dosing or participant's participation in the study. All SAEs and AEs will be assessed using NCI CTCAE v4.03.

Abbreviations: AE = adverse event; BMI = body mass index; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FSH = follicle stimulating hormone; IRT = Interactive Response Technologies; MRI = magnetic resonance imaging; MSI = microsatellite instability; MSS = microsatellite stable; NCI = National Cancer Institute; PE = physical examination; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; WOCBP = women of child bearing potential.

Table 2-2: Baseline for Cross-Over Procedural Outline - Cohort 1c to Cohort 5 - Cohort 3c to Cohort 4 (Closed per Revised Protocol 06) - Part 2 (CV202103)

Procedure	Day -28 to Day -1	Notes
Eligibility Assessments		
Informed Consent	X	Participants must sign informed consent for cross-over treatment in Arm C.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria for Arm C should be assessed at the cross-over baseline visit and confirmed prior to first dose.
ECOG Status Assessment	X	See Appendix 7.
Safety Assessments		
Physical Examination (PE)	X	If the cross-over baseline PE is performed within 24 hours prior to dosing on Day 1, then a single examination may count as both the cross-over baseline and pre-dose evaluation.
Physical Measurements	X	Includes weight.
Vital Signs	X	Includes body temperature, respiratory rate, pulse oximetry, 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.
Electrocardiogram (ECG)	X	ECGs should be recorded after the participant has been supine for at least 5 minutes.
Laboratory Tests		
Serology, Hematology, Serum Chemistry, Thyroid Panel, and Urinalysis	X	See Section 9.4.4
Pregnancy Test (Serum or Urine)	X	For WOCBP only. Serum or urine within 24 hours prior to first dose of assigned study treatment. See Section 6.1.
Disease Assessment	X	MSS status for CRC patients in Arm C.
Baseline Tumor Assessment	X	Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease within 28 days prior to date of first dose. Re-baseline of target lesions and non-target lesions should be performed as per RECIST v1.1.
Mandatory Pre-Treatment Biopsy	X	A mandatory pretreatment fresh tumor biopsy must be performed. Sufficient tumor tissue must be obtained and centrally or locally confirmed before start of study treatment (3 to 4 blocks or minimum of 30 slides), obtained by a core needle biopsy, incisional biopsy, or excisional biopsy.

Table 2-2: Baseline for Cross-Over Procedural Outline - Cohort 1c to Cohort 5 - Cohort 3c to Cohort 4 (Closed per Revised Protocol 06) - Part 2 (CV202103)

Procedure	Day -28 to Day -1	Notes
Biomarker Sample Collection	X	See Section 9.8 (Table 9.8-2). Residual samples may be retained for additional research. Genotyping/SNP sample will be not be collected. All other biomarker samples will be collected as per Table 9.8-2.
Adverse Event Reporting		
Monitor for Adverse Events	X	All AEs must continue to be collected for 100 days after discontinuation of the cross over.
Monitor for Serious Adverse Events	X	All SAEs must be collected from the date of participant's written consent until 100 days after discontinuation of dosing or participant's participation in the study. All SAEs and AEs will be assessed using NCI CTCAE v4.03.

Note: Cohort 4 was closed per Revised Protocol 6. Participants in Cohort 3c that progress on treatment cannot cross over to Cohort 4 per Revised Protocol 06.

Abbreviations: AE = adverse event; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FSH = follicle stimulating hormone; MRI = magnetic resonance imaging; MSS = microsatellite stable; NCI = National Cancer Institute; PE = physical examination; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SNP = single nucleotide polymorphism; WOCBP = women of child bearing potential.

Table 2-3: On-treatment Procedural Outline - BMS-813160/FOLFIRI (Arm A) - Parts 1 and 2 (CV202103)

	Part 1 Cycle 0 (2-wk monotherapy)						Part 1 and Part 2 Cycle 1 & Subsequent Cycles (4 wks/cycle) ± 3 days				
Procedure	**D -1**	**D1**	**D2**	**D3**	**D7**	**D14**	**D1**	**D15**	**D28**	**EOT**	**Notes**
Eligibility Assessments											
Inclusion/Exclusion Criteria	X						X				For Part 1 (C0D-1) & Part 2 (C1D1): Participants must meet all eligibility criteria before starting treatment.
Utilize IRT		X					X	X		X	For all participants at Cycle 1 Day 1, each subsequent dosing visit and to discontinue participant (EOT).
Safety Assessments											
Physical Examination		X			X		X	X		X	For Part 1 (C0D1) & Part 2 (C1D1) and Day 1 of each cycle: perform a complete physical examination within 24 hours of dose administration. On subsequent visits in each cycle, perform a symptom-directed physical examination within 24 hours of dose administration.
Vital Signs		X			X		X	X		X	Including weight, body temperature, respiratory rate, pulse oximetry, seated blood pressure and heart rate. Approximately the same time as the ECG. On days when there is a pre-dose and 2 hour post-dose ECG, vital signs except weight should be taken at the time of each ECG.
ECOG Assessment		X			X		X	X		X	
12-Lead ECG		X			X		X	X		X	ECGs should be recorded after the participant has been supine for at least 5 minutes. Collection prior to and 2 hours post BMS-813160 administration for Cycles 0, 1, and 2. Only pre-dose ECG will be obtained for

Table 2-3: On-treatment Procedural Outline - BMS-813160/FOLFIRI (Arm A) - Parts 1 and 2 (CV202103)

	Part 1 Cycle 0 (2-wk monotherapy)						Part 1 and Part 2 Cycle 1 & Subsequent Cycles (4 wks/cycle) ± 3 days				
Procedure	**D -1**	**D1**	**D2**	**D3**	**D7**	**D14**	**D1**	**D15**	**D28**	**EOT**	**Notes**
											subsequent cycles. Pre-dose ECGs must be done regardless of dosing schedule. Triplicate ECG at least one minute apart prior to C0D1 (Part 1) or C1D1 (Part 2) dose only.
Serious Adverse Event Assessment	All SAEs must be collected from the date of the participant's written consent until 30 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.										SAEs reported during this time period should be followed until resolved to baseline, stabilized or deemed irreversible.
Adverse Events Assessment	Nonserious adverse events are collected from first dose through 30 days after last dose of study treatment										AEs reported during this time period should be followed until resolved to baseline, stabilized or deemed irreversible.
Concomitant Medication Use		X			X		X	X		X	
Laboratory Tests											
Hematology, Chemistry		X			X		X	X		X	There will be a -3 day window for collection of Hematology & Chemistry laboratory tests. (See Section 9.4.4)
Thyroid Function Panel		X			X		X			X	Includes TSH, Free T3 and Free T4. There will be a -3 day window for collection of Thyroid Function Panel. (See Section 9.4.4)
Pregnancy Test (Serum or Urine)		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 regardless of dosing schedule.
Pharmacokinetics	See Table 9.5.1-1, Table 9.5.2-1, Table 9.5.4-1, and Table 9.5.4-2										See Section 9.5.1 (Table 9.5.1-1) for MATE-renal transporter blood and urine samples to be collected. See Section 6.3.1 for fasting requirements for PK sampling.
Biomarkers	See Table 9.5.1-1, Table 9.8-1, and Table 9.8-2										

Table 2-3: On-treatment Procedural Outline - BMS-813160/FOLFIRI (Arm A) - Parts 1 and 2 (CV202103)

	Part 1 Cycle 0 (2-wk monotherapy)						Part 1 and Part 2 Cycle 1 & Subsequent Cycles (4 wks/cycle) ± 3 days				
Procedure	**D -1**	**D1**	**D2**	**D3**	**D7**	**D14**	**D1**	**D15**	**D28**	**EOT**	**Notes**
Mandatory On-treatment Biopsy						X			X		Note: Biopsy on C0D14 of Part 1 OR C1D28 of Part 2. Monotherapy should continue if biopsy is collected beyond C0D14; combination with FOLFIRI should only begin after the biopsy in Part 1. Participants on bevacizumab or its biosimilar should be off bevacizumab or its biosimilar for at least 14 days or according to institutional guidelines to prevent any bleeding or delay in wound healing.
Progression Driven Biopsy		At disease progression (see note)									Tissue submission is optional and biopsy is not required by protocol.
Efficacy Assessments											
Tumor Response Assessment (CT/MRI)		To be performed every 8 weeks (± 1 week) from C1D1 in all arms. This was done since Part 1 has monotherapy for 2 weeks. The same modality that is selected at screening should be used for each assessment. Assessed by RECIST v1.1 criteria (see Appendix 5).									
Study Treatment											
BMS-813160		BMS-813160 is taken daily according to assigned dose.									Site to check participant's pill diary at each visit
FOLFIRI[a]							X	X			Infusions given on Day 1 and Day 15 of each cycle. (See Section 7.1) 5-FU infusion over 46 hours.

Note: In the event of multiple procedures are required at a single time point, the following is a list of procedures from highest priority to low: pharmacokinetic sampling, ECG and vital signs, and laboratory tests.

Abbreviations: 2L = second line; 5-FU = 5-fluorouracil; C0D1 = Cycle 0, Day 1; C0D14 = Cycle 0, Day 14; C1D1 = Cycle 1, Day 1; C1D28 = Cycle 1, Day 28; CT = computed tomography; D -1 = Day -1; D1 = Day 1; D14 = Day 14; D15 = Day 15; D2 = Day 2; D28 = Day 28; D3 = Day 3; D7 = Day 7; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; IRT = Interactive Response Technologies; MATE = multidrug and toxin extrusion protein; MRI = magnetic resonance imaging; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; wk(s) = week(s); WOCBP = women of child bearing potential

[a] Bevacizumab or its biosimilar can be added to 2L FOLFIRI if appropriate.

Table 2-4: On-treatment Procedural Outline - BMS-813160/Gemcitabine/Nab-paclitaxel/Nivolumab (Arm B) - Parts 1 and 2 (CV202103)

	Part 1 Cycle 0 (2-wk monotherapy)						Part 1 and Part 2 Cycle 1 & Subsequent Cycles (4 wks/cycle) ± 3 days					
Procedure	**D -1**	**D1**	**D2**	**D3**	**D7**	**D14**	**D1**	**D8**	**D15**	**D28**	**EOT**	**Notes**
Eligibility Assessments												
Inclusion/Exclusion Criteria	X						X					For Part 1 (C0D-1) & Part 2 (C1D1): Participants must meet all eligibility criteria before starting treatment.
Utilize IRT		X					X	X	X		X	For all participants at Cycle 1 Day 1, each subsequent dosing visit and to discontinue participant (EOT)
Safety Assessments												
Physical Examination		X			X		X		X		X	For Part 1 (C0D1) & Part 2 (C1D1) and Day 1 of each cycle: perform a complete physical examination within 24 hours of dose administration. On subsequent visits in each cycle, perform a symptom-directed physical examination within 24 hours of dose administration.
Vital Signs		X			X		X	X	X		X	Including weight, body temperature, respiratory rate, pulse oximetry, seated blood pressure and heart rate. Approximately the same time as the ECG. On days when there is a pre-dose and 2 hour post-dose ECG, signs except weight should be taken at the time of each ECG.
ECOG Assessment		X			X		X		X		X	

Table 2-4: On-treatment Procedural Outline - BMS-813160/Gemcitabine/Nab-paclitaxel/Nivolumab (Arm B) - Parts 1 and 2 (CV202103)

	Part 1 Cycle 0 (2-wk monotherapy)						Part 1 and Part 2 Cycle 1 & Subsequent Cycles (4 wks/cycle) ± 3 days					
Procedure	**D -1**	**D1**	**D2**	**D3**	**D7**	**D14**	**D1**	**D8**	**D15**	**D28**	**EOT**	**Notes**
12-Lead ECG		X			X		X		X		X	ECGs should be recorded after the participant has been supine for at least 5 minutes. ECG prior to and 2 hours post BMS-813160 administration for Cycles 0, 1, and 2. Only pre-dose ECG will be obtained for subsequent cycles. Pre-dose ECGs must be done regardless of dosing schedule. Triplicate ECG at least one minute apart prior to C0D1 (Part 1) & C1D1 (Part 2) dose only.
Serious Adverse Event Assessment	All SAEs must be collected from the date of the participant's written consent until 30 days or 100 days (Cohort 3b [Arm B, Part 2]) post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.											SAEs reported during this time period should be followed until resolved to baseline, stabilized or deemed irreversible.
Adverse Events Assessment	Nonserious adverse events are collected from first dose through 30 days or 100 days (Cohort 3b [Arm B, Part 2]) after last dose of study treatment											AEs reported during this time period should be followed until resolved to baseline, stabilized or deemed irreversible.
Concomitant Medication Use		X			X		X	X	X		X	
Laboratory Tests												
Hematology, Chemistry		X			X		X	X	X		X	There will be a -3 day window for collection of Hematology & Chemistry laboratory tests. (See Section 9.4.4)
Thyroid Function Panel		X			X		X				X	Includes TSH, Free T3 and Free T4. There will be a -3 day window for collection of Thyroid Function Panel. (See Section 9.4.4)
Pregnancy Test (Serum or Urine)		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 regardless of dosing schedule.

Table 2-4: On-treatment Procedural Outline - BMS-813160/Gemcitabine/Nab-paclitaxel/Nivolumab (Arm B) - Parts 1 and 2 (CV202103)

Procedure	Part 1 Cycle 0 (2-wk monotherapy)						Part 1 and Part 2 Cycle 1 & Subsequent Cycles (4 wks/cycle) ± 3 days				EOT	Notes
	D -1	D1	D2	D3	D7	D14	D1	D8	D15	D28		
Pharmacokinetics	See Table 9.5.1-1, Table 9.5.2-1, Table 9.5.4-1, and Table 9.5.4-2											See Section 9.5.1 (Table 9.5.1-1) for MATE-renal transporter blood and urine samples to be collected. See Section 6.3.1 for fasting requirements for PK sampling.
Biomarkers	See Table 9.5.1-1, Table 9.8-1, and Table 9.8-2											
Mandatory On-treatment Biopsy						X				X		Note: Biopsy on C0D14 of Part 1 OR C1D28 of Part 2 Monotherapy should continue if biopsy is collected beyond C0D14; combination with gemcitabine/nab-paclitaxel should only begin after the biopsy in Part 1.
Progression Driven Biopsy		At disease progression (see note)										Tissue submission is optional and biopsy is not required by protocol.
Efficacy Assessments												
Tumor Response Assessment (CT/MRI)		To be performed every 8 weeks (± 1 week) from date of first dose. The same modality that is selected at screening should be used for each assessment. Assessed by RECIST v1.1 criteria (see Appendix 5).										
Study Treatment												
BMS-813160		BMS-813160 is taken daily according to assigned dose.										Site to check participant's pill diary at each visit
Gemcitabine /nab-paclitaxel							X	X	X			
Nivolumab							X					Nivolumab infusion given over 30 minutes on Day 1 of each cycle for Cohort 3b in Part 2.

Note: In the event of multiple procedures are required at a single time point, the following is a list of procedures from highest priority to low: pharmacokinetic sampling, ECG and vital signs, and laboratory tests.

Abbreviations: C0D1 = Cycle 0, Day 1; C0D14 = Cycle 0, Day 14; C1D1 = Cycle 1, Day 1; C1D28 = Cycle 1, Day 28; CT = computed tomography; D -1 = Day -1; D1 = Day 1; D14 = Day 14; D15 = Day 15; D2 = Day 2; D28 = Day 28; D3 = Day 3; D7 = Day 7; D8 = Day 8; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; IRT = Interactive Response Technologies; MATE = multidrug and toxin extrusion protein; MRI =

magnetic resonance imaging; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; wk(s) = week(s); WOCBP = women of child bearing potential.

Table 2-5: On-treatment Procedural Outline - BMS-813160/Nivolumab (Arm C) - Parts 1 and 2 (Including Cross Over) [CV202103]

	Part 1 Cycle 0 2-wk monotherapy						Part 1 and Part 2 Cycle 1 & Subsequent Cycles (4 wks/cycle) ± 3 days				
Procedure	**D -1**	**D1**	**D2**	**D3**	**D7**	**D14**	**D1**	**D15[a]**	**D28**	**EOT**	**Notes**
Eligibility Assessments											
Inclusion/Exclusion Criteria	X						X				For Part 1 (C0D-1) & Part 2 (C1D1): Participants must meet all eligibility criteria before starting treatment.
Utilize IRT		X					X			X	For all participants at Cycle 1 Day 1, each subsequent dosing visit and to discontinue participant (EOT)
Safety Assessments											
Physical Examination		X			X		X	X		X	For Part 1 (C0D1) & Part 2 (C1D1) and Day 1 of each cycle: perform a complete physical examination within 24 hours of dose administration. On subsequent visits in each cycle, perform a symptom-directed physical examination within 24 hours of dose administration.
Vital Signs		X			X		X	X		X	Including weight, body temperature, respiratory rate, pulse oximetry, seated blood pressure and heart rate. Approximately the same time as the ECG. On days when there is a pre-dose and 2 hour post-dose ECG, vital signs except weight should be taken at the time of each ECG.
ECOG Assessment		X			X		X	X		X	
12-Lead ECG		X			X		X	X		X	ECGs should be recorded after the participant has been supine for at least 5 minutes. ECG prior to and 2 hours post BMS-813160 administration for Cycles 0, 1, and 2. Only pre-dose ECG will be obtained for subsequent cycles.

Table 2-5: On-treatment Procedural Outline - BMS-813160/Nivolumab (Arm C) - Parts 1 and 2 (Including Cross Over) [CV202103]

Procedure	Part 1 Cycle 0 2-wk monotherapy						Part 1 and Part 2 Cycle 1 & Subsequent Cycles (4 wks/cycle) ± 3 days			EOT	Notes
	D -1	D1	D2	D3	D7	D14	D1	D15[a]	D28		
											Triplicate ECG at least one minute apart prior to C0D1 (Part 1) & C1D1 (Part 2) dose only.
Serious Adverse Event Assessment	All SAEs must be collected from the date of the participant's written consent until 100 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.										SAEs reported during this time period should be followed until resolved to baseline, stabilized or deemed irreversible.
Adverse Events Assessment	Nonserious adverse events are collected from first dose through 100 days after last dose of study treatment										AEs reported during this time period should be followed until resolved to baseline, stabilized or deemed irreversible.
Concomitant Medication Use		X			X		X	X		X	
Laboratory Tests											
Hematology, Chemistry		X			X		X	X		X	There will be a -3 day window for collection of Hematology & Chemistry laboratory tests. (See Section 9.4.4)
Thyroid Function Panel		X			X		X			X	Includes TSH, Free T3 and Free T4. There will be a -3 day window for the collection of Thyroid Function Panel. (See Section 9.4.4)
Pregnancy Test (Serum or Urine)		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 regardless of dosing schedule.
Pharmacokinetics	See Table 9.5.1-1 and Table 9.5.3-1										See Section 9.5.1 (Table 9.5.1-1) for MATE-renal transporter blood and urine samples to be collected. See Section 6.3.1 for fasting requirements for PK sampling.
Biomarkers	See Table 9.5.1-1, Table 9.8-1, and Table 9.8-2										

Table 2-5: On-treatment Procedural Outline - BMS-813160/Nivolumab (Arm C) - Parts 1 and 2 (Including Cross Over) [CV202103]

	Part 1 Cycle 0 2-wk monotherapy						Part 1 and Part 2 Cycle 1 & Subsequent Cycles (4 wks/cycle) ± 3 days				
Procedure	**D -1**	**D1**	**D2**	**D3**	**D7**	**D14**	**D1**	**D15[a]**	**D28**	**EOT**	**Notes**
Immunogenicity		See Table 9.5.3-1									
Mandatory On-treatment Biopsy						X		X	X		Biopsy on C0D14 and C1D15 of Part 1 OR C1D28 of Part 2 Monotherapy should continue if biopsy is collected beyond C0D14; combination with nivolumab should only begin after the biopsy in Part 1.
Progression Driven Biopsy		At disease progression (see note)									Tissue submission is optional and biopsy is not required by protocol.
Efficacy Assessments											
Tumor Response Assessment (CT/MRI)		To be performed every 8 weeks (± 1 week) from date of first dose. The same modality that is selected at screening should be used for each assessment. Assessed by RECIST v1.1 criteria (see Appendix 5).									
Study Treatment											
BMS-813160		BMS-813160 is taken daily according to assigned dose.									Site to check participant's pill diary at each visit
Nivolumab							X				Nivolumab infusion given over 30 minutes on Day 1 of each cycle

Note: In the event of multiple procedures are required at a single time point, the following is a list of procedures from highest priority to low: pharmacokinetic sampling, ECG and vital signs, and laboratory tests.

Abbreviations: C0D1 = Cycle 0, Day 1; C0D14 = Cycle 0, Day 14; C1D1 = Cycle 1, Day 1;C1D15 = Cycle 1, Day 15; C1D28 = Cycle 1, Day 28; CT = computed tomography; D -1 = Day -1; D1 = Day 1; D14 = Day 14; D15 = Day 15; D2 = Day 2; D28 = Day 28; D3 = Day 3; D7 = Day 7; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; IRT = Interactive Response Technologies; MATE = multidrug and toxin extrusion protein; MRI = magnetic resonance imaging; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; wk(s) = week(s); WOCBP = women of child bearing potential

[a] After 4 cycles, Day 15 visits are optional if the participant is tolerating study treatment well.

Table 2-6: On-treatment Procedural Outline - BMS-813160 Monotherapy (Arm D) - Part 2 only (CV202103)

	Cycle 1 to 4 (4 wks/cycle) ± 3 days			Cycle 5 and Subsequent Cycles (4 wks/cycle) ± 3 days		
Procedure	**D1**	**D15**	**C1D28**	**D1**	**EOT**	**Notes**
Eligibility Assessments						
Inclusion/Exclusion Criteria	X					Participants must meet all eligibility criteria before starting treatment.
Utilize IRT	X	X		X	X	For all participants at Cycle 1 Day 1, each subsequent dosing visit and to discontinue participant (EOT)
Safety Assessments						
Physical Examination	X	X		X	X	C1D1: Perform a complete physical examination on Day 1 of each cycle within 24 hours of dose administration. On subsequent visits in each cycle, perform a symptom-directed physical examination within 24 hours of dose administration.
Vital Signs	X	X		X	X	Including weight, body temperature, respiratory rate, pulse oximetry, seated blood pressure and heart rate. Approximately the same time as the ECG. On days when there is a pre-dose and 2 hour post-dose ECG, vital signs except weight should be taken at the time of each ECG.
ECOG Assessment	X	X		X	X	
12-Lead ECG	X	X		X	X	ECGs should be recorded after the participant has been supine for at least 5 minutes. ECG prior to and 2 hours post BMS-813160 administration for Cycles 1 and 2. Only pre-dose ECG will be obtained for subsequent cycles.

Table 2-6: On-treatment Procedural Outline - BMS-813160 Monotherapy (Arm D) - Part 2 only (CV202103)

	Cycle 1 to 4 (4 wks/cycle) ± 3 days			Cycle 5 and Subsequent Cycles (4 wks/cycle) ± 3 days		
Procedure	**D1**	**D15**	**C1D28**	**D1**	**EOT**	**Notes**
						Triplicate ECG at least one minute apart prior to C1D1 dose only.
Serious Adverse Event Assessment	All SAEs must be collected from the date of the participant's written consent until 30 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.					SAEs reported during this time period should be followed until resolved to baseline, stabilized or deemed irreversible.
Adverse Events Assessment	Nonserious adverse events are collected from first dose through 30 days after last dose of study treatment					AEs reported during this time period should be followed until resolved to baseline, stabilized or deemed irreversible.
Concomitant Medication Use	X	X		X	X	
Laboratory Tests						
Hematology, Chemistry	X	X		X	X	There will be a -3 day window for collection of Hematology & Chemistry laboratory tests. (See Section 9.4.4)
Thyroid Function Panel	X			X	X	Includes TSH, Free T3 and Free T4. There will be a -3 day window for collection of Thyroid Function Panel. (See Section 9.4.4)
Pregnancy Test (Serum or Urine)	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 regardless of dosing schedule.
Pharmacokinetics	See Table 9.5.3-1					
Biomarkers	See Table 9.8-1 and Table 9.8-2					
Mandatory On-treatment Biopsy			X			

Table 2-6: On-treatment Procedural Outline - BMS-813160 Monotherapy (Arm D) - Part 2 only (CV202103)

	Cycle 1 to 4 (4 wks/cycle) ± 3 days			Cycle 5 and Subsequent Cycles (4 wks/cycle) ± 3 days		
Procedure	**D1**	**D15**	**C1D28**	**D1**	**EOT**	**Notes**
Progression Driven Biopsy	At disease progression (see note)					Tissue submission is optional and biopsy is not required by protocol.
Efficacy Assessments						
Tumor Response Assessment (CT/MRI)	To be performed every 8 weeks (± 1 week) from date of first dose. The same modality that is selected at screening should be used for each assessment. Assessed by RECIST v1.1 criteria (see Appendix 5).					
Study Treatment						
BMS-813160	BMS-813160 is taken daily according to assigned dose.					Site to check participant's pill diary at each visit

Note: In the event of multiple procedures are required at a single time point, the following is a list of procedures from highest priority to low: pharmacokinetic sampling, ECG and vital signs, and laboratory tests.

Abbreviations: C1D1= Cycle 1, Day 1; C1D28= Cycle 1, Day 28; CT = computed tomography; D1 = Day 1; D15 = Day 15; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; IRT = Interactive Response Technologies; MRI = magnetic resonance imaging; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; wks = weeks; WOCBP = women of child bearing potential

Table 2-7: Follow-up Procedural Outline (CV202103)

Procedure	Safety Follow-up				Survival Follow-up[d] (Q12W)	Notes
	Cross-Over Follow-up 30 Days[a] (± 7 Days)	FU 1 30 Days[b] (± 7 Days)	FU 2 60 Days[c] (± 7 Days)	FU 3 100 Days[c] (± 7 Days)		
Safety Assessments						
Physical Examination	X	X	X	X		
Vital Signs and Weight	X	X	X	X		Including weight, body temperature, respiratory rate, pulse oximetry, seated blood pressure and heart rate.
ECOG Status	X	X	X	X		
Review of Concomitant Medications	X	X	X	X		
Laboratory Tests						
Hematology and Serum Chemistry	X	X	X	X		
Pregnancy Test (Serum or Urine)	X	X		X		For WOCBP only.
12-Lead ECG	X	X	X	X		ECGs should be recorded after the participant has been supine for at least 5 minutes.
Adverse Event Reporting						AEs reported during this time period should be followed until resolved to baseline, stabilized or deemed irreversible.
Monitor for Nonserious AEs	X	X	X	X		Nonserious AEs must be collected from first dose until 30 days (100 days for Arm C and Cohort 3b [Arm B, Part 2]) following the last dose of study treatment. All SAEs and AEs will be assessed using NCI CTCAE v4.03.
Monitor for SAEs	X	X	X	X		All SAEs must be collected from the date of the participant's written consent until 30 days (100 days for Arm C and Cohort 3b [Arm B, Part 2]) post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.

Table 2-7: Follow-up Procedural Outline (CV202103)

Procedure	Safety Follow-up				Survival Follow-up[d] (Q12W)	Notes
	Cross-Over Follow-up 30 Days[a] (± 7 Days)	FU 1 30 Days[b] (± 7 Days)	FU 2 60 Days[c] (± 7 Days)	FU 3 100 Days[c] (± 7 Days)		
						All SAEs and AEs will be assessed using NCI CTCAE v4.03. SAEs reported during this time period should be followed until resolved to baseline, stabilized or deemed irreversible.
Efficacy Assessments	Participants who discontinue study treatment for reasons other than progression of disease should continue tumor assessment every 8 weeks (± 1 week) until progression, meeting discontinuation criteria, or withdrawal of consent.					
New Anti-cancer Therapy	X	X	X	X	X	New anti-cancer therapy including radiotherapy, surgery, and systemic therapy
Assessment of Participant Survival Status					X	Subject status will be assessed by either a clinic visit or telephone contact.

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FU = follow-up; NCI = National Cancer Institute; Q12W = every 12 weeks; SAE = serious adverse event; WOCBP = women of child bearing potential.

[a] Cross-over follow-up visit applies only to participants planning to cross over to Arm C.

[b] FU 1 should only be used by participants who will not receive additional study treatment on protocol CV202103, including after completion of cross-over treatment.

[c] Arm C and Cohort 3b [Arm B, Part 2] only

[d] All participants begin after completion of safety follow-up every 12 weeks (± 2 weeks) until 2 years after last dose of study treatment.

3 INTRODUCTION

This is a first-in-oncology study of BMS-813160, a dual antagonist of cysteine-cysteine (C-C) chemokine receptor 2 (CCR2) and C-C chemokine receptor 5 (CCR5) in participants with advanced solid tumors. This study will evaluate the safety profile, tolerability, pharmacokinetics (PK), pharmacodynamics, and preliminary efficacy of BMS-813160 in combination with either chemotherapy or nivolumab or chemotherapy plus nivolumab in participants with metastatic colorectal cancer (CRC) and pancreatic cancer. The study will be conducted in 2 parts. Part 1 will evaluate safety, tolerability, PK, and pharmacodynamics of different doses of BMS-813160 in combination with either FOLFIRI (Arm A), gemcitabine (Gem)/ nab-paclitaxel (ABRAXANE) (Arm B), or nivolumab (Arm C) in participants with advanced colorectal and pancreatic cancers. Part 2 is a dose expansion study to assess preliminary efficacy of BMS-813160 alone (Arm D) or in combination with either chemotherapy or nivolumab or chemotherapy plus nivolumab in participants with advanced CRC or pancreatic cancer.

3.1 Study Rationale

3.1.1 Rationale for Inhibiting CCR2/5 in Cancer

Immuno-oncology, which harnesses the immune system to fight cancer, has emerged as a major advancement in cancer treatment. Current approaches include blocking immunosuppressive signals with antagonistic antibodies and stimulating immunity with agonistic antibodies. Despite recent progress, many cancer types, including pancreatic cancer and CRC, have been resistant to the current immune approaches. Thus, new approaches targeting different immune mechanisms are needed to overcome the resistance to current immune therapies. Blocking both CCR2 and CCR5 with a small-molecule antagonist represents 1 such new approach with the potential to extend immuno-oncology benefits to patients not adequately served by existing therapies.

Patho-biologically, cancer progression exploits an evolving interplay among different cell types within the tumor microenvironment (TME). In addition to cancer cells, immune cell types, especially myeloid cells and T-regulatory (Tregs) cells, accumulate during cancer progression. The accumulation of both cell types is mediated by chemokine receptors interacting with their ligands (chemokines), which drives the migration and infiltration of these immune cell types into the TME. Of these chemokine receptors, CCR2 and CCR5 have been shown to be key drivers of the migration and accumulation of myeloid cells, including tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs), into the TME. Moreover, both receptors have been shown to be important players in the trafficking of Tregs to the TME. Besides its primary role in driving immune cell migration to the TME, CCR5 inhibition has been recently shown to repolarize TAMs from M2- to M1-like in the TME.

Chemokine (C-C motif) ligand 2 (CCL2) is secreted by tumors and recruits CCR2 positive inflammatory monocytes from the bone marrow to the TME where they transform to immuno-suppressive TAMs and prevent effective anti-tumor immunity. Previous studies have shown that the ratio of bone marrow to blood inflammatory monocytes is prognostic and inhibition of this axis showed responses in preclinical tumor models.[1,2]

Similarly, chemokine (C-C motif) ligand 5 (CCL5) is produced by T cells at invasive margins of CRC liver metastasis. Its receptor CCR5 is found on tumor cells, TAM, and circulating Tregs, and plays a role in immune exploitation by tumor cells promoting tumor growth. CCR5 inhibition with maraviroc showed reduction in tumor promoting cytokines, tumor death in explant models and was prognostic for responses to chemotherapy.[3,4]

Since tumors leverage the CCL2-CCR2 and CCL5-CCR5 axis to promote tumor growth through Tregs and TAM, blocking of this axis may be able to overcome the immunosuppressive TME and promote effective anti-tumor immunity.

3.1.2 Rationale for Selecting Patients with Pancreatic and Colorectal Cancers and Combining with Chemotherapy

The CCR2/CCL2 axis, considered important in mediating myeloid and Treg cell migration to the TME, is preclinically validated in multiple tumor types including pancreatic cancer and CRC.[1,5] CCR5/CCL3 and CCL5, also important in mediating myeloid and Treg cell migration to the TME as well as TAM repolarization within the TME, are also preclinically validated in multiple tumor types, including pancreatic cancer and CRC. TAMs and MDSCs in the TME may also mediate chemotherapy resistance.

Recent clinical data supports targeting CCR2 to reverse the immunosuppressive TME in pancreatic cancer. Nywening et al evaluated the clinical activity of the combination of PF-04136309, a small molecule antagonist of CCR2, with FOLFIRINOX chemotherapy in the treatment of borderline resectable or locally advanced (ie, first-line [1L]) pancreatic cancer.[6] Of 39 patients treated, 32 achieved local tumor control and 16 of 33 evaluable patients (49%) achieved an objective tumor response, which was greater than the prior expectation of 25% objective response rate (ORR). There was increase in CCR2 positive inflammatory monocytes in the bone marrow and decrease in CCR2 positive inflammatory monocytes in the peripheral blood of patients treated with the combination of CCR2 inhibitor and FOLFIRINOX. This was reversed in patients treated with FOLFIRINOX alone. Quantitative polymerase chain reaction (PCR) of patients' tumor showed an increase in immuno-stimulating and a decrease in immunosuppressive gene expression profiles with the combination of CCR2 inhibitor and chemotherapy compared with chemotherapy alone. In 6 patients with paired tumor biopsies, there was a decrease from baseline in TAM, an increase in CD4+ and CD8+ T cells, and a sharp decrease in the fraction of CD4+ T cells with a Treg phenotype following treatment with FOLFIRINOX and CCR2 inhibitor. Although preliminary, these results support further study of CCR2 inhibition in combination with chemotherapy in pancreatic cancer.

Similarly, CCR5 has been targeted in the treatment of CRC. Halama et al employed maraviroc, a small-molecule antagonist of CCR5, in the treatment of patients with treatment refractory CRC after 2 to 7 previous lines of treatment.[4] On paired biopsies during maraviroc monotherapy treatment, reduced tumor cell proliferation and increased tumor cell death were seen, along with a variety of immune changes consistent with increased anti-tumor immunity. Specifically, inhibition of CCR5 in patient-derived explant models showed decrease in tumor promoting cytokines, selective tumor death and repolarization of TAMs. In addition, 5 of the patients also received

maraviroc in combination with (previously received) chemotherapy. In these patients, 3 (60%) achieved an objective partial response (PR), which was unexpected given the multiple lines of previous therapy.

Given the clinical data with CCR2 and CCR5 antagonism individually in cancer, the potential exists that dual CCR2/5 targeting in combination with chemotherapy may lead to even greater benefit. Inhibition of the tumor promoting effects of CCR2 and CCR5 signaling in the TME may work synergistically with chemotherapy and the lack of overlapping toxicity with chemotherapy also supports combining chemotherapy with CCR2/5 inhibitor.

3.1.3 Rationale for the Chemotherapy Regimens in Arms A and B

Treatment options for patients with mCRC are predominantly 5-fluorouracil (5-FU) and leucovorin-containing regimens in combination with either oxaliplatin or irinotecan (FOLFOX or FOLFIRI) with a biologic agent such as bevacizumab. Epidermal growth factor receptor (EGFR) antibodies, cetuximab or panitumumab, are an option if RAS status is non-mutated. Both regimens are considered to be equivalent, with a 1L median progression-free survival (PFS) of 8.5 months for FOLFIRI and 8 months for FOLFOX.[7] Switching from FOLFOX to FOLFIRI in second line (2L) and vice versa showed no difference in survival in metastatic CRC with median overall survival (OS) of 21.5 months vs 20.6 months.[7] FOLFIRI is being used in this trial as 2L chemotherapy in CRC to avoid any potential drug-drug interaction (DDI) between BMS-813160 and oxaliplatin.

The choice of biologic is selected based on individual patient characteristics (RAS status, sidedness of tumor, and contraindications to the therapy), patient preferences (avoiding rash or diarrhea withe EGFR antibodies), and physician preference. In a Phase 3 trial of KRAS wild-type CRC patients, there was no difference in response rate, PFS, or OS in the cetuximab + chemotherapy group vs bevacizumab + chemotherapy group.[8] Continuation of bevacizumab with switch in chemotherapy showed improved OS in 2 pivotal studies in metastatic CRC.[9,10] Therefore, bevacizumab or its biosimilar can be added to 2L FOLFIRI if it is appropriate and available locally as part of standard of care, and will be administered in accordance with local Health Authority approved labeling.

Treatment options for patients with metastatic pancreatic cancer are limited. Gemcitabine combined with nab-paclitaxel is a United States (US) Food and Drug Administration (FDA) approved 1L treatment for patients with advanced pancreatic cancers.[11] This regimen showed a median PFS of 5.5 months and a median OS of 8.5 months and is the predominantly used regimen in metastatic pancreatic cancer.

3.1.4 Rationale for Selecting 2L CRC in Part 2 Arm A

Reported ORR with chemotherapy and biologic in 1L CRC vary widely from 45 to 65%.[12] The response rate can also vary significantly between vascular endothelial growth factor (VEGF) antibodies and EGFR antibodies when combined with chemotherapy. As the primary endpoint of the trial is response rate, 2L CRC was selected to test the response rate with FOLFIRI in combination with BMS-813160 in a homogenous patient population. Adding bevacizumab to 2L

chemotherapy did not show any difference in response rates in spite of improved OS.[9] The outcomes in 2L CRC patients with chemotherapy is generally poor with ORR of less than 20%, justifying the addition of an investigational agent to chemotherapy in an effort to improve patient outcomes in 2L CRC.

3.1.5 Rationale for Combining BMS-813160 with Nivolumab in Patients with Advanced Pancreatic and Colorectal Cancers in Arm C

Patients with advanced pancreatic cancer can be treated with 5-FU/liposomal irinotecan in the 2L setting and patients with advanced CRC are treated with regorafenib or trifluridine/tipiracil in the third-line (3L) setting. However, outcomes with these agents are generally poor with low ORR, a median PFS of only 2 to 3 months, and median OS of 6 to 7 months.[13,14,15] These regimens also have significant toxicity and additional options are clearly needed in advanced pancreatic and colorectal cancers. Development of newer and novel agents in the treatment of these diseases resistant to chemotherapy is an area of unmet need.

Anti-programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) monotherapy has no clinical activity in microsatellite stable (MSS) CRC or in pancreatic cancer.[16,17] This is likely due to the immunosuppressive effects of Tregs and MDSCs in TME leading to immune escape mechanisms.[18] Combination of anti-PD-1 agents with drugs that mitigate the immunosuppressive TME may offer therapeutic potential.[19] Recent data showed clinical responses in MSS CRC to a combination of a MEK inhibitor with a PD-L1 antibody suggesting that novel combinations have the potential for showing responses in this patient population, which has traditionally been resistant to checkpoint blockade alone.[20] The immune effects on the TME seen with targeting the CCR2/5 pathways suggest that combination with other immune agents such as nivolumab, a monoclonal antibody that blocks the PD-1 pathway and activates T cells, may provide additional benefit. Thus, this initial cancer trial of BMS-813160 will also study a combination of BMS-813160 with nivolumab in participants with advanced CRC or pancreatic cancer.

Both CCR2 and CCR5 mediate infiltration and immune suppression of tumor-associated myeloid cells and regulatory T cells, while PD-1 restrains effector T cell function in the TME. It is thus hypothesized that targeting both CCR2/CCR5 and PD-1 pathways will provide at least additive anti-tumor activities. Recent preclinical studies have shown that combination of a CCR2/5-dual antagonist mouse surrogate, BMS-687681 with an anti-PD-1 mouse surrogate antibody, BMT-144637, provides greater anti-tumor efficacy relative to either agent alone, as measured by both reduction in tumor volume and the number of tumor-free mice. These 2 mouse surrogates, BMS-687681 and BMT-144637, have comparable biological activities to BMS-813160 and nivolumab, respectively. For example, BMS-687681 potently blocks binding of MCP-1 to mouse CCR2-expressing cells and mouse MIP-1- to mouse CCR5-expressing cells, potently inhibits mouse MCP-1- and mouse MIP-1β-induced functions (calcium flux, integrin CD11b upregulation), and is structurally related to BMS-813160. Both BMS-687681 (administered at up to 100 mg/kg PO 2 times a day [BID] x 36 doses) and BMT-144637 (administered at up to 10 mg/kg x 3 doses), alone and in combination, were well tolerated; none of the treated mice showed any significant clinical signs of toxicity, including reductions in body weight, moribundity, or mortality; like the control

and monotherapy groups, combination of BMS-687681 and anti-PD-1 did not significantly affect the body weight over the course of study. In summary, targeting both CCR2/5 and PD-1 provides enhanced anti-tumor efficacy and is well tolerated pre-clinically, thus supporting the proposed clinical study with combination of BMS-813160 and nivolumab.

3.1.6 Rationale for Testing Lower Dose of BMS-813160

The testing of lower doses of BMS-813160 is primarily based on the preclinical PK/efficacy findings with BMS-687681, a mouse surrogate for BMS-813160, in combination with anti-PD-1 mouse surrogate, in tumor models. BMS-813160 is not suitable for in vivo efficacy studies due to its weak mouse potency for CCR2/5 as well as its poor mouse PK.

Dose-efficacy studies with BMS-687681 in combination with anti-PD-1 mouse surrogate in 3 different syngeneic mouse tumor models have shown robust synergistic efficacy against tumor progression with a plasma trough concentration ranging from 0.1 to 3-fold 90% inhibition concentration (IC90) for inhibiting CCR2/5 function. Moreover, BMS-687681 doses that provide a plasma trough concentration of 0.3 to 0.5-fold IC90 for inhibiting CCR2/5 function offer the most durable anti-tumor efficacy following both first tumor cell challenge and re-challenge, whereas those of > 3-fold IC90 result in significantly less efficacy. Therefore, testing lower doses of BMS-813160 will help further characterize the PK, pharmacodynamics, and preliminary efficacy of lower doses of BMS-813160.

3.1.7 Rationale for Testing BMS-813160 in Combination with Nivolumab, Gemcitabine, and Nab-Paclitaxel

Data from recent studies have shown benefit of combining chemotherapy and immunotherapy.[21,22] Cell death with chemotherapy has shown to release tumor antigens that prime the immune system, and decrease MDSCs and Tregs.[22] The combination of chemotherapy and anti-PD-1 agents have shown improved response rates, PFS, and OS when compared with chemotherapy alone in 1L lung cancer.[23,24] Pre-clinical and clinical studies show activity of CCR2 and CCR5 inhibitors in combination with anti-PD-1 agents and chemotherapy, respectively. Please see Section 3.1.2 for rationale combining BMS-813160 with chemotherapy and Section 3.1.5 for rationale combining BMS-813160 with anti-PD-1 agents.

All agents to be used in the proposed combination have shown well-defined toxicity profiles based on a safety database comprised of participants treated with either monotherapy or combinations across multiple tumor types. Combination of nivolumab with Gem/nab-paclitaxel in 1L pancreatic cancer has been shown to be safe in a Phase 1/2 study.[25,26] In this study, 50 participants with previously untreated pancreatic cancer were treated with nivolumab in combination with Gem/nab-paclitaxel. There was 1 dose-limiting toxicity (DLT) of Grade 3 non-immune hepatitis attributed to gemcitabine and the participant was able to continue on treatment with nivolumab and nab-paclitaxel without any further episodes of hepatitis. The most common (>10%) Grade 3 or higher adverse events (AEs) were anemia (36%), neutropenia (36%), gastrointestinal events (24%), hepatic toxicity (22%), peripheral neuropathy (16%), thrombocytopenia (12%), and colitis (12%). Respiratory failure (most likely pneumonitis) was the only Grade 5 AE. Of the 42 evaluable

participants, 1 had a complete response (CR), 8 had a PR, and 23 had stable disease (SD), which was encouraging for anti-tumor activity.

Evaluation of BMS-813160 in combination with Gem/nab-paclitaxel (Part 1, Arm B) and in combination with nivolumab (Part 1, Arm C) is ongoing in the current study. Based on the data available, the safety profile of BMS-813160 is manageable with either the 300 mg BID or 600 mg once per day (QD) dose in combination with gemcitabine and nab-paclitaxel or nivolumab. Please refer to Section 3.2.1.4 and the current BMS-813160 Investigator's Brochure (IB)[27] for further details.

Therefore, a cohort of participants will be treated with the combination of chemotherapy, nivolumab, and BMS-813160 to evaluate safety and preliminary efficacy of this combination. Please see Sections 3.3 and 5.1.3 for further details.

3.1.8 Rationale for Exploring Monotherapy in Arm D

Recent data showed clinical activity of CCR5 inhibitor maraviroc as monotherapy in advanced colorectal cancer.[4,28] Anti-PD-1 agents did not show any activity in MSS CRC or pancreatic cancer and any activity seen with the combination could be from BMS-813160 alone.[16,17] In this regard, if the BMS-813160 in combination with nivolumab arm (Arm C) shows an ORR of approximately 15% or durable responses (defined as a continuous response [objective CR or PR] beginning within 12 months of treatment and lasting ≥ 6 months) are seen with the combination, the Sponsor will open Arm D to explore efficacy of BMS-813160 as a single agent.

3.2 Background

3.2.1 BMS-813160

CCR2 and CCR5 are 2 chemokine receptors that are expressed on myeloid cell and T cell infiltrates in the TME. Each receptor has been separately shown to be an important player in multiple models of cancer, including pancreatic cancer and CRC. Therefore, targeting both receptors with a small-molecule dual antagonist is a potential novel treatment for cancer where compelling evidence supports that myeloid and Treg play a key role in mediating immune suppression within the TME.

3.2.1.1 Nonclinical Pharmacology of BMS-813160

BMS-813160 is an equipotent dual antagonist of CCR2 and CCR5 that binds potently to both receptors and exhibits potent dual inhibition of in vitro receptor-mediated functions, including chemotaxis, calcium flux, non-hydrolyzable guanosine triphosphate analog (guanosine 5'-3-O-[thio]triphosphate) [GTP-γS] exchange, and Mac-1 (integrin α) [CD11b] upregulation, as well as CCR5 phosphorylation and internalization induced by ligand interaction. BMS-813160 is a full and reversible antagonist of both receptors and blocks CCR2- and CCR5-dependent functions in response to all known ligands. BMS-813160 is also at least 800-fold selective against a panel of other chemokine receptors (C-C chemokine receptor 1 [CCR1], C-C chemokine receptor 4 [CCR4], C-X-C chemokine receptor 2 [CXCR2], C-X-C chemokine receptor 3 [CXCR3], and C-X-C chemokine receptor 5 [CXCR5]) and a panel of G protein-coupled receptors (GPCRs)/transporters (21 targets).

In CCR2 pharmacodynamic models, BMS-813160 significantly reduced blood monocytes in human CCR2 knock-in (hCCR2 KI) mice and increased serum levels of monocyte chemotactic protein (MCP)-1 (ligand for CCR2) in hCCR2 KI mice and in monkeys at doses providing plasma concentrations that are greater than or equal to the CCR2 binding concentration at which 90% inhibition is observed (IC90). The compound also reduced blood monocytes in monkeys although the reduction was not statistically significant due to inter-animal variability. These data support the use of these 2 measurements, serum MCP-1 and absolute monocyte count, as CCR2 PD biomarkers in studies of BMS-813160.

In CCR5 homeostatic models in the mouse, preliminary studies show that BMS-813160 robustly inhibited ex vivo-stimulated whole blood CD11b upregulation at doses providing plasma concentrations that are greater than or equal to the mouse CCR5 binding / CD11b IC90. When tested in naïve monkeys for its effect on CCR5 phosphorylation with or without ex vivo stimulation and CCR5 internalization with ex vivo stimulus, BMS-813160 significantly inhibited phosphorylation and internalization at plasma concentrations greater than or equal to the IC90 of CCR5.

When studied in 48-hour thioglycollate (TG) peritonitis model using hCCR2 KI mice, BMS-813160 substantially reduced monocyte/macrophage influx into the peritoneal cavity, providing an estimated in vivo free plasma concentration required to yield 50% of the maximal response (EC50) value of 4.9 nM, which correlated well with the in vitro binding 50% inhibition concentration (IC50) of 5.8 nM (mouse binding to human peripheral blood mononuclear cells [hPBMCs]). Maximal inhibition of monocyte/macrophage infiltration was achieved with approximately 98% receptor occupancy.

Additional details are provided in the current version of the IB.[27]

3.2.1.2 Nonclinical Pharmacokinetics and Metabolism of BMS-813160

Pharmacokinetic studies indicated that BMS-813160 was orally bioavailable (63 to 100%) in mice, rats, dogs, and monkeys. BMS-813160 exhibited a high volume of distribution at steady state (Vss), low serum protein binding in human and animal species, with a moderate (dogs and monkeys) to high (rodents) clearance rate. BMS-813160 and BMS-939429, a *t*-butyl hydroxylated metabolite, were found to be substrates for active liver uptake; however, the uptake does not appear to be governed by organic anion transporting polypeptide (OATP) or sodium-taurocholate cotransporting polypeptide (NTCP) transporters, and so is likely to occur via other hepatic uptake transporters (preliminary data).

The metabolic profiles of BMS-813160 were similar across species. Sixteen metabolites of BMS-813160 were observed in nonclinical in vitro and in vivo studies. Formation of BMS-939429, a *t*-butyl hydroxylated metabolite, represented a prominent metabolic pathway in all species studied. Additional biotransformation routes included other mono-oxidations or hydroxylation, oxidative deamination (N-dealkylation), glucuronidation of a hydroxylated metabolite, and combinations of multiple oxidative reactions. No unique metabolites were detected in human-derived in vitro systems. Metabolite profiling of steady-state plasma samples from mouse, rat, monkey, and human suggested that BMS-813160 was the major drug-related

component and BMS-939429 was the most prominent metabolite in the circulation in all species. In vitro receptor binding studies suggested that BMS-939429 was ≥ 15x and ≥ 50x less potent than the parent compound towards the CCR2 and CCR5 receptors, respectively, suggesting that the major metabolite is not likely to contribute substantially to the pharmacology of BMS-813160. In rat, monkey, and human, BMS-813160 was cleared by multiple pathways, including metabolism, direct urinary and biliary/fecal excretion. In humans, renal clearance (CLR) of BMS-813160 was greater than the glomerular filtration rate (GFR), indicating active renal secretion, however, the specific transporter(s) involved in the renal secretion have not been identified.

In vitro, the metabolism of BMS-813160 was primarily mediated via cytochrome P450 (CYP) 3A4, with some contribution from CYP3A5, and BMS-813160 was also a substrate for P glycoprotein (P-gp). Based on these results, the potential exists for a DDI if BMS-813160 is co-administered with inhibitors or inducers of CYP3A or P-gp. BMS-813160 and its hydroxylated metabolite (BMS-939429) did not inhibit CYP enzymes (IC50 > 40 μM) in human liver microsomes (HLM) and BMS-813160 and BMS-939429 showed low potential to inhibit uridine 5'-diphospho-glucuronosyltransferase (UGT) 1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7 at concentrations up to 100 μM (preliminary data). BMS-813160 also did not induce CYP1A2, CYP2B6, or CYP3A4/5 in primary human hepatocytes; therefore, BMS-813160 is not expected to alter the clearance of compounds that are CYP, UGT, or P-gp substrates. BMS-813160 was not a substrate of human transporters OATP1B1, OATP1B3, NTCP, BCRP, OAT1, OAT3, OCT2, multidrug and toxin extrusion protein 1 (MATE1), and MATE2-K. BMS-813160 and BMS-939429 are unlikely to inhibit BCRP, P-gp, OAT1, OAT3, NTCP, BSEP, MRP2, OATP1B1, OATP1B3, OCT2, and MATE2-K. However, BMS-813160 and BMS-939429 inhibited MATE1 with IC50 values of 4.6 and 32.1 μM, respectively. Refer to Section 5.4.5 for rationale for collection of biomarkers to evaluate potential for MATE1 inhibition by BMS-813160, and Sections 7.7.1 and 7.7.2 for restrictions on co-medications.

Additional details are provided in the BMS-813160 IB.[27]

3.2.1.3 Clinical Pharmacokinetics of BMS-813160

Single dose PK of BMS-813160 was evaluated in 48 healthy participants over a dose range of 5 mg to 2000 mg (Study CV202001[29]). The median time of maximum observed concentration (Tmax) of BMS-813160 was between 2.5 and 3 hours for doses up to 60 mg and decreased at doses ≥ 150 mg, ranging from 0.5 to 1.8 hours. The plasma apparent terminal phase half life (T-HALF) was consistent across the dose groups that had a well-characterized terminal phase (ie, 60 mg to 2000 mg) and ranged from 12 to 18 hours. The fitted power models suggest that the single dose PK parameters of BMS-813160 deviate from dose proportionality (ie, the exposure increases were higher than dose proportional). Renal CLR of BMS-813160 did not appear to change with BMS-813160 dose, while the amount of BMS-813160 excreted in urine as measured by %UR increased with dose. BMS-813160 CLT/F decreased with increasing dose and since T-HALF and CLR appeared similar across doses, this suggests a constant clearance with a changing oral bioavailability (F). Together, these data are consistent with a dose-related increase in oral bioavailability of BMS-813160 with increasing dose.

After giving a group of participants (n = 6) 150 mg [^{14}C]BMS-813160, a total of 81.5% of the administered radiolabeled dose was recovered as [^{14}C]: the majority in feces (58.7%) and the remaining amount in urine (22.8%). BMS-813160 was the predominant drug-related component in the plasma, and BMS-939429 was a prominent metabolite, accounting for 53 and 30% of total [^{14}C]. The parent drug, together with selected metabolites that were quantified with an exploratory liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay, comprised approximately 87% of the circulating radioactivity.

Multiple dose PK of BMS-813160 was evaluated in 42 participants over a dose range of 10 mg to 300 mg QD (n = 24) and 300 mg to 900 mg BID (n = 18) for 14 days (Study CV202002[30]). The increases in systemic exposures of BMS-813160 were generally greater than dose proportional within the QD and BID dose panels. The last dose (Day 14) mean terminal phase half-life values in this study (~12 to 16 hours) were consistent with the observed time to steady-state (3 to 5 days for QD dosing and generally within 3 days for BID dosing) and the observed accumulation ratios (up to 1.5 for QD panels and up to 1.7 for BID panels). Approximately 10% to 22% (QD) and 23% to 39% (BID) of the orally administered dose of BMS-813160 was recovered in urine as unchanged BMS-813160. The renal CLR of both BMS-813160 and BMS-939429 were greater than GFR, indicating net tubular secretion of both analytes. Based on the first-dose PK relative to steady-state PK, no time dependency in BMS-813160 PK was observed at any dose or either regimen studied. Steady-state systemic exposures of BMS-939429 were less than 50% those of parent BMS-813160.

Relative bioavailability study (Study CV202005,[31] N=12) showed that there was no meaningful formulation effect in healthy participants in this study. The relative bioavailability of BMS-813160 administered as a single 300 mg (6 x 50 mg) oral dose in capsules was very similar to that from a 300 mg oral dose in solution. The study also examined the effect of food on the capsule formulation. There was a modest effect, with consumption of a high-fat meal, on the systemic exposure of BMS-813160 administered in the capsule formulation. Administration of a 300-mg dose of BMS-813160 in capsule form to participants fed a high-fat, high-calorie meal resulted in a 45% decrease in maximum concentration (Cmax) and a 16% decrease in AUC(0-T) and AUC(INF). It is likely that this effect would be diminished in the presence of a meal of more normal content. Thus, lacking a substantial food effect, administration of BMS-813160 in solid formulations regardless of the fed/fasting status of participants may be a viable approach.

Preliminary PK evaluation in participants with advanced solid tumors receiving 300 mg BID or 600 mg QD monotherapy dose (Study CV202103) showed PK of BMS-813160 in cancer patients are consistent with previous results in healthy subjects, with slightly greater inter-subject variability. The median Tmax at steady-state (Day 14) ranged from 2 to 3 hours for 300 mg BID and from 1 to 3 hours for 600 mg QD. The geometric mean (CV%) Cmax at steady-state are 767 (68) ng/mL and 2290 (57) ng/mL for 300 mg BID and 600 mg QD, respectively. AUC(0-24) at steady-state are 8184 (70.3) ng•h/mL and 11975 (47) ng•h/mL for 300 mg BID and 600 mg QD, respectively. The geometric mean (CV%) accumulation ratio based on AUC(0-24) between Day 1 and Day 14 was estimated to be 1.55 (50) for 300 mg BID and 1.50 (36) for 600 mg QD. Based

on preliminary monotherapy data from oncology study (CV202103), there was no consistent difference in PK parameters between tested tumor types (or arms). Please refer to the IB[27] for further details.

3.2.1.4 Clinical Safety of BMS-813160

BMS-813160 was previously evaluated and found to be relatively safe and well tolerated in both healthy participant studies and in participants with diabetic kidney disease (DKD). To date, BMS-813160 has been studied in more than 5 clinical trials. Altogether, more than 390 participants have received at least 1 dose of BMS-813160 (108 healthy participants; 59 participants with DKD; more than 243 participants with advanced cancer).

Healthy Participants

In the single ascending dose (SAD) study CV202001, BMS-813160 was safe after single dose administrations up to 2,000 mg in healthy participants.[29] There were no deaths, serious adverse events (SAEs) or discontinuations due to AEs. All reported AEs were mild in intensity. At the 2,000 mg dose there was an increased incidence of central nervous system (CNS)-related AEs (dizziness and euphoric mood). Dizziness occurred in 5 participants (7.1%), all receiving BMS-813160, and all but 1 was considered by the investigator to be related to study drug (n = 1 each in the 150 mg and 1,200 mg groups, and n = 3 in the 2000 mg group). There were 2 participants in the 2,000 mg BMS-813160 group and 1 participant in the placebo group who had AEs of euphoria.

In the multiple ascending dose study CV202002, multiple doses of BMS-813160 were safe and generally well tolerated in healthy participants across the dose range of 10 to 300 mg QD (n = 24) and 300 to 900 mg BID (n = 18) for 14 days.[30] There were no deaths, SAEs, or discontinuations due to AEs in this study. AEs were reported by 17 participants (40.5%) receiving any dose of BMS-813160 and in 3 participants (21.4%) receiving placebo. There was no apparent dose relationship with respect to AEs. One AE of headache in a participant receiving BMS-813160 10 mg QD was considered moderate in intensity. All other AEs were considered to be mild in intensity. There were concentration-dependent increases in QRS and PR intervals and heart rate at 600 mg BID and 900 mg BID, without any electrocardiogram (ECG)-related AEs or clinical sequalae. The increases in PR (mean < 16 msec at peak), QRS (mean < ~10 msec at peak), and heart rate (< ~10 bpm at peak) were not considered clinically significant. Concentration-response assessment showed no QTc prolongation.

Participants with Diabetic Kidney Disease

BMS-813160 was generally safe and well-tolerated when administered for 12 weeks to participants with DKD; 88 participants received BMS-813160 150 mg QD (n = 29), BMS-813160 300 mg BID (n = 30), or placebo (n = 29). AEs were reported for 43 (48.9%) of the 88 treated participants, with the most frequently reported AEs being edema peripheral (6.8% of participants), fatigue (5.7% of participants), diarrhea (3.4% of participants), headache (3.4% of participants), and back pain (3.4% of participants). There were no marked differences in AE frequencies in participants receiving BMS-813160 (any dose) compared with placebo, and no dose-related trends were apparent in the frequency of any AEs. The majority of AEs were mild or moderate in severity.

Seven participants had on-treatment SAEs, but only 1 SAE (lobar pneumonia) was assessed as related to treatment; this event resolved with study treatment interruption and medical treatment, and the participant resumed study treatment and completed the treatment period. PR intervals > 200 msec appeared to be more frequent in the drug-treated participants (300 mg BID, 8 of 30 participants [26.7%], 150 mg QD, 8 of 29 participants [27.6%]) compared with placebo (4 of 29 participants [13.8%]), although the apparent difference does not take into account changes from baseline, including baseline values that were > 200 msec. QRS intervals > 120 msec were similar to placebo (10% of each group). QTcF intervals > 450 msec were similar between the groups, although there were numerically more > 30 msec changes from baseline in the drug-treated groups (150 mg QD, 4 of 29 participants [13.8%]; 300 mg BID, 3 of 30 participants [10%]) than in placebo (1 of 29 participants [3.4%]).

Participants with Advanced Colorectal and Pancreatic Cancers

Safety evaluation of BMS-813160 in advanced cancer patients with a 2-week monotherapy lead-in followed by combination with chemotherapy or nivolumab in Part 1 of Study CV202103 is complete. As of the data cutoff date of 30-Oct-2019 for the ongoing study CV202103, safety data are available for 243 participants who have received at least 1 dose of BMS-813160 (Part 1 Arm A [n = 18], Arm B [n = 21], Arm C [n = 36]; Part 2 Arm A [n = 44], Arm B [n = 76], Arm C [n = 48]). The safety profile of BMS-813160 is manageable with all doses tested. One DLT (Grade 3 rash) was observed with BMS-813160 300 mg BID in combination with gemcitabine and nab-paclitaxel, and 1 DLT (pericardial effusion with pericarditis) was observed with BMS-813160 600 mg QD in combination with gemcitabine and nab-paclitaxel. Both of these participants have continued on the study treatment with 1 dose reduction in both study drug (BMS-813160 600 mg QD reduced to 300 mg QD) and chemotherapy (gemcitabine 1000 mg/m^2 reduced to 800 mg/m^2 and nab-paclitaxel 125 mg/m^2 reduced to 100 mg/m^2) and tolerated further treatment well. There were no DLTs in Part 2 Arm B Cohort 3b. Overall, the AE profile appears to be similar to expected frequency in these cancers when combined with chemotherapy or nivolumab. Please refer to the IB for further details.[27]

3.2.2 Nivolumab

Nivolumab is a fully human, immunoglobulin G4 (IgG4) [kappa] isotype monoclonal antibody that binds to PD-1 with nanomolar affinity (dissociation constant [Kd], 3.06 nM) and a high degree of specificity. Nivolumab blocks binding of PD-1 to its ligands PD-L1 and PD-L2. Nonclinical in vitro testing of nivolumab demonstrated that binding to PD-1 results in enhanced T-cell proliferation and release of interferon gamma (IFNγ) in vitro in mixed lymphocyte reaction and cytomegalovirus assays.

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.[32] 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.[33]

There is a potential for enhanced toxicity when combined with other immunotherapeutic agents. Combination nonclinical toxicology studies with BMS-813160 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 20,200 participants.[33] 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 or metastatic melanoma (as a single agent and in combination with ipilimumab), metastatic non-small cell lung cancer (NSCLC) after disease progression on or after platinum based chemotherapy, advanced renal cell carcinoma (RCC) previously treated with anti-angiogenic therapy, recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after a platinum-based therapy, classical Hodgkin lymphoma (cHL) that has relapsed or progressed, locally advanced or metastatic urothelial cancer after disease progression on or after platinum based chemotherapy, and other cancers.[33]

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 (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level. AEs have included pulmonary toxicity, renal toxicity (including acute renal failure), endocrine abnormalities, gastrointestinal (GI) toxicity, dermatologic toxicity (including rash), and hepatotoxicity. A pattern of immune-related AEs has been defined, for which management algorithms have been developed; these are provided in Appendix 6. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms. There is no relationship between the incidence, severity, or causality of AEs and the nivolumab dose level.

There is a potential for enhanced toxicity when combined with other immunotherapeutic agents. Nivolumab in combination with chemotherapy has been evaluated in multiple studies and many clinical trials are in progress. These trials so far have not shown any synergistic toxicity when immunotherapy was combined with chemotherapy. Additional details on the safety profile of nivolumab, including results from other clinical studies, are summarized in the nivolumab IB.[33]

3.2.2.1 Nonclinical Pharmacokinetics and Metabolism of Nivolumab

Please see the nivolumab IB[33] for current data.

3.2.2.2 Clinical Pharmacokinetics of Nivolumab

Single-dose PK of nivolumab was evaluated in 39 participants with multiple tumor types in CA209001 in the dose range of 0.3 to 10 mg/kg. The median Tmax across dose levels ranged from

1.6 to 3.1 hours with individual values ranging from 0.9 to 7 hours. The PK of nivolumab was linear in the range of 0.3 to 10 mg/kg with dose-proportional increase in Cmax and AUC(INF). Geometric mean clearance after a single intravenous (IV) dose ranged from 0.13 to 0.19 mL/h/kg, while mean volume of distribution of terminal phase (Vz) varied between 83 to 113 mL/kg across doses. The mean terminal T-HALF of nivolumab was 17 to 25 days, consistent with half-life of endogenous IgG4, indicating that the elimination mechanism of nivolumab may be similar to IgG4. Both elimination and distribution of nivolumab appeared to be independent of dose within the dose range studied.

The multiple dose PK of nivolumab given every 2 weeks (Q2W) in participants with multiple tumor types was determined from the CA209003 study as well as population PK (PPK) analyses using data from 909 participants across nivolumab studies. Multiple-dose PK of nivolumab following Q2W dosing was linear with dose-proportional increase in Cmax and area under the concentration-time curve in 1 dosing interval (AUC[TAU]) in the studied range of 0.1 to 10 mg/kg. The geometric mean of terminal T-HALF was 26.7 days and the typical CLR was 8.7 mL/h, which are consistent with those of full human immunoglobulin antibodies.

Nivolumab 480 mg every 4 weeks (Q4W) is currently under active clinical evaluation across multiple tumor types. Using a PPK model, nivolumab 480 mg Q4W is predicted to provide average steady-state concentrations (Cavgss) similar to nivolumab 3 mg/kg Q2W. Nivolumab 480 mg Q4W is predicted to provide greater (approximately 40%) maximum observed plasma concentration at steady state (Cmaxss) and lower (approximately 20%) trough steady-state concentrations (Cminss). Nivolumab has been shown to be safe and well tolerated up to doses of 10 mg/kg Q2W and has not demonstrated a clear dose response or exposure-response safety relationship. Based on these safety findings, the predicted Cmaxss at 480 mg Q4W is not considered to put patients at increased risk for AEs. The approved doses of 3 mg/kg Q2W and 240 mg Q2W have shown survival benefit across multiple tumor types compared to respective standards of care. Nivolumab exposure was not a predictor of survival in exposure-response efficacy analyses conducted for multiple tumor types. The Cminss values following nivolumab 480 mg Q4W are predicted to be in the range of those on the flat part of the exposure-response efficacy curves and are not expected to impact efficacy.

Clinical safety data across multiple studies and tumors (CA209511 [Part 2], CA209384, CA209017, CA209025, CA209057, and CA209066) support the modeling above. In addition, these studies suggest that there is no substantive difference in the safety profile of nivolumab 3 mg/kg or 240 mg Q2W compared with 480 mg Q4W in terms of Grade 3/4 AEs, SAEs, AEs leading to discontinuation, and immune-mediated AEs. No new safety concerns were identified. These data show that the safety profiles of nivolumab 3 mg/kg Q2W, 240 mg Q2W, and 480 mg Q4W were similar, despite the increase in the Cmax with 480 mg Q4W. Nivolumab 480mg Q4W has been implemented in several trials across the nivolumab program. Nivolumab 480 mg Q4W infused over 30 minutes was FDA approved in March 2018 for most approved indications. The European Medicines Agency has also approved nivolumab 480 mg Q4W for the treatment of patients with melanoma (advanced or adjuvant treatment) and previously treated RCC.

Additional details are provided in the current version of the nivolumab IB.[33]

3.3 Benefit/Risk Assessment

Patients who have advanced solid tumors, including metastatic colorectal and pancreatic cancer, have a poor prognosis and no curative options. There is no prior oncology experience with BMS-813160; therefore, clinical benefit has not been established in patients with advanced cancer.

BMS-813160 has been evaluated in multiple clinical trials and established a well-tolerated safety profile. In CV202002 study, there were concentration-dependent increases in QRS and PR intervals and heart rate at 600 mg BID and 900 mg BID, without any ECG-related AEs or clinical sequalae.[30] The increases in PR (mean < 16 msec at peak), QRS (mean < ~10 msec at peak), and heart rate (< ~10 bpm at peak) were not considered clinically significant. Concentration-response assessment showed no QTc prolongation. The most frequently reported AEs in CV202010 study were edema peripheral (6.8% of subjects), fatigue (5.7% of subjects), diarrhea (3.4% of subjects), back pain (3.4% of subjects), and headache (3.4% of subjects).[34] This first-in-oncology assessment was based on preclinical and clinical data supporting clinical activity of either CCR2 or CCR5 inhibition in combination with chemotherapy in pancreatic or CRC, respectively.

In combination with chemotherapy, BMS-813160 may potentiate chemotherapy-induced side effects in Arm A and B. However, clinical studies showed that the combination of either CCR2 or CCR5 inhibitors with chemotherapy in pancreatic cancer and CRC was tolerable and no unexpected toxicities were seen with the combinations.[4,6] The toxicity profiles for the chemotherapy regimens in this study have been well characterized and oncologists are trained in managing these common toxicities with supportive care medications and dose interruptions or reductions. While these chemotherapy regimens have shown to improve survival of patients with metastatic colorectal and pancreatic cancer, more than half of CRC and three-fourths of pancreatic cancer patients have progression within 1 year of diagnosis on these regimens. Therefore, better treatment options are clearly needed.

As of 30-Oct-2019, the safety profile of BMS-813160 is manageable with either 300-mg BID and 600-mg QD dose. One DLT (Grade 3 rash) was observed with 300 mg BID BMS-813160 in combination with gemcitabine and nab-paclitaxel, and 1 DLT (pericardial effusion with pericarditis) was observed with 600 mg QD of BMS-813160 in combination with gemcitabine and nab-paclitaxel. Both of these participants have continued on the study treatment with 1 dose reduction for both BMS-813160 and chemotherapy and tolerated further treatment well. Overall, the AE profile appears to be similar to expected frequency in these cancers when combined with chemotherapy. The safety of the chemotherapy combinations with BMS-813160 will continue to be carefully monitored. Please refer to the IB for safety data of BMS-813160 in combination with chemotherapy in the study.[27]

In combination with nivolumab therapy, BMS-813160 may potentiate immune-mediated adverse reactions caused by nivolumab in Arm C. The combination with nivolumab was well tolerated in Part 1 of the study with no DLTs. The safety profile of nivolumab monotherapy is well defined and is based on experience with greater than 20,200 participants evaluated in clinical trials. 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 nivolumab IB.[33]

Management algorithms for immune-induced AEs involving GI, renal, pulmonary, hepatic, endocrinopathy, skin, neurologic systems, and myocarditis are included in the protocol (see Appendix 6). The safety of the combination with nivolumab will be carefully monitored.

The combination of Gem/nab-paclitaxel, nivolumab, and BMS-813160 has not been evaluated in previous clinical trials; however, based on well-tolerated safety profiles of respective double combinations and data from Part 2 Arm B Cohort 3b of the current study (CV202103) showing that no DLTs occurred in the 6 DLT-evaluable participants who received BMS-813160 + nivolumab + Gem/nab-paclitaxel, this combination is expected to be tolerable. Please see Section 3.1.7 for further details. The combination was not started until at least 6 participants were treated with BMS-813160 300 mg BID in combination with Gem/nab-paclitaxel (Part 1, Arm B) and in combination with nivolumab (Part 1, Arm C) and all cleared the DLT period.

The mandated biopsies pose limited risk to the participant, and include discomfort, pain, and bleeding. Because of the need to understand the effect of BMS-813160 in tumors and the need for development of predictive biomarkers to select the patients most likely to benefit from BMS-813160, the limited risk of a research biopsy is considered appropriate in an early phase clinical trial research setting. Biopsies will be performed only if deemed an acceptable clinical risk as judged by the investigator.

Continuous safety assessments will be utilized by the Investigators and Bristol-Myers Squibb (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 BMS-813160 is an experimental agent, 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 treatment in this patient population with an unmet medical need.

3.3.1 Safety Monitoring on Study Treatment

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. In addition, BMS has developed a multi-layered process to ensure safety monitoring through close collaboration of study site investigators, the BMS study team, and the BMS Global Pharmacovigilance and Epidemiology (GPVE) led Safety Management Team (SMT), which is composed, at a minimum, of the GPVE medical safety assessment physician (Chairman of the SMT) and GPVE single case review physician, the study Medical Monitor, the study biostatistician, and epidemiologist; all of whom, analyze the data in an unblinded fashion. Furthermore, the SMT routinely monitors for actual or potential issues related to participant safety that could result in a change in the medical risk-benefit balance associated with the use of study treatment(s). This collaborative process constitutes the safety monitoring plan for the study. To support safety oversight, BMS has established ongoing processes for collection, review, analysis, and submission of individual AE reports and their aggregate analyses. Because this is an open-label

study, GPVE, the BMS Medical Monitor, and the investigators will have access to all data necessary for safety evaluation. Treatment of AEs will follow institutional guidelines and recommended management algorithms, as listed in the IBs and prescribing information, as applicable, for each combination agent and contemporaneous control comparator, and provided as appendices to this protocol. Specific algorithms for the management of immune-related AEs are provided in Appendix 6 and are applicable to immune-related AEs for all immuno-oncology study treatment combinations.

4 OBJECTIVES AND ENDPOINTS

The objectives and endpoints for the primary, secondary, and exploratory analyses of this study are shown in Table 4-1 (Part 1) and Table 4-2 (Part 2).

Table 4-1: Objectives and Endpoints (Part 1)

Objectives	Endpoints
Primary	
1) To assess the safety and tolerability of BMS-813160 in combination with either FOLFIRI (Arm A), Gem + nab-paclitaxel (Arm B), or nivolumab (Arm C) in participants with advanced CRC or pancreatic cancer	1a) Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and death; Incidence of laboratory abnormalities
2) To assess the pharmacodynamic effects of BMS-813160 in tumor samples	1b) Additional safety endpoints: summary measures of vital signs or ECGs 2) Decrease in Treg or TAM in tumor samples
Secondary	
1) To assess the preliminary efficacy of BMS-813160 in combination with either FOLFIRI (Arm A), Gem + nab-paclitaxel (Arm B), or nivolumab (Arm C) in participants with advanced CRC or pancreatic cancer	1) ORR, median DOR, and PFS rate at 24 weeks
2) To characterize the PK of BMS-813160 and its metabolite (BMS-939429) when administered alone, and in combination with either Gem + nab-paclitaxel, FOLFIRI or nivolumab	2a) PK parameters, such as Cmax, Tmax, Ctrough, C24, AUC(0-8), AUC(0-24), CLT/F, AI, CLR, %UR, MR_Cmax, and MR_AUC(0-24), if data permit 2b) Cmax and Ctrough concentrations of BMS-813160 during combination therapy
3) To characterize the immunogenicity of nivolumab when administered in combination with BMS-813160	3) Frequency of positive ADA to nivolumab during combination therapy
Exploratory	
1) To characterize the PK of nivolumab when administered in combination with BMS-813160	1) Concentrations at end of infusion and Ctrough for nivolumab during combination therapy
2) To assess the potential effect of BMS-813160 monotherapy on the CLR of NMN an endogenous biomarker for multidrug and toxin extrusion transporters (MATE1 and MATE2-K)	2,3) Change of NMN in plasma and urine and CL change of creatinine levels in plasma and urine and CLR
3) To assess the potential effect of BMS-813160 monotherapy on levels of NMN, an endogenous marker for renal transporters	4) Change of MCP-1 and CCR2 positive monocyte count in peripheral blood
4) To assess the pharmacodynamic effects of BMS-813160 in peripheral blood	5) OS rate at 1 year and 2 years
5) To assess OS	

Abbreviations: %UR = percent urinary recovery over dosing interval; ADA = anti-drug antibody; AEs = adverse events; AI = accumulation index; AUC(0-8) = area under the concentration-time curve from time 0 to 8 hours post dose; AUC(0-24) = area under the concentration-time curve from time 0 to 24 hours post dose; C24 = observed plasma concentration at 24 hours post dose (for QD dosing only); CCR2 = cysteine-cysteine chemokine receptor 2; CL = clearance; CLR = renal clearance; CLT/F = apparent total body clearance; Cmax = maximum observed plasma concentration; CRC = colorectal cancer; Ctrough = trough observed plasma concentration; DLT = dose limiting toxicity; DOR = duration of response; ECGs = electrocardiograms; FOLFIRI = FOL (folinic acid [leucovorin]) F (fluorouracil [5-fluorouracil]) IRI (irinotecan [CAMPTOSAR]); Gem = gemcitabine; MATE = multidrug and toxin extrusion protein; MCP-1 = monocyte chemotactic protein-1; MR_AUC(0-24) = ratio of metabolite AUC(0-24) to parent AUC(0-24), corrected for molecular weight; MR_Cmax = ratio of metabolite Cmax to parent Cmax, corrected for molecular weight; NMN = N-methylnicotinamide; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic(s); SAEs = serious adverse events; TAM = tumor-associated macrophages; Tmax = time of maximum observed plasma concentration; Treg = regulatory T cells.

Table 4-2: Objectives and Endpoints (Part 2)

Objectives	Endpoints
Primary	
1) To assess the preliminary efficacy of BMS-813160 in combination with either FOLFIRI (Arm A), Gem + nab-paclitaxel or nivolumab + Gem + nab-paclitaxel (Arm B), or nivolumab (Arm C), and as monotherapy (Arm D) in participants with advanced CRC or pancreatic cancer	1) ORR as assessed by investigator using RECIST v1.1, median DOR, and PFS rate at 24 weeks
Secondary	
1) To assess the safety and tolerability of BMS-813160 in combination with either FOLFIRI (Arm A), Gem + nab-paclitaxel or nivolumab + Gem + nab-paclitaxel (Arm B), or nivolumab (Arm C), and as monotherapy (Arm D) in participants with advanced CRC or pancreatic cancer 2) To assess the pharmacodynamic effects of BMS-813160 in tumor samples	1a) Incidence of AEs, SAEs, AEs leading to discontinuation, and death; incidence of laboratory abnormalities. 1b) Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria in Cohort 3b 1c) Additional safety endpoints: summary measures of vital signs or ECG 2) Decrease in Treg & TAM in tumor samples
Exploratory	
1) To assess the PK of BMS-813160 when administered as monotherapy and with different chemotherapy or nivolumab combination regimens 2) To characterize the immunogenicity of nivolumab when administered in combination with BMS-813160 or BMS-813160 plus chemotherapies 3) To assess the pharmacodynamic effects of BMS-813160 in peripheral blood 4) To assess the PK of irinotecan and nab-paclitaxel in a subset of participants when combined with BMS-813160 5) To assess OS	1a) Cmax and Ctrough concentrations of BMS-813160 during monotherapy and combination therapy 1b) Concentrations at end of infusion and Ctrough for nivolumab during combination therapy 2) Frequency of positive ADA to nivolumab during combination therapy 3) Change of MCP-1 and CCR2 positive monocyte count in peripheral blood 4) Cmax, Tmax, AUC(0-24), Ctrough of irinotecan, SN-38, and nab-paclitaxel 5) OS rate at 1 year and 2 years

Abbreviations: ADA = anti-drug antibody; AEs = adverse events; AUC(0-24) = area under the concentration-time curve from time 0 to 24 hours post dose; CCR2= cysteine-cysteine chemokine receptor 2; Cmax = maximum observed plasma concentration; CRC = colorectal cancer; Ctrough = trough observed plasma concentration; DLT = dose-limiting toxicity; ECGs = electrocardiograms; FOLFIRI = FOL (folinic acid [leucovorin]) F (fluorouracil [5-fluorouracil]) IRI (irinotecan [CAMPTOSAR]); Gem = gemcitabine; MCP-1 = monocyte chemotactic protein-1; ORR = objective response rate; OS = overall survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; SAEs = serious adverse events; TAM = tumor-associated macrophages; Tmax = time of maximum observed plasma concentration; Treg = regulatory T cells.

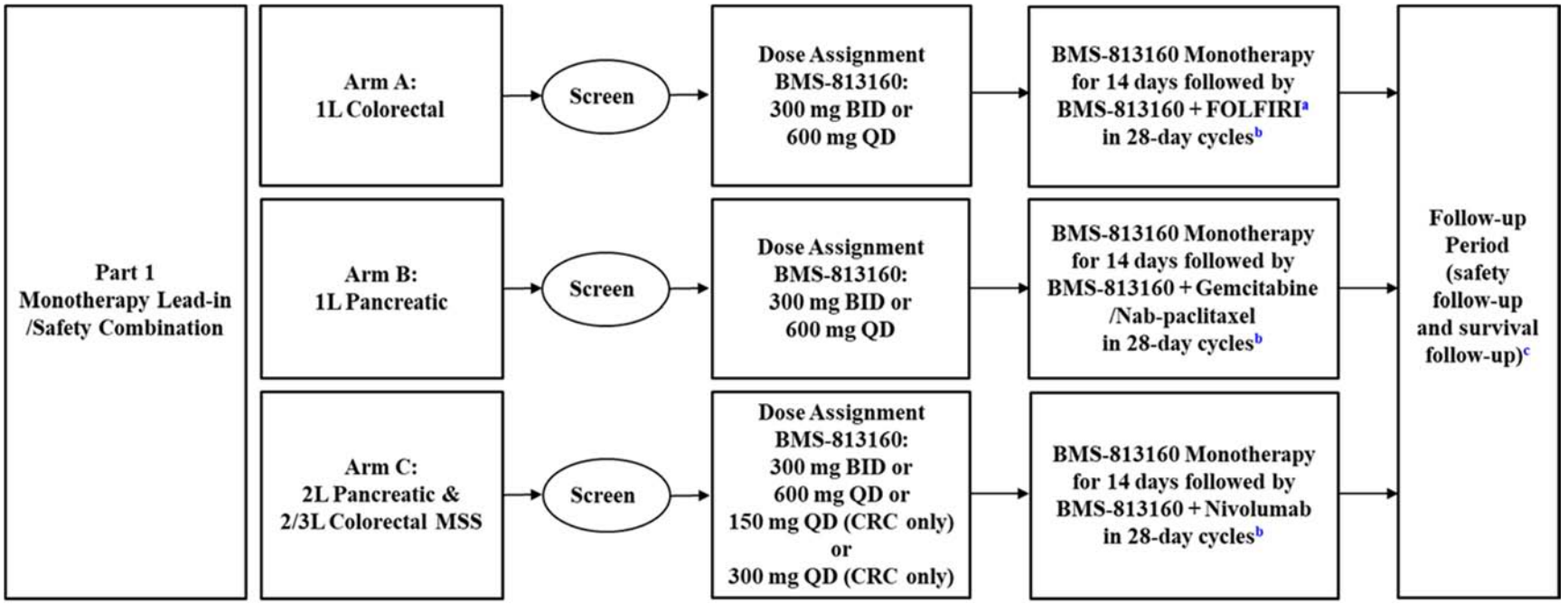
5 STUDY DESIGN

5.1 Overall Design

This is a Phase 1b/2, open-label, 2-part, multicenter trial to assess the safety, tolerability, PK, pharmacodynamics, and preliminary efficacy of BMS-813160 alone or in combination with either FOLFIRI, Gem/nab-paclitaxel, Gem/nab-paclitaxel and nivolumab, or nivolumab in participants with advanced CRC or pancreatic cancer.

The study is divided into 3 periods: Screening, Treatment, and Follow-up (Safety and Survival Phases). The study design scheme is presented in Figure 5.1-1 (Part 1) and Figure 5.1-2 (Part 2).

Figure 5.1-1: Study Design Schematic (Part 1)



Note: FOLFIRI (irinotecan 180 mg/m^2 over 90 minutes; leucovorin 400 mg/m^2 over 2 hours [leucovorin may be given concurrently with irinotecan]; 5-FU 400 mg/m^2 bolus followed by 2400 mg/m^2 over 46 hours continuous infusion) on Days 1 and 15 of a 28-day cycle.

Note: The recommended dose of nab-paclitaxel (ABRAXANE) is 125 mg/m^2 administered as an intravenous 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.

Note: Nivolumab 480 mg administered as an intravenous infusion over 30 minutes every 4 weeks.

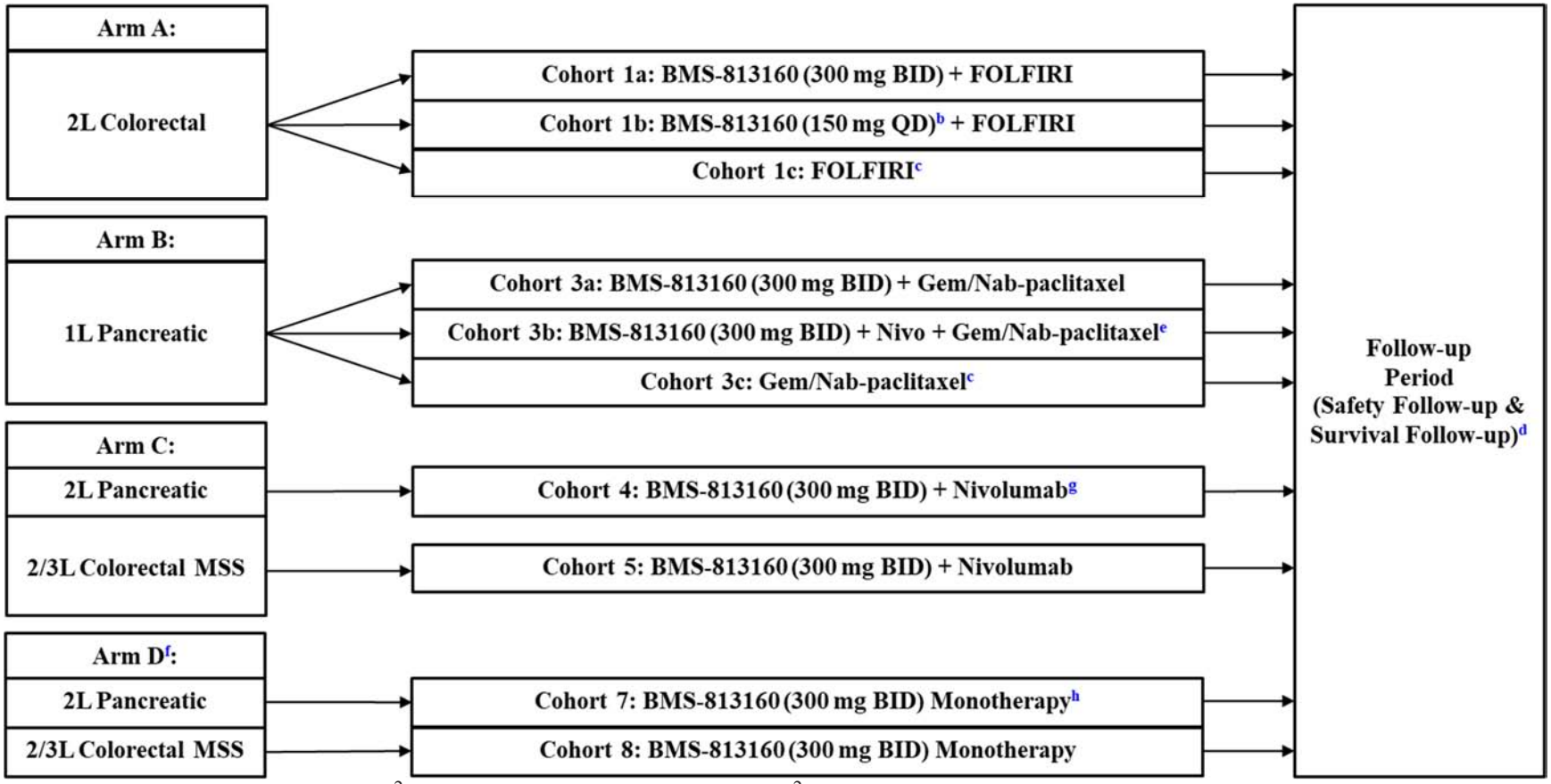
Abbreviations: 1L = first-line; 2L = second-line; 3L = third-line; 5-FU = 5-fluorouracil; BID = twice a day; CRC = colorectal cancer; FOLFIRI = FOL (folinic acid [leucovorin]) F (fluorouracil [5-fluorouracil]) IRI (irinotecan [CAMPTOSAR]); m2 = square meter; MSS = microsatellite stable; QD = once daily.

[a] Bevacizumab, cetuximab, or panitumumab can be added to 1L FOLFIRI if appropriate.

[b] Participants will continue on the combination until disease progression, intolerance to treatment, meeting discontinuation criteria, or withdrawal of consent.

[c] Safety follow-up: 30 days for Arms A and B and 100 days for Arm C. Survival follow up to begin after completion of safety follow-up every 12 weeks (± 2 weeks) until 2 years after last dose of study treatment.

Figure 5.1-2: Study Design Schematic (Part 2) - Combination Therapy Expansion



Note 1: FOLFIRI (irinotecan 180 mg/m^2 over 90 minutes; leucovorin 400 mg/m^2 over 2 hours [leucovorin may be given concurrently with irinotecan]; 5-FU 400 mg/m^2 bolus followed by 2400 mg/m^2 over 46 hours continuous infusion) on Days 1 and 15 of a 28-day cycle.

Note 2: The recommended dose of nab-paclitaxel (ABRAXANE) is 125 mg/m^2 administered as an intravenous 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.

Note 3: Nivolumab 480 mg administered as an intravenous infusion over 30 minutes every 4 weeks. In Cohort 3b, administer nivolumab followed by chemotherapy 30 minutes later.

Abbreviations: 1L = first-line; 2L = second-line; 3L =third-line; 5-FU = 5-fluorouracil; BID = twice a day; FOLFIRI = FOL (folinic acid [leucovorin]) F (fluorouracil [5-fluorouracil]) IRI (irinotecan [CAMPTOSAR]); Gem = gemcitabine; MSS = microsatellite stable; Nivo = nivolumab; ORR = objective response rate; PD = progressive disease progression; QD = once daily

[a] Participants will continue on the combination until disease progression (PD), intolerance to treatment, meeting discontinuation criteria, or withdrawal of consent.

[b] Lower dose: BMS-813160 150 mg QD (see Section 3.1.6 for further details).

[c] Participants in Cohort 1c will be allowed to cross over to Cohort 5 at the time of PD if it's felt to be in their best interest by their treating physician and participants meet all eligibility criteria to enroll in Arm C. Participants will have to meet all eligibility criteria to re-enter the study, undergo baseline assessment (Table 2-2) and need a 28-day washout period prior to first dose of study treatment in the new arm.

[d] Safety follow-up: 30 days for Arms A, B (Cohorts 3a and 3c), and D; 100 days for Arm C and Cohort 3b (see Table 2-7 for further details). Survival follow up to begin after completion of safety follow-up every 12 weeks (± 2 weeks) until 2 years after last dose of study treatment.

[e] The Gem/nab-paclitaxel in combination with nivolumab and BMS-813160 cohort had a safety lead-in of approximately 6 participants who were treated with BMS-813160 300 mg BID and monitored for 4 weeks before additional participants are added to the cohort. In addition a staggered dosing (sentinel participant) approach was used for the first 3 participants. The first participant to be dosed was observed for 5 days, before additional participants (ie, participant 2 and 3) received study treatments.

[f] Arm D (BMS-813160 monotherapy) will only open if participants in Arm C show an ORR of approximately 15% or durable responses are seen with the combination of nivolumab and BMS-813160.

[g] Cohort 4 was closed per Revised Protocol 06. Participants in Cohort 3c can no longer crossover to Cohort 4 per Revised Protocol 06.

[h] Cohort 7 will not open for enrollment due to Cohort 4 being closed due to futility per Revised Protocol 06.

5.1.1 Screening Period

The screening period will last for up to 28 days. The screening period begins by establishing the participant's initial eligibility upon signing of the informed consent form (ICF). The screening assessments are shown in Table 2-1. If a participant surpasses the 28-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 procedure in this participant population. Participants will be treated in 1 of 3 arms as described in the following sections. Allocation will be based on availability of slots in each of the 3 arms and participants meeting cohort-specific eligibility criteria.

5.1.2 Treatment Period (Part 1)

Treatment period (Part 1) will have a 2-week monotherapy lead-in with BMS-813160 prior to combination with either FOLFIRI, Gem/nab-paclitaxel, or nivolumab. All 3 arms will enroll participants in parallel. Participants will be assigned to the BMS-813160 300 mg BID or 600 mg QD cohort in each arm of the study. Participant assignment is detailed in Section 7.2. Approximately 6 evaluable participants will be treated at each BMS-813160 dose (ie, 300 mg BID or 600 mg QD) for a total of approximately 12 participants per arm. Up to 6 additional participants will be added to evaluate BMS-813160 dose of 150 mg QD and 300 mg QD to better characterize PK and PD of lower doses of BMS-813160 in combination with nivolumab (see Section 3.1.6 for details on the rationale). Approximately 6 additional participants may be added to a dose cohort to better characterize the safety, PK, or pharmacodynamic profile and inform Part 2 dose selection of BMS-813160 if needed after discussion with the Sponsor and investigators.

The BMS-813160 monotherapy lead-in allows assessment of initial tolerability in cancer participants, facilitating the characterization of the added or synergistic toxicity of the subsequent combination regimens, and enables a biopsy at 2 weeks to characterize PD effects of BMS-813160. After 2 weeks of BMS-813160 monotherapy, participants will start the combination phase with either FOLFIRI, Gem/nab-paclitaxel, or nivolumab along with continued treatment with BMS-813160 after a mandatory biopsy (± 3 days) is performed. Monotherapy should continue if biopsy is collected beyond 2 weeks and combination with chemotherapy or nivolumab should only begin after the biopsy is performed. Participants will continue on combination until disease progression, intolerance, meeting criteria for treatment discontinuation (Section 8), or withdrawal of consent.

5.1.3 Treatment Period (Part 2)

Treatment period (Part 2) will explore the preliminary signals of efficacy of BMS-813160 with various combinations as described below. The recommended Phase 2 dose of BMS-813160 in Part 2 was chosen based on safety, PK, and pharmacodynamic data available from Part 1 of the study. Based on these considerations, BMS-813160 300 mg BID dosing regimen was selected for primary investigation in this study. A regimen of BMS-813160 150 mg QD in combination with

FOLFIRI will be also evaluated in Arm A. Participants in Part 2 will be treated with BMS-813160 alone or in combination with either FOLFIRI, Gem/nab-paclitaxel, Gem/nab-paclitaxel and nivolumab, or nivolumab without a BMS-813160 monotherapy lead-in.

There will be 4 study arms (Arms A, B, C, and D) containing a total of 10 cohorts. Arm D (BMS-813160 monotherapy) will only open if participants in Arm C show an ORR of approximately 15% or durable responses are seen with the combination of nivolumab and BMS-813160 where durable response is defined as a continuous response (objective CR or PR) beginning within 12 months of treatment and lasting ≥ 6 months. Please see Section 3.1.8 for further details on Arm D.

Participants in Arm A will include 2L CRC and will be randomized to 1 of 3 arms. FOLFIRI in combination with BMS-813160 300 mg BID or 150 mg QD, or FOLFIRI alone. Please see Section 3.1.6 for rationale for BMS-813160 150 mg QD dose.

Participants in Arm B will include 1L pancreatic cancer and will be randomized to 1 of 3 arms: Gem/nab-paclitaxel in combination with BMS-813160 300 mg BID, Gem/nab-paclitaxel in combination with BMS-813160 300 mg BID and nivolumab 480 mg Q4W, or Gem/nab-paclitaxel alone. The Gem/nab-paclitaxel in combination with nivolumab and BMS-813160 300 mg BID (Cohort 3b) will have a safety lead-in of approximately 6 participants who will be treated and monitored for 4 weeks before additional participants are added to the cohort. In addition a staggered dosing (sentinel participant) approach will be used for the first 3 participants. After the first 3 participants are treated, at a 5-day interval, with the combination, the subsequent 3 participants may be enrolled competitively. Approximately 6 participants will be monitored for 4 weeks before additional participants may be treated in the same cohort. After approximately 6 evaluable participants are randomized in Cohort 3b, it will be paused for enrollment for safety evaluation while Cohort 3a and Cohort 3c will continue to randomize participants. These participants will be monitored closely for DLTs as per DLT criteria described in 7.4.1. If greater than 33% (2 or more) meet DLT criteria, then 1 dose level lower will be explored.

Participants in Arm C will include 2L pancreatic cancer (**Cohort 4 closed per Revised Protocol 06**) and 2/3L MSS CRC and will be treated with BMS-813160 300 mg BID in combination with nivolumab.

Participants in Arm D will include 2L pancreatic cancer and 2/3L MSS CRC and will be treated with BMS-813160 300 mg BID alone.

A biopsy will be obtained 4 weeks (± 3 days) after the first dose in Part 2 for correlative studies. Participants on bevacizumab or its biosimilar in Arm A should be off bevacizumab or its biosimilar for at least 14 days or according to institutional guidelines to prevent any bleeding or delay in wound healing.

Participants will continue on combination until disease progression, intolerance, meeting criteria for treatment discontinuation (Section 8), or withdrawal of consent.

5.1.4 Treatment Period (Parts 1 and 2)

Blood, urine, and tumor biopsy samples and ECGs will be collected and participants will receive study treatments as per the schedule of activities (Table 2-3, Table 2-4, Table 2-5, and Table 2-6). Participants will have baseline imaging within approximately 28 days of 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 disease progression, clinical deterioration, toxicity, meeting criteria for discontinuation of study treatment (Section 8), or withdrawal of consent. Participants who go off treatment will be followed for safety assessments and survival status as defined in Table 2-7.

Treatment beyond disease progression (Arm C only) may be allowed in select participants with initial RECIST v1.1 defined progressive disease (PD) after discussion and agreement with the BMS Medical Monitor that the benefit/risk assessment favors continued administration of study treatment (eg, participants are continuing to experience clinical benefit as assessed by the investigator, tolerating treatment, and meeting other criteria specified in Section 7.4.8). Participants in Cohort 1c will be allowed to cross over to Cohorts 5 at the time of disease progression if it's felt to be in their best interest by their treating physician and participants meet all eligibility criteria to enroll in Arm C. Participants in Cohort 3c will not be allowed to cross over to Cohort 4 at the time of disease progression since Cohort 4 was closed per Revised Protocol 06. Participants will have to meet all eligibility criteria to re-enter the study, undergo baseline assessment (Table 2-2) and need a 28-day washout period prior to the first dose of study treatment in the new arm. If Cohort 5 is closed due to safety or futility, participants will not be allowed to cross over from Cohort 1c.

Participants with a response of SD, PR, or 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) PD, 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 8, or 5) withdrawal of consent.

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 multiple procedures are required at a single time point, the following is a list of procedures from highest priority to low: PK sampling, ECG and vital signs, and laboratory tests. Participants will be closely monitored for AEs throughout the study. Blood and urine samples will be collected at baseline and after study treatment administration for PK and multidrug and toxin extrusion (MATE)-renal transporter biomarker analyses according to the schedules outlined in Section 9.5.

5.1.5 Follow-up Period (Parts 1 and 2)

During Follow-up, participants will follow the Follow-up Procedural Outline in Section 2 (Table 2-7).

5.1.5.1 Safety Follow-up

For all participants, the end of treatment (EOT) visit will be the most recent on-treatment visit (with all available safety and response data) and does not need to be repeated, and will be considered the start of the Week 1 Clinical/Safety Follow-up visit.

Participants must be followed for at least 30 days (± 7 days) in all cohorts in Arms A, Cohorts 3a and 3c in Arm B, and Cohorts 7 and 8 in Arm D after the last dose of study treatment to monitor for AEs. Follow-up visits in Cohort 3b in Arm B and Cohorts 4 (**closed per Revised Protocol 06**) and 5 in Arm C should occur at Days 30, 60, and 100 (± 7 days) after the last dose of study treatment to monitor for AEs to account for the long half-life of nivolumab. All participants, except those participants who withdraw consent for study participation, will be required to complete Clinical/Safety Follow-up visits regardless of whether they start a new anti-cancer therapy.

If participants cannot be seen in clinic for any of the follow up visits, at least a telephone follow up is recommended.

5.1.5.2 Survival Follow-up

After completion of the Safety Follow-up Phase, all participants will enter the Survival Follow-up Phase. Participants will be followed up (by telephone or clinic visit) every 12 weeks (Q12W) [± 2 weeks], from the last dose of study treatment for 2 years or until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first.

The duration of this phase is up to 2 years following the last dose of study treatment, although a longer follow-up phase could be considered in selected cases if an efficacy signal is apparent.

Data from imaging assessments for participants who have ongoing clinical benefit may continue to be collected while participants complete the survival phase of the study.

5.1.6 Data Monitoring Committee and Other External Committees

BMS has elected not to use a Data Monitoring Committee for this study. In addition to the comprehensive safety monitoring plan outlined below, the following key points were considered for this decision:

- This is an open label study.
- The eligibility criteria exclude participants with disease characteristics that could predispose to higher risk of morbidity, eg, history of interstitial lung disease, recent history of coronary thrombosis, etc.
- 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 during dose escalation.
- 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.

BMS has in place a multi-layered process for ensuring participant safety through close collaboration of study site investigators, the BMS study team, and the BMS GPVE-led SMT. This collaborative process constitutes the Data Safety Monitoring Plan for the study as detailed below:

Study safety is evaluated continuously by representatives of BMS GPVE, who operate independently from the clinical team and monitor safety across all BMS protocols. AEs are monitored continuously by GPVE. Signal detection is performed at least monthly and ad hoc throughout the study by the SMT composed, at a minimum, of the GPVE medical safety assessment physician (Chairman of the SMT) and GPVE single case review physician, the study Medical Monitor(s), the study biostatistician, and epidemiologist. The SMT monitors actual or potential issues related to participant safety that could result in a significant change in the medical risk-benefit balance associated with the use of study treatments. Furthermore, investigators will be kept updated of important safety information, such as DLTs, during teleconferences between investigators and the BMS clinical team that will be held approximately every 2 weeks during Part 1 dose selection and at least monthly during Part 2 cohort expansion. If appropriate, select safety issues may be escalated to a senior level, multidisciplinary, BMS wide Medical Review Group for further evaluation and action.

To support safety oversight, BMS has established ongoing processes for collection, review, analysis, and submission of individual AE reports and their aggregate analyses. Because this is an open label study, the BMS Medical Monitor and the investigators will have access to all data necessary for safety evaluation.

All participants in this study represent individuals with high unmet medical need as the prognosis for advanced/metastatic solid tumors is generally very poor.

5.2 Number of Participants

Approximately 54 evaluable participants (6 to 9 participants per dose per treatment arm) may be treated in Part 1 (monotherapy lead-in/combination safety). If additional participants are enrolled (as indicated in Section 5.1.2), approximately 48 additional participants could be enrolled in Part 1 (6 participants per dose per treatment arm or per lower doses [150 mg QD and 300 mg QD] of BMS-813160 in combination with nivolumab). Approximately 308 evaluable participants may be treated in Part 2, Cohorts 1a to 8 (efficacy expansion) [approximately 35 evaluable participants per tumor indication per treatment in Arms A and B and approximately 31 evaluable participants per tumor indication per treatment in Arm C, details are given in Section 10.1]. For each of the pancreatic and CRC MSS cohorts, approximately 18 additional evaluable participants will be treated in a treatment Arm D (BMS-813160 monotherapy) [opens if ORR of approximately 15% or durable responses are seen in Arm C]. The number of participants will be continuously monitored such that the number of evaluable participants in Part 2 will not exceed 40 in any cohort. If the study is expanded further to add more participants, a protocol amendment will be submitted justifying the sample size (see Section 10 for further details).

5.3 End of Study Definition

The start of the trial is defined as the first visit for first participant screened. End of trial is defined as the last visit or scheduled procedure shown in the schedule of activities (see Section 2) for the

last participant. Study completion is defined as the final date on which data for the primary endpoint is expected to be collected.

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for Monotherapy Lead-in Part 1

This first-in-oncology study has been designed to balance the need to evaluate safety of BMS-813160 and preliminary signal of efficacy of BMS-813160 in combination with either chemotherapy or nivolumab in patients with advanced CRC or pancreatic cancer. The 2-week monotherapy lead-in will determine safety, PK, and pharmacodynamic effects of BMS-813160 alone before it is combined with other agents.

5.4.2 Rationale for Testing 2 Different Doses of BMS-813160 in Part 1

BMS-813160 is well tolerated in both QD and BID dosing regimens in prior studies. The BID dosing appears to engage target receptor for the whole 24 hours. Once a day dosing is preferable in oncology patients due to patient convenience and better compliance, and based on the T-HALF may also allow target engagement for the full 24 hours. In addition there are differences in Cmax and potential differences in DDI with once a day and twice a day dosing. Participants receiving BMS-813160 in combination with either chemotherapy or nivolumab will be closely monitored for any side effects. Exploring 2 different dosing regimens in Part 1 will enable BMS to move forward to Part 2 with a dose and schedule of BMS-813160 based on data generated from Part 1.

5.4.3 Rationale for 2-Stage Design in Cohorts in Arm C

Participants in these cohorts are receiving study treatments with no proven activity in these specific patient populations. Nivolumab and BMS-813160 are being tested in pancreatic cancer (**Cohort 4 closed per Revised Protocol 06**) and MSS CRC (Cohort 5) where nivolumab or BMS-813160 has not shown any significant clinical activity. A 2-stage design will provide a guide for futility and preliminary antitumor activity, and avoid exposing a large number of participants to a regimen which may be inactive (see Section 10.1).

5.4.3.1 Rationale for Closing Cohort 4

Following a predetermined analysis at Stage 1, Part 2 Cohort 4 (BMS 813160 in combination with nivolumab in 2L pancreatic cancer) was closed to enrollment due to futility and all participants have completed study treatment.

Revised Protocol 06 implements the following:

- Participant enrollment in Part 2 Cohort 4 is closed due to futility. Closure of this cohort was not due to safety concerns.
- Participants in Part 2 Cohort 3c who progress on 1L chemotherapy can no longer cross over to Cohort 4 since it was closed due to lack of clinical response.
- Participants in Cohort 4 who have received treatment with BMS-813160 + nivolumab will continue to be followed through the study follow-up phases (Table 2-7) or until study discontinuation criteria have been met, whichever occurs first.

- Cohort 7 (BMS-813160 monotherapy; 2L pancreatic cancer) will not open for enrollment because opening of this cohort was dependent on an ORR of approximately 15% or durable responses observed in Cohort 4, which was closed due to lack of clinical response.

5.4.4 Rationale for Control Arms

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 control may not be fully representative of the patient population in this study.

The control arms for Arm A (FOLFIRI) and Arm B (Gem/nab-paclitaxel) are added to better evaluate safety and efficacy of BMS-813160 combined with either FOLFIRI or Gem/nab-paclitaxel ± nivolumab, respectively. These control arms provide a reference for safety and efficacy of FOLFIRI and Gem/nab-paclitaxel alone and help interpret the data in terms of the comparison between a treatment arm and control arm. Stratification by tumor sidedness in Arm A and by prior neoadjuvant/adjuvant therapy or not in Arm B was planned, but in error was omitted from the IRT system. As the cohorts were largely enrolled when the error was discovered, stratification was removed from the protocol with Revised Protocol 06. All of the planned stratification factors have been collected and can be analyzed retrospectively; thus, the lack of stratification is not expected to affect the scientific validity of the study. Microsatellite instability (MSI) status will be collected on all patients if available locally, and BMS plans to perform MSI testing retrospectively on all patients. BMS will conduct exploratory analyses to evaluate MSI status as a prognostic biomarker in the different treatment cohorts.

5.4.5 Rationale for MATE1-renal Biomarker Sample Collection

BMS-813160 is an inhibitor of MATE1, with an IC50 value of 4.6 μM. In contrast, it showed low potential to inhibit MATE2-K (the IC50 value was > 300 μM, the highest concentration tested). Based on the human steady state Cmax values at doses within the anticipated clinical range (300 to 600 mg BID, Study CV202002[30]), 925.1 to 2547.8 ng/mL (~1.9 to 5.3 μM), BMS-813160 may reduce the renal CLR and increase the renal accumulation of drugs that are substrates of MATE1, although overlap in substrate specificity between the 2 transporters may mitigate this effect. The CLR of creatinine and N-methyl nicotinamide (NMN), endogenous substrates of MATE1 and MATE2-K transporters and biomarkers of renal transporter function, will be determined before and during BMS-813160 treatment to provide insight to the potential effect of BMS-813160 on renal transport function of MATE substrates such as cisplatin and oxaliplatin.

5.4.6 Rationale for Using BMS-813160 Tablet

BMS-813160 film-coated tablets, 75 mg and 300 mg for oral administration have been developed for clinical studies. The change from capsules to film-coated tablets involves making minor compositional changes to the current capsule formulation. The process to produce granules for compression into tablets is largely unchanged except with the introduction of fluid bed drying vs tray drying of material used in capsules. The biorelevant dissolution profiles in simulated intestinal fluid of capsules and tablets at the 300 mg dose are similar (300 mg film coated tablet vs two 150 mg capsules). In addition, BMS-813160 drug substance is highly soluble over the pH range of

1 - 6.8.[27] The relative bioavailability of BMS-813160 administered as a single 300 mg (6 × 50 mg) oral dose in capsules was very similar to that from a 300 mg oral dose in solution, and there was no meaningful formulation effect in healthy subjects in Study CV202005.[27] Based on the biorelevant dissolution similarity, minor change in composition, and given that BMS-813160 is a highly soluble compound, it is expected that there will be no impact on exposure due to the change from capsules to tablets.

5.5 Rationale for Dose

5.5.1 Rationale for Dose Selection of BMS-813160

Based on safety, PK, and pharmacodynamic findings from SAD and multiple ascending dose studies, the BMS-813160 300 mg BID dosing regimen was selected for investigation in Part 1 of this study. BMS-813160 trough plasma concentrations in healthy participants who received a 300 mg BID dose for 14 days exceeded the 2x IC90 concentrations for both CCR2 binding and MIP-1β stimulated CCR5 phosphorylation. Sustained inhibition of CCR2 and CCR5 on Day 14 was observed at doses ≥ 300 mg BID, indicating the achievement of target engagement. Additionally, the BMS-813160 300 mg BID dosing regimen was tolerable in healthy participants and participants with DKD.

As the half-life of BMS-813160 (~12 to 16 hours) may have supported the use of a QD regimen, the 600 mg QD regimen was also investigated in Part 1 of this study. The trough concentration of the 600 mg QD regimen at steady state exceeded the IC90 concentrations for both CCR2 binding and MIP-1β stimulated CCR5 phosphorylation. At 600 mg QD, CCR2 inhibition was saturated over the 24 hour dosing interval. CCR5 inhibition also appeared to reach a maximum, although the effect was not sustained over the 24 hour interval. Based on the ECG data observed in healthy participants, the 600 mg QD regimen is not expected to produce PR interval prolongation in patients.

The selection of the Part 2 dose for BMS-813160 in CV202103 is primarily based on available data from Part 1 of CV202103. At 300 mg BID, preliminary PK data suggested similar average plasma levels of BMS-813160 in cancer patients relative to that in healthy subjects. Based on the higher Cmax at steady state with the 600 mg QD dose and the lack of apparent difference in pharmacodynamics or safety between the 300 mg BID and 600 mg QD dose, 300 mg BID has been chosen as the primary dose to be evaluated in Part 2 of the study.

5.5.2 Rationale for Testing Lower Dose of BMS-813160

As the current 2 doses of BMS-813160, 600 QD and 300 BID, provide > 1-fold IC90 for CCR2/5 function, the Sponsor proposes to add a lower dose of 150 mg QD and 300 mg QD for subjects with 2/3L MSS CRC that provides a trough concentration of 0.3 to 0.5-fold IC90 for inhibiting CCR2/5 function. See Section 3.1.6 for further details.

5.5.3 Rationale for Dose Selection of FOLFIRI

FOLFIRI will be given as per standard of care for metastatic CRC. Please see Section 7 for dosing and dose modifications. Bevacizumab or its biosimilar can be added to FOLFIRI for 2L therapy if it is available locally and appropriate as per investigator discretion. Bevacizumab or its biosimilar

should be held for biopsies for at least 14 days or according to institutional guidelines to prevent any bleeding or delay in wound healing.

5.5.4 Rationale for Dose Selection of Gemcitabine/Nab-Paclitaxel

Gemcitabine/nab-paclitaxel will be given as per standard of care for metastatic pancreatic cancer. Please see Section 7 for dosing and dose modifications.

5.5.5 Rationale for Dose Selection of Nivolumab

Nivolumab 240 mg Q2W has been approved in many countries for use as monotherapy in patients with melanoma, RCC, NSCLC, and other indications. The safety and efficacy of the 480 mg Q4W flat dose of nivolumab are expected to be similar to the approved nivolumab dose of 240 mg flat doses or 3 mg/kg Q2W. The nivolumab dose of 480 mg Q4W was selected based on clinical data and modeling and simulation approaches using PPK and exposure-response analyses of data from studies in multiple tumor types (melanoma, NSCLC, and RCC) where body weight normalized dosing (mg/kg) has been used. 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 CLR and volume of distribution were found to increase as the 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 model, the overall distributions of nivolumab average steady state exposures are comparable after treatment with either nivolumab 3 mg/kg Q2W or nivolumab 480 mg Q4W, although the flat dose regimen of 480 mg Q4W is predicted to result in approximately 40% higher Cmaxss and approximately 20% lower steady-state trough concentrations compared to the reference regimen of 3 mg/kg Q2W. Across the various tumor types in the clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy and safety has been found to be relatively flat. Although nivolumab Cmaxss is predicted to be higher following 480 mg Q4W, these exposures are predicted to be lower than or within the exposure ranges observed at doses up to 10 mg/kg Q2W used in the nivolumab clinical program and are not considered to put patients at increased risk. The exposures predicted following administration of nivolumab 480 mg Q4W are on the flat part of the exposure-response curves for previously investigated tumors (melanoma and NSCLC) and are not predicted to affect efficacy. Based on these data, nivolumab 480 mg Q4W is expected to have similar efficacy and safety profiles to nivolumab 3 mg/kg Q2W.

Of note, as an immunoglobulin G4 (IgG4) monoclonal antibody, nivolumab does not interact directly with cytochrome P450 (CYP) enzyme systems. Systemic cytokine modulation data indicated that there were no meaningful changes in cytokines known to have indirect effects on CYP enzymes across all dose levels of nivolumab (0.3, 2, and 10 mg/kg) during the course of treatment. Therefore, it is unlikely that nivolumab administered at either 240 mg Q2W or 480 mg Q4W will affect the systemic exposures of BMS-813160.

5.5.6 Rationale for Nivolumab 30-minute Infusion

Long infusion times place a burden on participants and treatment centers. Establishing that nivolumab can be safely administered using shorter infusion times of 30 minutes duration in participants will diminish the burden provided no change in safety profile. Nivolumab has been administered safely at doses ranging up to 10 mg/kg over these treatment durations. Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across multiple clinical studies, and all have been managed by following the safety algorithms. Infusion duration of 30 minutes for 480 mg nivolumab is not expected to present any safety concerns compared with the prior experience at 10 mg/kg nivolumab dose infused over the 60-minute duration. Nivolumab 480 mg Q4W infused over 30 minutes was FDA approved in Mar-2018 for the majority of the approved indications.

5.6 Treatment Duration

Participants will be treated until disease progression, intolerance to treatment, meeting discontinuation criteria, or withdrawal of consent. Participants who discontinue chemotherapy in part or whole due to intolerance can continue BMS-813160 or BMS-813160 and nivolumab (Cohort 3b) on study after investigator's discussion with the Medical Monitor or Sponsor designee. Participants in Arm C will be permitted to continue on study treatment beyond initial RECIST v1.1-defined PD as long as they meet the criteria described in Section 7.4.8. Participants in Cohort 1c may also be able to cross over as described in Section 5.1.4. Participants will continue to get all study evaluations as per schedule of events in Table 2-3, Table 2-4, Table 2-5, and Table 2-6.

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) The participant must sign the ICF prior to the performance of any study related procedures that are not considered part of standard of care.

2) Type of Participant and Target Disease Characteristics

a) Participants with a histological or cytological confirmed diagnosis of an advanced solid tumor as defined below.

b) In general, discontinuation of 1 drug in a multi-drug regimen and continuation of other drug(s) are considered 1 line of treatment. Switching from IV (5-FU) to an oral formulation (capecitabine) of the same drug is also considered one line.

i) Part 1 (Phase 1b)

1. Arm A: Metastatic CRC previously untreated or recurring systemically after surgery or > 6 months post adjuvant therapy. Local recurrence alone not allowed.
2. Arm B: Metastatic pancreatic adenocarcinoma previously untreated or recurring systemically after surgery or > 6 months post neoadjuvant/adjuvant therapy. Local recurrence alone not allowed.
3. Arm C: Metastatic pancreatic adenocarcinoma previously treated with 1 line of systemic chemotherapy or progressing on or within 6 months after neoadjuvant/adjuvant therapy. Locally advanced pancreatic adenocarcinoma which has progressed to metastatic disease previously treated with 1 line of systemic therapy is allowed.

   - OR -

   Metastatic MSS colorectal adenocarcinoma treated with systemic chemotherapy in the metastatic setting. Participants must have received an oxaliplatin-containing regimen and an irinotecan- containing regimen (or a combined oxaliplatin- and irinotecan-containing regimen) but no more than 2 lines of systemic chemotherapy for metastatic disease. Chemotherapy administered in the adjuvant setting is considered a line only if there was disease progression within 6 months after completion of the adjuvant therapy. (Note: MSS is defined as expression of MLH1, MSH2, MSH6 and PMS2 by immunohistochemistry [IHC] or absence of instability in microsatellite markers by PCR as determined by local laboratory.) Patients who are tested by PCR and found to be MSI-low can enroll on this arm.

ii) Part 2 (Phase 2)

1. **Not applicable per Protocol Revision 03.** Arm A - Cohort 1 (1L Colorectal): Metastatic CRC previously untreated or recurring systemically after surgery or > 6 months post adjuvant therapy. Local recurrence alone not allowed.
2. **Not applicable per Protocol Revision 03.** Arm A - Cohort 2 (3L Colorectal): Metastatic CRC treated with no more than 2 lines of systemic chemotherapy for metastatic disease. Adjuvant chemotherapy or radiation is not considered 1L if more than 6 months from completion of therapy. Progression on or shortly after

FOLFIRI required, but it does not have to be the last treatment given. Participants must have also received an oxaliplatin-containing regimen (including as part of a combined oxaliplatin- and irinotecan-containing regimen). This may include chemotherapy administered in the adjuvant setting only if there was disease progression within 6 months after completion of the adjuvant therapy.

3. **Not applicable per Protocol Revision 03.** Arm B - Cohort 3 (1L Pancreatic): Metastatic pancreatic adenocarcinoma previously untreated or recurring systemically after surgery or > 6 months post adjuvant therapy. Local recurrence alone not allowed.
4. **Not applicable per Protocol Revision 03.** Arm C - Cohort 4 (2L Pancreatic): Metastatic pancreatic adenocarcinoma previously treated with 1 line of systemic chemotherapy or progressing on or within 6 months after adjuvant therapy. Locally advanced pancreatic adenocarcinoma which has progressed to metastatic disease previously treated with 1 line of therapy is allowed.
5. **Not applicable per Protocol Revision 03.** Arm C - Cohort 5 (2L or 3L Colorectal): Metastatic MSS colorectal adenocarcinoma treated with 1 or 2 prior lines of systemic chemotherapy in the metastatic setting. Participants must have received an oxaliplatin-containing regimen and an irinotecan-containing regimen (including as part of a combined oxaliplatin- and irinotecan-containing regimen). This may include chemotherapy administered in the adjuvant setting only if there was disease progression within 6 months after completion of the adjuvant therapy. (Note: MSS is defined as expression of MLH1, MSH2, MSH6 and PMS2 by immunohistochemistry [IHC] or absence of instability in microsatellite markers by PCR as determined by a local laboratory.)
6. **Not applicable per Protocol Revision 03.** Arm C - Cohort 6 (MSI-high colorectal): Metastatic MSI-high colorectal adenocarcinoma progressed after anti-PD1/PDL1 therapy, and previously treated with a fluoropyrimidine, an oxaliplatin-containing regimen, and an irinotecan containing regimen (including as part of a combined oxaliplatin- and irinotecan-containing regimen). This may include chemotherapy administered in the adjuvant setting only if there was disease progression within 6 months after completion of the adjuvant therapy. (Note: MSI-high is defined as loss or expression of MLH1, MSH2, MSH6 or PMS2 by IHC or presence of instability in microsatellite markers by PCR as determined by a local laboratory.) Participants who are tested by PCR and found to be MSI-low are not allowed to be enrolled on this arm but can enroll on MSS arm.
7. Arm A - Cohorts 1a, 1b, and 1c (2L Colorectal): Metastatic CRC previously treated with 1 line of oxaliplatin-based systemic therapy in the metastatic setting or progression on or within 6 months of adjuvant oxaliplatin based chemotherapy. Adjuvant chemotherapy for CRC or neoadjuvant chemoradiation for rectal cancer is not considered a line if more than 6 months from completion of such therapy.
8. Arm B - Cohorts 3a, 3b, and 3c (1L Pancreatic): Metastatic pancreatic adenocarcinoma previously untreated or recurring systemically after surgery or > 6 months post neoadjuvant/adjuvant therapy. Local recurrence alone not allowed.
9. Arms C and D - Cohort 4 (**Cohort 4 closed per Revised Protocol 06**) and 7 (2L Pancreatic): Metastatic pancreatic adenocarcinoma previously treated with 1 line

of systemic therapy or progressing on or within 6 months after neoadjuvant/adjuvant therapy. Locally advanced pancreatic adenocarcinoma which has progressed to metastatic disease previously treated with 1 line of systemic therapy is allowed. Chemotherapy in the neoadjuvant or adjuvant setting is not considered a line if progression occurred more than 6 months after completion of therapy.

10. Arms C and D - Cohort 5 and 8 (2L or 3L Colorectal): Metastatic MSS colorectal adenocarcinoma treated with systemic therapy in the metastatic setting. Participants must have received an oxaliplatin-containing regimen and an irinotecan-containing regimen or a combined oxaliplatin- and irinotecan-containing regimen but no more than 2 lines of systemic chemotherapy for metastatic disease. Chemotherapy administered in the adjuvant setting is considered 1 line only if there was disease progression within 6 months after completion of the adjuvant therapy. (Note: MSS is defined as expression of MLH1, MSH2, MSH6 and PMS2 by immunohistochemistry [IHC] or absence of instability in microsatellite markers by PCR as determined by a local laboratory.)

3) General Inclusion Criteria

a) Participants must have measurable disease by RECIST v1.1 (Appendix 5).

b) Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1.

c) Ability to swallow tablets or capsules.

d) All participants will be required to undergo mandatory pre and on-treatment biopsies. 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 Medical Monitor and availability of formalin-fixed paraffin embedded (FFPE) blocks or unstained slides as delineated below. Participants will however be required to undergo on-treatment biopsy at acceptable clinical risk as judged by the investigator in all arms.

   i) Pre-treatment tissue must be collected and centrally or locally confirmed for adequate tissue quantity and quality during the screening period prior to first dose of study treatment. Please refer to lab manual for detailed biopsy collection instructions. Up to 15% of treated participants in each arm may be enrolled without confirmation of adequate tissue, after discussion with the Medical Monitor.

   ii) The tumor tissue specimen must be a core needle biopsy, excisional or incisional biopsy. Fine needle biopsies, drainage of pleural effusions with cytospins, or punch biopsies are not considered adequate for biomarker review. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable. 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; > 1500/μL allowed for Arms C and D

   ii) Neutrophils ≥ 1500/μL; > 1000/μL allowed for Arms C and D

   iii) Platelets ≥ 100 × 10^3/μL; > 75,000/μL allowed for Arms C and D

   iv) Hemoglobin ≥ 8.5 g/dL

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

i) Alanine aminotransferase (ALT) and (aspartate aminotransferase) AST ≤ 3x institutional upper limit of normal (ULN)

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

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

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

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

g) Ability to comply with study visits, treatment, procedures, PK and PD sample collection, and required study follow-up.

4) Age and Reproductive Status

a) Males and Females, ages 18 or age of majority or older at the time of consent

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

c) Women must not be breastfeeding

d) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception (defined in Appendix 04 and study ICF) for the duration of study therapy plus 10 months after completion of treatment.

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

f) Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section. Continuous abstinence must begin at least 30 days prior to initiation of study therapy (see Appendix 4).

g) WOCBP are permitted to use hormonal contraception methods as described in Appendix 4.

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, which have a failure rate of < 1% when used consistently and correctly (see Appendix 4).

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

6.2 Exclusion Criteria

1) Target Disease Exceptions

a) Histology other than adenocarcinoma (neuroendocrine or acinar cell). If mixed tumor, the predominant histology must be adenocarcinoma.

b) Suspected, known, CNS metastases (Imaging required only if participants are symptomatic). Participants with adequately treated CNS metastasis are eligible if the participant's neurologic function returned to baseline and are not currently on steroids for at least 2 weeks prior to study entry. Participants with history of brain metastasis require baseline MRI of the brain prior to study entry.

2) Medical History and Concurrent Diseases

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 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 study treatment administration except for adrenal replacement steroid doses > 10 mg daily prednisone equivalent in the absence of active autoimmune disease.

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

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

d) 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) **Not applicable per Protocol Revision 04.** QT interval corrected for heart rate using Fridericia's formula (QTcF) prolongation > 480 msec.

v) History of other clinically significant heart disease (eg, cardiomyopathy, congestive heart failure with New York Heart Association functional classification III-IV, pericarditis, significant pericardial effusion, or myocarditis)

vi) Cardiovascular disease-related requirement for daily supplemental oxygen therapy

e) 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 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.*

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

g) Other active malignancy requiring concurrent intervention.

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) 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)

m) Any significant acute or chronic medical illness which in the opinion of the investigator is detrimental for participation on the trial.

n) Current or recent (within 3 months of study treatment administration) gastrointestinal disease that could impact upon the absorption of study treatment

o) Any gastrointestinal surgery that is likely impact upon the absorption of study treatment. Whipple or other upper GI surgery is allowed if there is no clinical evidence of malabsorption.

p) **Not applicable per Protocol Revision 04.** Inability to tolerate oral medication.

q) **Not applicable per Protocol Revision 04.** Inability to be venipunctured and/or tolerate venous access.

r) Participants who have received a live / attenuated vaccine within 30 days of first treatment.

3) Prior Therapy

a) Prior treatment with CCR2 and/or CCR5 inhibitors, PD-1, PD(L)-1 or cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibodies

b) Any anti-cancer therapy (eg, chemotherapy, biologics, vaccines, or hormonal treatment) including investigational drugs within 4 weeks prior to the first dose of study treatment administration, except for non-cytotoxic therapies, for which at least 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 is shorter than 4 weeks, agreement with the Medical Monitor must be obtained.

4) Restricted Concomitant Therapy

a) Prior use of strong/moderate CYP3A4 inhibitors or inducers within 4 weeks or 5 half-lives (whichever is shorter) prior to the first dose of BMS-813160. (See Appendix 8).

b) For Part 1 only: MATE inhibitors within 4 weeks or 5 half-lives (whichever is shorter) prior to the first dose of BMS-813160 and for the first 2 weeks of BMS-813160 monotherapy. (See Appendix 9).

c) Prior use of strong inhibitors of UGT1A1 in FOLFIRI arm within 4 weeks or 5 half-lives (whichever is shorter) prior to starting FOLFIRI (see Appendix 10) or participants with known UGT1A1 deficiency is prohibited.

d) **Not applicable per Revised Protocol 06**. Class I antiarrhythmics (eg, quinidine, procainamide, dysopiramide, lidocaine, phenytoin, mexiletine, tocainide, flecainide, propafenone, and moricizine)

e) Class 1A antiarrhythmics (eg, quinidine, procainamide, dysopiramide) are prohibited

f) Class 1C antiarrhythmics (eg, flecainide, propafenone, and moricizine) are prohibited.

g) Tricyclic antidepressants are prohibited.

h) Caution is warranted with concomitant use with Class 1B antiarrhythmics (lidocaine, phenytoin, mexiletine, tocainide) and methadone (in particular at high doses) due to potential sodium channel blockade.

5) Physical and Laboratory Test Findings

a) Ascites needing paracentesis or medical management (Grade 2 or higher)

b) Peripheral Neuropathy greater than Grade 1 for Arm B receiving nab-paclitaxel

c) Albumin less than 3 g/dL (pancreatic cancer arms only)

d) 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

e) Any of the following on 12-lead ECG prior to study treatment administration, confirmed by repeat

i) QRS ≥ 120 msec, except right bundle branch block or intraventricular conduction delay which is not considered clinically significant

ii) QTcF ≥ 480 msec, except right bundle branch block

6) Allergies and Adverse Drug Reaction

a) History of allergy to study treatments or any of its components of the study arm that participant is enrolling

7) Other Exclusion Criteria

a) 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 or permitted to continue as a participant. Strict conditions apply and BMS approval is required.)

b) 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

6.3.1 Meals and Dietary Restrictions

Study treatment should be taken at approximately the same time each day. For participants in Part 1, during the first 6 weeks of study treatment when the intensive PK samples are collected on C0D1, C0D14 (Arms A, B, and C), C1D15 (Arm B), and C2D1 (Arm A), and for a subset of participants in Part 2 (Arms A and B) on Cycle 2 Day 1 when the intensive PK samples are collected, participants are required to fast for at least 8 hours prior to the collection of specimens for PK analysis. Light meal (total calories: ~330 kcal, fat ≤ 15%, protein ≤ 10%) can be allowed 2 hour post dose (eg, participants may receive study treatment at 7:00/8:00 AM and eat breakfast at 9:00/10:00 AM). For evening doses (if applicable), no food is allowed 2 hour prior to or 2 hour after dose (eg, participants may eat dinner at 5:00/6:00 PM and receive study treatment at 7:00/8:00 PM). After 6 weeks in Part 1 and other than Cycle 2 Day 1 for a subset of participants in Part 2, where intensive PK samples are collected, BMS-813160 can be taken regardless of food intake.

6.3.2 Caffeine, Alcohol, and Tobacco

No restrictions.

6.3.3 Activity

No restrictions.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. 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 or Lead-In Period

Participant Re-enrollment: This study permits the re-enrollment of a participant that has discontinued the study as a screen failure. 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 enrollment 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 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 treatment assignment.

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

An investigational product, also known as investigational medicinal product 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-investigational products.

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 CV202103

Product Description / Class and Dosage Form	Potency	IP/Non-IMP[a]	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
BMS-813160-01 Capsule	150 mg	IP	Open-label	Capsule	2 to 25°C, Store in a tightly closed container
BMS-813160-01 Tablet	300 mg	IP	Open-label	Film Coated Tablet	2 to 25°C, Store in a tightly closed container
BMS-813160-01 Tablet	75 mg	IP	Open-label	Film Coated Tablet	2 to 25°C, Store in a tightly closed container
Nivolumab (BMS-936558) Solution for injection[b]	100 mg/vial (10 mg/mL)	IP	Open-label	Vial	2 to 8°C, Protect from light and freezing
Nivolumab (BMS-936558) Solution for injection[b]	40 mg/vial (10 mg/mL)	IP	Open-label	Vial	2 to 8°C, Protect from light and freezing
Gemcitabine Concentrate for Solution for Injection[c]	1000 mg/vial and various strengths	IP	Open-label	Vial and various packaging configurations	Refer to the label on container or package insert / summary of product characteristics
Nab-paclitaxel (ABRAXANE) Concentrate for Solution for Injection[c]	100 mg/vial and various strengths	IP	Open-label	Vial and various packaging configurations	Refer to the label on container or package insert / summary of product characteristics
5-FU Solution for Injection[c]	Various strengths	IP	Open-label	Vial and various packaging configurations	Refer to the label on container or package insert / summary of product characteristics
Leucovorin Solution for Injection[c]	Various strengths	IP	Open-label	Vial and various packaging configurations	Refer to the label on container or package insert / summary of product characteristics
Irinotecan Solution for Injection[c]	Various strengths	IP	Open-label	Vial and various packaging configurations	Refer to the label on container or package insert / summary of product characteristics

Abbreviations: 5-FU = 5-fluorouracil; IP = investigational product; Non-IMP = non-investigational medicinal product

[a] Where allowed by local regulations, chemotherapy treatments may be considered Non-IMP.

[b] Nivolumab (BMS-936558) will be supplied as a 240 mg kit - each kit containing (2) 100 mg vials and (1) 40 mg vial.

[c] These products will be obtained as local commercial product in countries if allowed by local regulations or through investigating site's standard prescribing procedures, otherwise the Sponsor will supply these products.

7.1 Treatments Administered

The selection and timing of dose for each participant are presented in Table 7.1-1.

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Dosage level(s)	Frequency of Administration	Route of Administration
BMS-813160 (150 mg capsule or 300 mg tablet)	300 mg	BID	PO
BMS-813160 (150 mg capsule or 300 mg tablet)	600 mg	QD	PO
BMS-813160 (150 mg capsule or 75 mg tablet)	150 mg	QD	PO
BMS-813160 (150 mg capsule or 300 mg tablet)	300 mg	QD	PO
Nivolumab	480 mg IV	Q4W	IV infusion
5-FU	400 mg/m^2 Bolus AND 2400 mg/m^2 IV	Day 1, 15: Q4W	Bolus and IV infusion
Leucovorin	400 mg/m^2 IV	Day 1, 15: Q4W	IV infusion
Irinotecan	180 mg/m^2 IV	Day 1, 15: Q4W	IV infusion
Gemcitabine	1000 mg/m^2 IV	Day 1, 8, 15: Q4W	IV infusion
Nab-paclitaxel (ABRAXANE)	125 mg/m^2 IV	Day 1, 8, 15: Q4W	IV infusion

Abbreviations: 5-FU = 5-fluorouracil; BID = twice a day; IV = intravenous; PO = per os (by mouth [orally]); Q4W = every 4 weeks; QD = once daily

FOLFIRI (irinotecan 180 mg/m^2 over 90 minutes; leucovorin 400 mg/m^2 over 2 hours (leucovorin may be given concurrently with irinotecan); 5-FU 400 mg/m^2 bolus followed by 2400 mg/m^2 over 46 hours continuous infusion) on Days 1 and 15 of a 28-day cycle. Bevacizumab or its biosimilar can be added to 2L FOLFIRI if appropriate, and will be administered in accordance with local Health Authority approved labeling for these agents. Levoleucovorin can be substituted for leucovorin as per site's standard practice.

The recommended dose of nab-paclitaxel (ABRAXANE) is 125 mg/m^2 administered as an intravenous 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. Participants in Cohort 3b will be administered nivolumab first and followed by chemotherapy 30 minutes later.

Nivolumab 480 mg administered as an intravenous infusion over 30 minutes every 4 weeks.

Restrictions related to food and fluid intake are described in Section 6.3.1.

On days when PK blood samples or pre-dose ECGs are required, participants will take the morning dose of BMS-813160 at the clinic after all required samples and ECGs are collected and start of infusion if applicable. Please refer to Table 9.5.1-1, Table 9.5.2-1, Table 9.5.3-1, Table 9.5.4-1, and Table 9.5.4-2. On days PK samples or ECGs are not required, BMS-813160 can be taken at home or in clinic. Please see Section 6.3.1 for dietary restrictions during the first 6 weeks for participants in Part 1 when the intensive PK samples are collected, and on Cycle 2 Day 1 for a subset of participants with the intensive PK collection in Part 2 (Arms A and B).

Participants will receive FOLFIRI and Gem/nab-paclitaxel as per their site standard of care. All supportive care treatments including prophylactic treatment for nausea, diarrhea and infusion reaction will be given as per standard of care.

For participants on the nivolumab treatment, a 30-minute infusion of nivolumab will be followed by a 30-minute observation period, after all infusions for each participant.

7.2 Method of Treatment Assignment

Study treatment will be dispensed at the study visits as listed in Schedule of Activities (Section 2).

All participants must be assigned a participant number upon providing signed written informed consent. Based on the rate of participant enrollment, the Sponsor will implement an interactive response technology (IRT) to assign participant numbers, study treatment group and dose level, as well as manage treatment supply. During the screening visit, the investigative site will register the participant by an IRT designated by BMS for assignment of a 5-digit participant number that will be unique across all sites. Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with [redacted] for example, [redacted].

The PID will ultimately be composed of the site number and participant number. Specific instructions for using the IRT will be provided to the investigational sites in a separate instruction manual.

Each participant who is randomized will be assigned a unique randomization number. This is not the primary identifier for the participant, but is used for the randomization schedule. The primary identifier will be the PID described above, for use on the case report form (CRF) and source documents. A participant being reassigned to an Arm C cohort from another cohort will be assigned a different treatment assignment but will retain the same PID.

For Part 1, the first 3 participants will be enrolled into 1 dose cohort in each arm. Once approximately 3 participants enroll, the arm will enroll approximately another 3 participants to the other dose cohort in the same arm. For example, 3 participants in Arm A will be enrolled into the 300 mg BID dosing. The next 3 participants will be enrolled into the 600 mg daily arm. Participants will be followed for 6 weeks to assess DLTs for each dose and schedule. Participants will not be

replaced if they are discontinued from the study secondary to a DLT unless the AE can be determined to be unrelated to treatment or not a DLT.

For Part 2, participants in Arm A will be randomized in a 1:1:1 ratio to FOLFIRI in combination with BMS-813160 300 mg BID or FOLFIRI in combination with BMS-813160 150 mg QD, or FOLFIRI alone. Participants in Arm B will also be randomized in a 1:1:1 ratio to BMS-813160 300 mg BID in combination with Gem/nab-paclitaxel or BMS-813160 300 mg BID in combination with Gem/nab-paclitaxel and nivolumab, or Gem/nab-paclitaxel alone. Stratification by tumor location and prior treatment in Arms A and B, respectively, was planned, but in error was omitted from the IRT system. As the cohorts were largely enrolled when the error was discovered, **stratification was removed from the protocol with Revised Protocol 06**. All of the planned stratification factors have been collected and can be analyzed retrospectively; thus, the lack of stratification is not expected to affect the scientific validity of the study. BMS will create a randomization schedule that will be uploaded into the IRT.

7.3 Blinding

This is an open-label randomized study. Once participants are randomized, designated personnel of the Sponsor will have access to randomization assignments prior to database lock to facilitate data analysis (see Section 10.3.9).

7.4 Dosage Modification

7.4.1 Dose Limiting Toxicity

For the purpose of guiding dose regimen, DLTs will be defined based on the incidence, duration and grade of AEs for which no alternate cause can be identified. AEs will be evaluated according to the NCI CTCAE v4.03. The incidence of DLT(s) during the first 6 weeks of treatment in Part 1 (the DLT evaluation period) and 4 weeks for Part 2 will be used. Every attempt must be made to assign relationship to BMS-813160, to the chemotherapy or nivolumab regimen, or to both. DLTs are toxicities that are attributed to BMS-813160 or the combination regimen. Toxicities that are well recognized and expected with the chemotherapy backbone, will not automatically be counted as dose limiting. Also, to meet criteria for dose limiting, AEs have to be related to study treatment, and not to disease progression, be clinically relevant, and a clinically relevant shift from baseline. Consideration will be given to a participant's tolerability during the lead-in phase (BMS-813160 alone) and discussed with the Medical Monitor. Participants experiencing a DLT may be treated at 1 dose reduction as long as they recover from the toxicity, do not meet discontinuation criteria, and it is in the best interest of the participant as per the treating physician and discussed with the Medical Monitor. Participants who withdraw from the study during the DLT evaluation interval for reasons other than a DLT may be replaced at the same dose of BMS-813160. The total DLT period is 6 weeks in Part 1 and 4 weeks in Part 2, and participants must have received at least 75% of the BMS-813160 doses and 1 dose of chemotherapy/nivolumab with observation for a minimum of 21 days following the first combination treatment dose to be considered evaluable for DLT.

In Part 1, within each dose level per arm, if 0 or 1 out of the first 3 participants experience a DLT, then an additional 3 participants will be enrolled as planned. If 2 out of 6 participants experience a DLT, the cohort will be expanded to 9 participants. If the observed DLT rate is less than 33%

and the number of DLT-evaluable subjects treated at a dose is approximately 6 subjects or more, then the dose level is deemed to be tolerable. If ≥ 2 of 3 or ≥ 3 of 6 or 9 participants experience DLTs within a dose cohort during the DLT evaluation interval, then that dose level or combination will be determined to be not tolerated, and 1 level lower or alternate treatment schedules will be explored after a discussion between the investigators and the Sponsor.

DLTs can include the following AEs (meeting the preceding criteria):

1) Hepatic DLT

a) Any of the following events will be considered a hepatic DLT:
   i) Any ≥ Grade 3 elevation of AST, ALT, or total bilirubin
   ii) Grade 2 AST or ALT with symptomatic liver inflammation (eg, right upper quadrant tenderness, jaundice, pruritus)
   iii) AST or ALT > 3x ULN and concurrent total bilirubin > 2x ULN without initial findings of cholestasis (elevated serum alkaline phosphatase, eg, findings consistent with Hy's law or FDA definition of potential drug-induced liver injury [DILI])* *Note that this special category of DLT uses ULN rather than Common Toxicity Criteria Grade for definition.

2) Hematologic DLT

a) Grade 4 neutropenia ≥ 7 days in duration
b) Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding, or any requirement for platelet transfusion
c) Grade ≥ 3 febrile neutropenia
d) Grade ≥ 3 hemolysis (ie, requiring transfusion or medical intervention such as steroids)
e) Grade 4 anemia not explained by underlying disease

3) Nonhepatic Nonhematologic DLT

a) Any of the following events will be considered a nonhepatic nonhematologic DLT:
   i) Grade 2 or greater episcleritis, uveitis, or iritis
   ii) Any other Grade 2 eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment
   iii) Grade 2 myocarditis
   iv) Grade 3 pneumonitis, bronchospasm, or neurologic toxicity requires discontinuation
   v) Any Grade 3 or greater nondermatologic, nonhepatic, nonhematologic toxicity will be considered a DLT with the following specific EXCEPTIONS:
      (1) Grade 3 electrolyte or laboratory abnormalities that are not complicated by associated clinical adverse experiences, last less than 48 hours and either resolve spontaneously or respond to conventional medical intervention
      (2) Grade 3 nausea, vomiting, or diarrhea that lasts less than 48 hours and either resolves spontaneously or responds to conventional medical intervention
      (3) Isolated Grade 3 or 4 asymptomatic elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis

(4) Isolated Grade 3 fever not associated with hemodynamic compromise (eg, hypotension, clinical or laboratory evidence of impaired end-organ perfusion)

(5) Grade 3 endocrinopathy that is well-controlled by hormone replacement

(6) Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to site of known or suspected tumor)

(7) Grade 3 fatigue

(8) Grade 3 infusion reaction that returns to Grade 1 in less than 6 hours

4) Dermatologic DLT

a) Grade 3 rash if no improvement (ie, resolution to ≤ Grade 1) after a 1- to 2-week dosing delay. Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.

b) Grade 4 rash of any duration

7.4.1.1 Stopping Rules During Part 2

Continuous evaluation of toxicity events in the Part 2 cohorts will be performed. If at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria in a cohort exceeds 33%, the findings will be discussed with the investigators and further enrollment may be interrupted. If a cohort is discontinued due to toxicity, a new cohort at a previously tested alternative dose level which was found to be safe in Part 1 may be considered based on the aggregate safety experience and in consultation and agreement between Investigators and Sponsor. A revised protocol reflecting any such new cohort will be submitted prior to enrollment to the cohort.

7.4.2 Management Algorithms for Immuno-oncology Agents

Immuno-oncology agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab and BMS-813160 are considered immuno-oncology agents in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed from extensive experience with nivolumab and ipilimumab to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathies
- Skin
- Neurological
- Myocarditis

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

7.4.3 General Guidelines for Dose Modifications

Participants will be monitored continuously for AEs while on study therapy. Participants will be instructed to notify their physician for any and all AEs. Dose modifications in this section for chemotherapy are meant as a general guidance. Modifications should be applied by the investigator's judgment. In case of an AE relationship assignment to chemotherapy alone, dose modifications for chemotherapy alone are allowed. In case of doubt, both chemotherapy and BMS-813160 doses should be modified. Also, in case of assignment of AE relationship to BMS-813160 alone, dose reduction for chemotherapy is not mandated. Specific algorithms for the management of immune-related AEs are provided in Appendix 6 and are applicable to immune-related AEs for all immuno-oncology study treatment combinations. For chemotherapy agents, the package insert and local standard of care rules for dose reduction should also be applied. Nivolumab dose modifications do not apply; nivolumab dose delays are described in Section 7.4.7.1.

For common cumulative lower grade toxicity (Grade 2 or less) for chemotherapy (eg, neurotoxicity, fatigue, GI toxicity) 'drug holidays' are allowed after the DLT observation period in Part 1 and 2 cycles in Part 2 have been completed (and after consultation with the Sponsor's Medical Monitor) when the investigator believes this is in the participant's best interest. Restarting without dose modification is allowed upon recovery. Any laboratory only abnormalities without clinical manifestations or electrolyte abnormalities that may be managed with supplements also do not need dose modification.

For an AE requiring dose modification, BMS-813160, chemotherapy, and/or nivolumab should be interrupted to allow recovery from the AE. Re-initiation of study treatment cannot occur until the AE decreases to ≤ Grade 1 or baseline assessment. In case of delayed recovery to ≤ Grade 1 or baseline from treatment-related AEs that result in a delay of treatment for > 28 days, the participant will not receive additional protocol-related therapy and will be removed from study unless discussed and agreed upon by the Investigator and Sponsor/Medical Monitor that it is in the best interest of the participant to receive additional therapy with BMS-813160 and/or other study treatments.

7.4.4 BMS-813160 Dose Modifications

- New onset of QTcF intervals > 500 msec or prolongation > 50 msec over baseline, new onset QRS intervals > 140 msec, new onset bundle branch block or symptomatic bradycardia, Type 2 second or third-degree heart block will require dose interruption and restarting at 1 dose level lower when ECG changes resolve to baseline. Any electrolyte abnormalities should be corrected and ECG should be repeated with cardiology consultation if clinically indicated.
- Grade 3 non-hematologic toxicity or Grade 4 hematologic toxicity attributed to BMS-813160 will require a dose delay until recovery and 1 dose level reduction.

- Any Grade 3 laboratory only abnormalities without clinical manifestations or electrolyte abnormalities that may be managed with supplementation can be managed with dose delay and do not automatically need dose modification.
- Participants who hold BMS-813160 for less than 7 days for reasons other than drug toxicity will skip those days and continue on BMS-813160 treatment for the rest of the cycle.
- Participants who hold BMS-813160 for more than 7 days or for drug toxicity will hold treatment for the remainder of the cycle and start at a reduced dose for the next cycle unless the delay was from chemotherapy alone or unrelated to study treatment.
- Participants who miss a dose at the specified time can take it as long as there is 8 hour between doses for BID dosing and 16 hours for QD dosing. If less than 8 hours for BID dosing and 16 hours for QD dosing, that dose should be skipped and noted in the participant pill diary.
- Participants who have vomited a dose will not retake the dose unless the vomiting occurred within 15 minutes of taking the dose and intact capsules or tablets are seen. Otherwise, that dose will be skipped and participant will take BMS-813160 at the next scheduled time.
- If chemotherapy or nivolumab is delayed due to toxicity attributable to chemotherapy or nivolumab alone or due to scheduling issues, participants can continue on BMS-813160 alone.
- Participants who need a dose reduction for toxicity attributable to BMS-813160 will continue on the reduced dose of BMS-813160 for the remainder of the study.
- If a participant needs more than 1 dose reduction of BMS-813160 for toxicity, the participant will be taken off BMS-813160 but can continue chemotherapy and/or nivolumab if it is determined to be in the participant's best interest as per the treating investigator and discussed with the Medical Monitor.
- If a participant is off BMS-813160 for more than 28 days, the participant will permanently discontinue treatment and be taken off study, unless it is determined to be in the participant's best interest as per the treating investigator and discussed with the Medical Monitor.

BMS-813160 dose modifications are presented in Table 7.4.4-1.

Table 7.4.4-1: Recommended Dose Modifications for BMS-813160

	BMS-813160	BMS-813160	BMS-813160	BMS-813160
Starting Dose	150 mg QD	300 mg QD	300 mg BID	600 mg QD
Dose Reduction 1	150 mg QOD - Or - 75 mg QD	150 mg QD	150 mg BID	300 mg QD

Abbreviations: BID = twice a day; QD = once daily; QOD = once every other day

7.4.5 FOLFIRI Dose Modifications

Suggested dose modifications for FOLFIRI (5-FU, leucovorin, and irinotecan) are presented in Table 7.4.5-1. Recommended dose modifications for irinotecan/5-FU/leucovorin combination schedules are provided in Table 7.4.5-2.

Table 7.4.5-1: Suggested Dose Modifications for FOLFIRI (5-FU, Leucovorin, and Irinotecan)

	5-FU Bolus	Infusion 5-FU	Irinotecan	Leucovorin
Starting Dose	400 mg/m^2	2400 mg/m^2	180 mg/m^2	400 mg/m^2
Dose Reduction 1	320 mg/m^2	2000 mg/m^2	150 mg/m^2	400 mg/m^2
Dose Reduction 2	200 mg/m^2	1600 mg/m^2	90 mg/m^2	400 mg/m^2

Source: Modified from Table 1 of irinotecan US Package Insert[35]
Abbreviation: 5-FU = 5-fluorouracil

Table 7.4.5-2: Recommended Dose Modifications for Irinotecan/5Fluorouracil (5FU)/Leucovorin (LV) Combination Schedules

Participants should return to pre-treatment bowel function without requiring antidiarrhea medications for at least 24 hours before the next chemotherapy administration. A new cycle of therapy should not begin until the granulocyte count has recovered to ≥ 1500/mm^3, and the platelet count has recovered to ≥ 75,000/mm^3, and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the participant has not recovered after a 2-week delay, consideration should be given to dose reduction for the next dose.

Toxicity NCI CTC Grade[a] (Value)	During a Dose of Therapy
No toxicity	Maintain dose level
Neutropenia	
1 (1500 to 1999/mm^3)	Maintain dose level
2 (1000 to 1499/mm^3)	↓ 1 dose level
3 (500 to 999/mm^3)	Omit dose until resolved to ≤ Grade 2, then ↓ 1 dose level
4 (< 500/mm^3)	Omit dose until resolved to ≤ Grade 2, then ↓ 2 dose levels
Neutropenic fever	Omit dose until resolved, then ↓ 2 dose levels
Other hematologic toxicities	Dose modifications for thrombocytopenia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.
Diarrhea	
1 (2 - 3 stools/day > pretreatment)	Delay dose until resolved to baseline, then give same dose
2 (4 - 6 stools/day > pretreatment)	Omit dose until resolved to baseline, then ↓ 1 dose level
3 (7 - 9 stools/day > pretreatment)	Omit dose until resolved to baseline, then ↓ 1 dose level
4 (≥ 10 stools/day > pretreatment)	Omit dose until resolved to baseline, then ↓ 2 dose levels
Other nonhematologic toxicities[b]	
1	Maintain dose level
2	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
3	Omit dose until resolved to ≤ Grade 2, then ↓ 1 dose level
4	Omit dose until resolved to ≤ Grade 2, then ↓ 2 dose levels *For mucositis/stomatitis decrease only 5-FU, not irinotecan*

Source: Modified from Table 2 of irinotecan US Package Insert[35]

[a] National Cancer Institute Common Toxicity Criteria (version 1.0)

[b] Excludes alopecia, anorexia, asthenia

7.4.6 Gemcitabine + Nab-Paclitaxel Dose Modifications

Dose modification will be performed according to the nab-paclitaxel (ABRAXANE) package insert (Table 7.4.6-1, Table 7.4.6-2, and Table 7.4.6-3).

Table 7.4.6-1: Dose Level Reductions for Patients with Adenocarcinoma of the Pancreas

Dose Level	ABRAXANE (mg/m^2)	Gemcitabine
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[36]

Table 7.4.6-2: Dose Recommendation and Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or within a Cycle for Patients with Adenocarcinoma of the Pancreas

Cycle Day	ANC (cells/mm^3)		Platelet Count (cells/mm^3)	ABRAXANE / 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[36]

Abbreviations: ANC = absolute neutrophil count

Table 7.4.6-3: Dose Modifications for Other Adverse Drug Reactions in Patients with Adenocarcinoma of the Pancreas

Adverse Drug Reaction	ABRAXANE	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[36]

Since FOLFIRI and Gem/nab-paclitaxel are standard therapies for CRC and 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.

7.4.7 Nivolumab Dose Modifications

No dose modifications are allowed.

Participants should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.7.4.

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed.

7.4.7.1 Dose Delays in Nivolumab (Cohort 3b of Arm B and All Cohorts of Arm C)

Participants who experience the following must have all study treatment(s) delayed:

- Grade 2 non-skin, nivolumab-related AE, with the exception of fatigue, nausea, vomiting, and anemia.
- Grade 2 drug-related creatinine, AST, ALT, and/or total bilirubin abnormalities.
- Grade 3 skin, drug-related AE.
- Grade 3 drug-related fatigue, nausea, vomiting, and anemia.
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase elevations do not require dose delay.
  - Grade > 3 AST, ALT, total bilirubin will require dose discontinuation (see Section 8.1).
- Any AE, laboratory abnormality, or intercurrent illness, which in the judgment of the investigator, warrants delaying the dose of study medication.

Criteria for participants who are required to permanently discontinue study treatments are listed in Section 7.4.7.3. Participants not meeting guidelines for permanent discontinuation will be permitted to resume therapy based on the criteria specified below in Section 7.4.7.2. Participants eligible to resume study therapy will resume study therapy at the next scheduled treatment visit following their last received study medication dose.

7.4.7.2 Criteria to Resume Treatment in Nivolumab (Arm C and Cohort 3b)

Participants experiencing AEs not meeting criteria for permanent discontinuation as outlined in Section 7.4.7.3 may resume treatment with study treatment under the following criteria:

1) Participants may resume treatment with study treatment when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value with the following EXCEPTIONS:
    a) Participants may resume treatment in the presence of Grade 2 fatigue.
    b) Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
2) Grade 2 eye pain or blurred vision not meeting DLT criteria (Section 7.4.1) must resolve to baseline prior to resuming study treatment.
3) Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.
4) Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.
5) If the criteria to resume treatment are met, the participant should restart treatment at the next scheduled time point per protocol.
6) The consideration to re-initiate study treatment under these exceptions will be made on a case-by-case basis after considering the overall benefit/risk profile and in consultation between the investigator and the BMS Medical Monitor. Any AE with clinical risk will be assessed on a case-by-case basis with the investigator and the BMS Medical Monitor to determine the risks and benefits of continuing therapy following resolution vs discontinuing therapy permanently.
7) If treatment with study treatment is delayed > 6 weeks, the participant must be permanently discontinued from study treatment, except as specified in Section 7.4.1.

7.4.7.3 Guidelines for Permanent Discontinuation in Nivolumab (Arm C and Cohort 3b)

Participants will be required to permanently discontinue nivolumab for the following AEs:

1) Clinical deterioration, as assessed by the investigator.
2) Grade 3 infusion reaction that does not return to Grade 1 in less than 6 hours.
3) Grade 3 pneumonitis.
4) Life-threatening skin toxicity (toxic epidermal necrolysis).
5) Grade 3 uveitis.
6) Grade 3 myocarditis.
7) Any Grade 4 AE; however, an exception may be made for the following upon consultation between the investigator and BMS Medical Monitor:

a) Grade 4 electrolyte abnormalities < 72 hours in duration.
b) Grade 4 neutropenia < 5 days in duration.
c) Grade 4 lymphopenia.
d) Grade 4 increase in amylase or lipase that is not associated with clinical or radiographic evidence of pancreatitis.

8) Abnormal liver function tests meeting criteria for a potential DILI.
9) Any dosing delay lasting > 6 weeks will be cause for permanent discontinuation. Extensions to the period of dose delays may be granted for individual participants on a case-by-case basis after specific consultation and agreement between the investigator and BMS Medical Monitor in settings where benefit/risk may justify continued study treatment (eg, participant deriving clinical benefit who requires prolonged steroid taper for management of non-DLT immune-related AEs or experiences delays for management of a non-drug-related AE).
   a) Accordingly, dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Additionally, dosing delays > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor.
   b) Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks, the BMS Medical Monitor must be consulted.
   c) Tumor assessments should continue as per protocol even if dosing is delayed.

All participants who discontinue study treatment should comply with protocol-specified follow-up procedures as outlined in Table 2-7. 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 (eg, is 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.

7.4.7.4 Treatment of Treatment-related Infusion Reactions

Nivolumab and the combination therapies may induce infusion or hypersensitivity reactions. If such a reaction were to occur, it may manifest with fever, chills, rigors, headache, rash, pruritus, arthralgia, hypo- 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 Sponsor's Medical Monitor or designee, and reported as an SAE if it meets the criteria.

It may be unclear if an infusion reaction is due to the combination therapy, nivolumab, or to both. Therefore, 1 set of treatment recommendations (based on the most conservative treatments for infusion reactions due to either study treatment) 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, rash), requires infusion rate to be decreased; intervention may be indicated.

- Decrease the rate of the study treatment 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, combination therapy can be given (without prophylactic medications) if the infusion reaction resolves within 3 hours. For scheduling purposes, 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, prophylactic pre-infusion medications should be given prior to all subsequent infusions.
- The following prophylactic pre-infusion medications are recommended prior to future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol (acetaminophen) 325 to 1,000 mg at least 30 minutes before additional study treatment 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 [BP] > 80 mm Hg), requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, IV fluids); prophylactic pre-infusion medications indicated for ≤ 24 hours.

- Interrupt the study treatment infusion.
- Begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol (acetaminophen) 325 to 1,000 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 treatment 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, combination therapy infusion can be given (without prophylactic medications) if the infusion reaction resolves within 3 hours. For scheduling purposes, the combination therapy 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 a combination therapy, prophylactic pre-infusion medications should be given prior to all subsequent infusions.

- The following prophylactic pre-infusion medications are recommended prior to future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol (acetaminophen) 325 to 1,000 mg should be administered at least 30 minutes before additional study treatment administrations. If necessary, corticosteroids (up to 25 mg of SOLU-CORTEF® or equivalent) may be used.
- The amount of study treatment infused must be recorded.

For Grade 3 or Grade 4 symptoms: Severe reaction such as bronchospasm, generalized urticaria, systolic BP < 80 mm Hg, 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 treatment infusion. No further study treatment will be administered. The amount of study treatment infused must be recorded on the CRF.
- Begin an IV infusion of normal saline, and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1.0 mg of a 1:1,000 solution for subcutaneous (SC) administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed.
- 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).

7.4.8 Treatment Beyond Progression (Arm C only)

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[37]

Participants will be permitted to continue treatment beyond initial RECIST v1.1 defined PD, assessed by the investigator, as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Tolerance of study treatment
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)

- Participant provides written informed consent prior to receiving additional treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

A radiographic assessment/scan should be performed at the next scheduled scan to determine whether there has been a decrease in the tumor size or continued PD. 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 study treatment.

If the investigator feels that the participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the trial and continue to receive monitoring according to the Time and Events Schedule (Section 2).

For the participants who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD. Study treatment should be discontinued permanently upon documentation of further progression. The tumor burden volume from time of initial progression should be used as the reference baseline for comparison with the post progression assessment.

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

7.5 Preparation/Handling/Storage/Accountability

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study Participants. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

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

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure treatment is accurately administered. This includes documentation of treatment storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

For study treatments not provided by BMS and obtained commercially by the site, storage should be in accordance with the product label.

Storage facilities for controlled substances must be securely locked and substantially constructed, with restricted access to prevent theft or diversion, as applicable by local regulations.

- Further guidance and information for final disposition of unused study treatment are provided in Appendix 2 and as specified by the protocol team (eg, Study Reference Manual).

7.6 Treatment Compliance

Study treatment compliance, including infusions administered in the clinical facility by trained medical personnel, will be periodically monitored by treatment accountability and review of dosing diary cards. Treatment accountability should be reviewed by the site study staff at each visit to confirm treatment compliance. Sites should discuss discrepancies with the participant at each on-treatment study visit.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to study treatment administration in the study are described below. Medications taken within 4 weeks prior to study treatment administration must be recorded on the CRF.

In limited circumstances (eg, life threatening illness) the use of the below medications may be permitted. The investigator should contact and confirm agreement with the BMS Medical Monitor (and acknowledgement from the contract research organization medical monitor, if any) prior to the administration of any concomitant medications which are restricted or prohibited.

7.7.1.1 Prohibited Treatments

- In vitro, the metabolism of BMS-813160 was primarily mediated via CYP3A4, with some contribution from CYP3A5, and BMS-813160 was also a substrate for P-glycoprotein (P-gp). Based on these results, the potential exists for DDI if BMS-813160 is co-administered with inhibitors or inducers of CYP3A or P-gp. Therefore use of any strong inhibitors or inducers of CYP3A4 or P-gp is not allowed (see Appendix 8).
- Grapefruit and Seville oranges and their juices can inhibit CYP3A4 and must not be consumed while on study.
- MATE inhibitors for the first 2 weeks of BMS-813160 monotherapy (Part 1). (See Appendix 9)
- Concomitant use of strong inhibitors of UGT1A1 in FOLFIRI arm. (See Appendix 10)
- Exposure to any investigational drug or placebo within 4 weeks of study treatment administration.
- Class IA antiarrhythmics (eg, quinidine, procainamide, dysopiramide)
- Class IC antiarrhythmics (eg, flecainide, propafenone, moricizine)
- Tricyclic antidepressants

- Any live / attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose.

7.7.1.2 Restricted Treatments

- **Caution** is warranted with concomitant use of BMS-813160 and:
  - MATE1 substrates with a narrow therapeutic index (see Appendix 11).
  - Moderate inhibitors or inducers of CYP3A4. Moderate CYP3A4 modulators (ie, inhibitor or inducer) are allowed with caution only after the first 7 weeks. See Appendix 8 for a list of CYP3A4 modulators.
  - Class IB antiarrhythmic drugs (eg, lidocaine, tocainide, mexilitine) due to potential sodium channel blockade
  - Methadone (in particular at high doses) due to potential sodium channel blockade

7.7.2 Other Restrictions and Precautions

- Caution should be used for participants with renal or hepatic impairment in Gemcitabine/nab-paclitaxel, or FOLFIRI arms.

7.7.2.1 Imaging Restriction 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/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis. Magnetic resonance imaging 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.

7.7.3 Permitted Therapy

- Inhaled or intranasal corticosteroids (with minimal systemic absorption may be continued if the participant is on a stable dose) and adrenal replacement steroid doses of prednisone > 10 mg daily or equivalent are permitted in the absence of active autoimmune disease. Non absorbed intra-articular steroid injections will be permitted.
- Immunosuppressive agents and the use of systemic corticosteroids are permitted in the context of treating AEs. Corticosteroids are allowed for prophylaxis in the chemotherapy arms if clinically indicated as part of standard of care. Participants receiving corticosteroids must be

at prednisone < 10 mg daily or equivalent prior to re-initiation of study treatment. Participants may continue to receive hormone replacement treatment.

- The inactivated seasonal influenza vaccine can be given to participants while on treatment without restriction. Influenza vaccines containing live virus or other clinically indicated vaccinations for infectious diseases (ie, PNEUMOVAX®, varicella vaccine, etc) may be permitted but must be discussed with the BMS Medical Monitor (or designee) and may require a study treatment washout period prior to and after administration of the vaccine.

7.7.4 Palliative Local Therapy

Palliative and supportive care for disease-related symptoms may be offered to all participants on the study. Limited radiation treatment or surgery to control isolated lesions is permitted for participants following consultation with the BMS Medical Monitor (or designee).

Participants should not receive study treatment during radiation because the potential for overlapping toxicities with radiotherapy and study treatment is not known. If palliative radiotherapy in short courses and for isolated fields is required to control symptoms not clearly related to disease progression, then study treatment administration should be withheld, if possible, for at least 1 week before radiation and for at least 1 week after its completion.

Participants should be closely monitored for any potential toxicity during and after receiving radiotherapy. Prior to resuming study treatment, radiotherapy-related AEs should resolve to Grade ≤ 1 or baseline, and participants must meet relevant eligibility criteria as determined by the BMS Medical Monitor (or designee) in discussion with the investigator. The BMS Medical Monitor (or designee) must be consulted prior to re-initiating study treatment in a participant with a dosing delay lasting > 8 weeks from the previous dose.

Details of palliative radiotherapy should be documented in the source records and CRF. Details in the source records should include dates of treatment, anatomic site, dose administered and fractionation schedule, and AEs. Symptoms requiring palliative radiotherapy should be evaluated for objective evidence of disease progression. Participants receiving palliative radiation of target lesions will have the evaluation of ORR just prior to radiotherapy, but these participants will no longer be evaluable for the determination of response subsequent to the date palliative radiation occurs.

For participants who need to undergo surgery during the study, it is recommended to hold study treatment(s) for at least 2 weeks before (if elective) and 2 weeks after surgery, or until the participant recovers from the procedure, whichever is longer. Prior to resuming study treatment, surgically related AEs should resolve to Grade 1 or baseline, and participants must meet relevant eligibility criteria as determined by the BMS Medical Monitor (or designee) in discussion with the investigator. The BMS Medical Monitor (or designee) must be consulted prior to re-initiating study treatment in a participant with a dosing delay lasting > 8 weeks from the previous dose.

7.8 Treatment After the End of the Study

At the end of the study or study part, 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 investigational product (and non-investigational product 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 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 the BMS.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: under certain 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.)
- Progression of Disease except as described in Section 7.4.8.
- Pregnancy

In the case of pregnancy, the investigator must immediately notify within 24 hours of awareness of the pregnancy, 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, Pregnancy.

All participants who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 2. 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, is 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 Post Study Treatment Study Follow-up

In this study, safety is a key endpoint 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 and Table 2-7 until death, 30 days (Arm A,

Cohorts 3a and 3c [Arm B; Part 2], and Arm D) and 100 days (Arm C and Cohort 3b [Arm B, Part 2]) post EOT, 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 participant to 1 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 date and cause of death.
- If investigator's use of 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 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.

8.4 Study Termination

The use of a 2-stage design allows for possible early termination of enrollment into an expansion cohort based on anti-tumor activity evaluation of Stage I patients. While there is no formal stopping rule based on efficacy, a futility signal based on Sponsor's assessment may also lead to cohort termination.

BMS continuously evaluates the benefit/risk of the program and may choose to hold further recruitment in a particular cohort or at a particular site, or terminate the development of BMS-813160 for reasons including, but not limited to, safety and efficacy.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- 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 treatment. 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.

9.1 Efficacy Assessments

Tumor assessments at other time points may be performed if clinically indicated, and should be submitted to the central imaging vendor as soon as possible. Unscheduled CT/MRI should be submitted to central imaging vendor. X-rays and bone scans that clearly demonstrate interval progression of disease, for example most commonly as unequivocal lesions that are unmistakably new since the prior CT/MRI, should be submitted to central imaging vendor. Otherwise, X-rays and bone scans do not need to be submitted centrally.

Disease assessment with computed tomography (CT) and/or MRI, as appropriate, will be performed at baseline and approximately every 8 weeks (± 1 week from Cycle 1 Day 1) until disease progression, treatment discontinuation, withdrawal from study, or start of subsequent treatment, whichever is earlier.

A best overall response of SD requires a minimum of 49 days on study from date of first dose to the date of the first imaging assessment.

9.1.1 Imaging Assessment for the Study

All radiologic images will be submitted to a centralized imaging core lab for storage and potential future blinded independent central review (BICR) per Sponsor request. Sites should be trained prior to scanning the first study participant. Image acquisition guidelines and submission process will be outlined in the CV202103 Imaging Manual to be provided by the core lab.

Tumor assessment with contrast-enhanced CT scans acquired on dedicated CT equipment is preferred for this study. Contrast-enhanced CT of the chest, abdomen, pelvis, and other known/suspected sites of disease should be performed for tumor assessments. 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.

CT and MRI scans 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 for all imaging time points.

Use of CT component of a positron emission tomography (PET)-CT scanner: Combined modality scanning such as with fluorodeoxyglucose (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 v1.1 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.

Participants with symptoms or history of brain metastasis should have a MRI of the brain without and with contrast. CT of the brain without and with contrast can be performed if MRI is contraindicated (see Table 2-1).

Bone scans should be performed if clinically indicated.

Assessments will be performed at baseline and at the time points described per RECIST v1.1 criteria (see Appendix 5), until disease progression per RECIST v1.1 criteria, or withdrawal from the study.

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).

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.

Contacts for SAE reporting are specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

Sections 5.6.1 and 5.6.2 in the BMS-813160 IB[27] represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting.

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within 30 days (Arms A, B [Cohorts 3a and 3c], and D) and 100 days (Arm C and Cohort 3b [Arm B, Part 2]) of discontinuation of dosing.

All nonserious AEs must be collected at the start of study treatment until the time points specified in the Schedule of Activities (Section 2).

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the CRF module.
- All SAEs will be recorded and reported to 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 updated information being available.

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

Adverse events 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 judgment in the context of known AEs, when appropriate for the program or protocol.

9.2.3 Follow-up of AEs and SAEs

- Nonserious 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 nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.2 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 institutional review board (IRB)/ independent ethics committee (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 10 months 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 reinitiation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

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 Sponsor or designee. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an ICF 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 nonserious AE CRF page or SAE Report Form electronic, 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 vs low hemoglobin value).

9.2.7 Potential Drug Induced Liver Injury (DILI)

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

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:

- Amino transferase (ALT or AST) elevation > 3 times ULN
- AND
- Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
- AND
- No other immediately apparent possible causes of aminotransferase 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 nonserious or serious AE, as appropriate, and reported accordingly.

9.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. Overdoses that meet the regulatory definition of SAE will be reported as an SAE (see Appendix 3).

For this study, any dose of 10% greater than the daily dose within a 24-hour time period (± 8 hours) will be considered an overdose. In the event of an overdose the investigator/treating physician should:

- Contact the Medical Monitor immediately

- Closely monitor the participant for AEs/SAEs and laboratory abnormalities until effects can no longer be detected systemically
- Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis)
- 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 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.

9.4.1 Physical Examinations

Refer to Schedule of Activities.

9.4.2 Vital Signs

Refer to Schedule of Activities.

9.4.3 Electrocardiograms

Refer to Schedule of Activities. ECGs will be evaluated by the investigator for any clinically significant changes or for changes meeting dose modifying criteria. In addition ECGs will be sent to the Sponsor for central read.

9.4.4 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- Results of clinical laboratory tests performed during the screening period must be available prior to dosing. All laboratory tests (except for pregnancy testing) may be performed up to 3 days prior to dosing, and the results MUST be reviewed prior to dosing. Pregnancy testing must be done within 24 hours prior to dosing

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Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Direct bilirubin Alkaline phosphatase Lactate dehydrogenase (LDH) Creatinine Blood Urea Nitrogen (BUN) Uric acid Lipase	Total Protein Albumin Sodium Potassium Chloride Calcium Phosphorus Magnesium Creatine kinase Amylase
Thyroid Panel (Includes TSH, Free T3 and Free T4)	
Urinalysis (screening and cross-over baseline only)	
Protein	
Glucose	
Blood	
Leukocyte esterase	
Specific gravity	
pH	
Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick	
Serology (screening and cross-over baseline only)	
Serum for hepatitis C antibody, hepatitis B surface antigen, HIV-1 and -2 antibody (as mandated by local requirement)	
Pregnancy test (WOCBP only) [Serum or urine pregnancy test must be performed within 24 hours prior to administration of study treatment and on Day 1 of each cycle regardless of dosing schedule.]	
Follicle stimulating hormone (FSH) [Screening only; only women not considered WOCBP. Refer to Appendix 4 for definitions and guidelines.]	

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.

9.5 Pharmacokinetics

9.5.1 Pharmacokinetic Assessment of BMS-813160 following BMS-813160 Monotherapy

Pharmacokinetics of BMS-813160 and its metabolite (BMS-939429) will be derived from plasma concentration vs time and urinary excretion data. Individual participant PK parameter values will be derived by noncompartmental methods by a validated PK analysis program. Actual times will be used for the analyses.

The PK parameters to be assessed for BMS-813160 following multiple dose administration in monotherapy phase include but not limited to the following:

Cmax	Maximum observed plasma concentration
Tmax	Time of maximum observed plasma concentration
AUC(0-24)	Area under the concentration-time curve from time 0 to 24 hours post dose
AUC(0-8)	Area under the concentration-time curve from time 0 to 8 hours post dose
C24	Observed plasma concentration at 24 hours post dose (QD dosing only)
Ctrough	Trough observed plasma concentration
CLT/F	Apparent total body clearance
AI	Accumulation index, calculated based on ratio of AUC(0-24) and Cmax at steady state to after the first dose
%UR	Percent urinary recovery over dosing interval
CLR	Renal clearance

In addition, the following PK parameters for BMS-813160 metabolite (BMS-939429) may also be assessed after multiple dose administrations, if data permit:

Cmax	Maximum observed plasma concentration
Tmax	Time of maximum observed plasma concentration
AUC(0-24)	Area under the plasma concentration-time curve from time zero to 24 hours post dose
AUC(0-8)	Area under the concentration-time curve from time 0 to 8 hours post dose
C24	Observed plasma concentration at 24 hours post dose
Ctrough	Trough observed plasma concentration

AI	Accumulation index, calculated based on ratio of AUC(0-24) and Cmax at steady state to after the first dose
%UR	Percent urinary recovery over 24 hours corrected for molecular weight
CLR	Renal clearance
MR_Cmax	Ratio of metabolite Cmax to parent Cmax, corrected for molecular weight
MR_AUC(0-24)	Ratio of metabolite AUC(0-24) to parent AUC(0-24), corrected for molecular weight

Individual participant PK parameter values will be derived by non-compartmental methods by a validated PK analysis program. Actual times will be used for the analyses.

Table 9.5.1-1 lists the blood and urine sampling schedule to be followed for the assessment of PK of BMS-813160, the BMS-813160 metabolite (BMS-939429), and MATE-renal transporter biomarkers. Further details of blood and urine collection and processing will be provided to the site in the laboratory procedure manual.

Table 9.5.1-1: Pharmacokinetic Sampling Schedule for BMS-813160 in 2-week Monotherapy in Part 1 (Arms A, B, and C)

Sample Collection Time		Time (Relative to Dosing) Hour: Min[b]	PK Plasma Sample[c]	MATE-renal Transporter Plasma Sample[d]	PK/MATE-renal Transporter Urine Sample[c,d]
Study Cycle[a] / Day	Time (Event)				
Cycle 0 Day -1	0 h	-24:00		X	X (0 h - 8 h cumulative)
	8 h	-16:00		X	
		-16:00 to 00:00			X[e] (8 h - 24 h cumulative for MATE) X (pre-dose urine sample for PK)
Cycle 0 Day 1	0 h (pre-dose)	00:00 (pre-dose)	X	X	
		00:30	X		X (0 h - 8 h cumulative)
		1:00	X		
		2:00	X	X	
		3:00	X		
		4:00	X	X	
		6:00	X	X	
		8:00	X	X	
		8:00 to 24:00			X (8 h - 24 h cumulative)
Cycle 0 Day 2	0 h (pre-dose)	00:00[f]	X	X	
Cycle 0 Day 3	0 h (pre-dose)	00:00[f]	X		
Cycle 0 Day 7	0 h (pre-dose)	00:00[f]	X		
Cycle 0 Day 14	0 h (pre-dose)	00:00[f]	X	X	X (0 h - 8 h cumulative)
		00:30	X		
		1:00	X		
		2:00	X	X	
		3:00	X		
		4:00	X	X	
		6:00	X	X	
		8:00	X	X	
		8:00 to 24:00			X (8 h - 24 h cumulative)
Cycle 1 Day 1	0 h	00:00[f]		X	

[a] 1 cycle = 4 weeks, except for Cycle 0 (2 weeks).

[b] The following windows serve as a guideline for PK sample collections and will be considered within window:
- ± 2 minutes for samples within the first 4 hours after dose.
- ± 15 minutes for samples after the first 4 hours through 24 hours after dose.
- ± 1 h for the remaining time points following 24 hours after dose.

[c] For the measurement of BMS-813160 and the metabolite BMS-939429 (M1). Apply to both BID and QD regimens in all combination arms.

[d] For the measurement of NMN and creatinine (MATE1/renal transporter biomarkers).

[e] Pre-dose urine concentration will be measured from 8 - 24 h pre-dose urine sample collected on Day -1. Total urine volume will be documented for 0 - 8 h and 8 - 24 h.

[f] Sample collected 12 h (BID regimen) or 24 h (QD regimen) after the previous dose (trough sample) and prior to the dose on that day.

9.5.2 Pharmacokinetic Assessment of BMS-813160 during Chemotherapy Combination Treatment in Part 1 (Arms A and B)

Plasma samples for BMS-813160 and metabolite BMS-939429 (M1) will be collected for all participants receiving the chemotherapy combination treatments (Arms A and B [Part 1]). In addition, following non-compartmental PK parameters will be reported, for BMS-813160 and BMS-939429 where data permit.

Cmax	Maximum observed plasma concentration
Tmax	Time of maximum observed plasma concentration
AUC(0-24)	Area under the concentration-time curve from 0 to 24 hours post dose
AUC(0-8)	Area under the concentration-time curve from time 0 to 8 hours post dose
C24	Observed plasma concentration 24 hours post dose (QD dosing only)
Ctrough	Trough observed plasma concentration

Table 9.5.2-1 lists the blood sampling schedule to be followed for the assessment of PK of BMS-813160 following the chemotherapy combination treatment (Arms A and B) in Part 1. Further details of blood collection and processing will be provided to the site in the procedure manual.

Table 9.5.2-1: Pharmacokinetic Sampling Schedule for BMS-813160 during Chemotherapy Combination Treatment in Part 1 (Arms A and B)

Sample Collection Time		Time (Relative to BMS-813160 Dosing) Hour: Min[b]	PK Plasma Sample[c]
Study Cycle[a] / Day	Time (Event)		
Cycle 1 Day 1	0 h (pre-dose)	00:00 (pre-dose)	X
		00:30	X
		2:00	X
Cycle 1 Day 8	0 h (pre-dose)	00:00[d]	X
Cycle 1 Day 15[e] OR Cycle 2 Day 1[f]	0 h (pre-dose)	00:00[d]	X
		00:30	X
		1:00	X
		2:00	X
		3:00	X
		4:00	X
		6:00	X
		8:00	X
Cycle 1 Day 16[e] OR Cycle 2 Day 2[f]	0 h (pre-dose)	00:00[d]	X
Cycle 3 Day 1	0 h (pre-dose)	00:00[d]	X
		00:30	X
		2:00	X
Cycle 5 Day 1	0 h (pre-dose)	00:00[d]	X

[a] 1 cycle = 4 weeks.

[b] The following windows serve as a guideline for PK sample collections and will be considered within window:
- ± 2 minutes for samples within the first 4 hours after dose.
- ± 15 minutes for samples after the first 4 hours through 24 hours after dose.
- ± 1 h for the remaining time points following 24 hours after dose.

[c] For the measurement of BMS-813160 and the metabolite BMS-939429 (M1). Apply to both BID and QD regimens in all combination arms. BMS-813160 should be administered at (1 hour window) the start of chemotherapy.

[d] Sample collected 12 h (BID regimen) or 24 h (QD regimen) after the previous dose (trough sample) and prior to the dose on that day.

[e] For Gem/nab-paclitaxel combination therapy, BMS-813160 PK samples will be collected on Cycle 1 Day 15 and Cycle 1 Day 16.

[f] For FOLFIRI combination therapy, BMS-813160 PK samples will be collected on Cycle 2 Day 1 and Cycle 2 Day 2.

9.5.3 Pharmacokinetic Assessment of BMS-813160, and Pharmacokinetic and Immunogenicity Assessment of Nivolumab in Part 1 (Arm C), and Part 2 (Arm C and Arm D)

Blood samples for BMS-813160 and metabolite BMS-939429 (M1) PK will be collected for all participants receiving BMS-813160 alone (Arm D [Part 2]), or in combination with nivolumab (Arm C [Part 1 and Part 2]).

Blood samples for nivolumab PK and immunogenicity assessments will be collected for all participants receiving nivolumab (Arm C [Part 1 and Part 2]).

Table 9.5.3-1 lists the blood sampling schedule to be followed for the assessment of PK of BMS-813160 and PK and immunogenicity of nivolumab. Further details of blood collection and processing will be provided to the site in the procedure manual.

Table 9.5.3-1: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS813160 and Nivolumab in Part 1 (Arm C), and Part 2 (Arm C [Including Cross Over] and Arm D)

Sample Collection Time		Time (Relative To Dosing) Hour: Min[b]	BMS-813160 Plasma Sample[c]	Nivolumab PK Serum Sample[d]	Nivolumab Immunogenicity Serum Sample[d]
Study Cycle[a] / Day	Time (Event) Hour				
Cycle 1 Day 1	0 h (pre-dose)	00:00 (pre-dose)	X	X	X
	EOI	00:30	X	X	
		2:00	X		
Cycle 1 Day 15	0 h (pre-dose)	00:00	X	X	
Cycle 2 Day 1	0 h (pre-dose)	00:00	X	X	
		2:00	X	X	
Cycle 3 Day 1	0 h (pre-dose)	00:00	X	X	X
		2:00	X		
Cycle 5 Day 1	0 h (pre-dose)	00:00	X	X	X
Cycle 9 Day 1	0 h (pre-dose)	00:00		X	X

[a] 1 cycle = 4 weeks.

[b] The following windows serve as a guideline for PK sample collections and will be considered within window:
- ± 2 minutes for samples within the first 4 hours after dose.
- ± 15 minutes for samples after the first 4 hours through 24 hours after dose.
- ± 1 h for the remaining time points following 24 hours after dose.

[c] For the measurement of BMS-813160 and the metabolite BMS-939429 (M1). Apply to both BID and QD regimens in all combination arms. BMS-813160 should be administered at the start of nivolumab infusion to minimize blood draws.

[d] Nivolumab PK and immunogenicity samples should only be drawn from participants receiving nivolumab in Arm C (Part 1 and Part 2). Pre-dose samples should be taken just prior to the start of infusion (preferably within

30 minutes). If the infusion is delayed and a pre-dose sample is already collected, there is no need to collect an additional pre-dose sample. End-of-infusion (EOI) samples should be taken as close to EOI as possible (preferably 2 minutes prior to EOI) on the contralateral arm (ie, the arm not used for the infusion).

9.5.4 *Pharmacokinetic Assessment of Irinotecan, Nab-Paclitaxel, and BMS-813160, and Pharmacokinetic and Immunogenicity Assessment of Nivolumab in Part 2 (Arm A and Arm B)*

The intensive PK sampling strategy in Table 9.5.4-1 will be followed in a subset of participants (approximately 12 per cohort) for Arm A (all cohorts) and Arm B (Cohorts 3a and 3c) in Part 2. Once the number of participants needed is reached, the Sponsor will notify the sites that sparse PK samples will be collected for the remaining participants in these cohorts as described in Table 9.5.4-2.

Plasma samples for irinotecan and its metabolite SN-38 will be collected for a subset of participants (approximately 12 per cohort) for Arm A in Part 2 who receive the FOLFIRI combination treatment as described in Table 9.5.4-1. Plasma samples for nab-paclitaxel will be collected for a subset of participants (approximately 12 per cohort) for Arm B (Cohorts 3a and 3c) in Part 2 who receive the Gem/nab-paclitaxel combination treatment as described in Table 9.5.4-1. Blood samples for BMS-813160 and metabolite BMS-939429 (M1) PK, and blood samples for nivolumab PK and immunogenicity assessments will also be collected as described in Table 9.5.4-1.

Individual PK parameters will be derived by non-compartmental methods by a validated PK analysis program.

Cmax	Maximum observed plasma concentration
Tmax	Time of maximum observed plasma concentration
AUC(0-24)	Area under the concentration-time curve from time 0 to 24 hours post dose
Ctrough	Trough observed plasma concentration

Sparse blood samples will be collected for BMS-813160 PK, nivolumab PK and immunogenicity assessments for the remaining participants in Arms A (all cohorts) and B (Cohorts 3a and 3c), and all participants in Cohort 3b of Arm B as described in Table 9.5.4-2.

Further details of blood collection and processing will be provided to the site in the procedure manual.

Table 9.5.4-1: Intensive Pharmacokinetic Sampling Schedule for FOLFIRI (Irinotecan), Abraxane (Nab-Paclitaxel), and BMS813160 for Arms A (all Cohorts) and B (Cohorts 3a and 3c) in Part 2 - Approximately 12 Participants in each Cohort

Sample Collection Time[a]					
Study Cycle[b]/Day	Time (Event)	Time (Relative to Dosing)[c,d] Hour: Min	Irinotecan PK Plasma Sample[e] (Arm A)	Nab-Paclitaxel PK Plasma Sample (Cohorts 3a & 3c of Arm B)	BMS-813160 PK Plasma Sample[f] (Cohorts 1a & 1b of Arm A; Cohort 3a of Arm B)
Cycle 1 Day 1	0 h (pre-dose)	00:00 (pre-dose)	X	X	X
		2:00	X	X	X
Cycle 1 Day 15	0 h (pre-dose)	00:00 (pre-dose)	X	X	X
		2:00	X	X	X
Cycle 2 Day 1	0 h (pre-dose)[g]	00:00	X	X	X
	0.5 h (EOI)[h]	0:30		X	X
	1 h 30 min (EOI)[h]	1:30	X		X
		2:00		X	X
		4:00	X	X	X
		8:00	X	X	X
Cycle 2 Day 2	24 h	24:00	X	X	X
Cycle 3 Day 1	0 h (pre-dose)	00:00			X
		2:00			X
Cycle 5 Day 1	0 h (pre-dose)	00:00			X
Cycle 9 Day 1	0 h (pre-dose)	00:00			

[a] The intensive PK sampling strategy in Table 9.5.4-1 will be followed in a subset of participants (approximately 12 per cohort) for Arm A (all cohorts) and Arm B (Cohorts 3a and 3c) in Part 2. Once the number of participants needed is reached, the Sponsor will notify the sites that sparse PK samples will be collected for the remaining participants in these cohorts as described in Table 9.5.4-2.

[b] 1 cycle = 4 weeks.

[c] Pre-dose samples should be taken just prior to the administration of the first drug (preferably within 30 minutes) during that day. If BMS-813160 dose or the infusion is delayed and a pre-dose sample is already collected, there is no need to collect an additional pre-dose sample. Sampling time other than pre-dose sample is relative to the dosing for the PK sample being collected (ie, sample for chemotherapy or BMS-813160). BMS-813160 should be administered at the start of irinotecan and nab-paclitaxel infusions to minimize blood draws.

[d] The following windows serve as a guideline for PK sample collections and will be considered within window:

- ± 2 minutes for samples within the first 4 hours after dose.
- ± 15 minutes for samples after the first 4 hours through 24 hours after dose.
- ± 1 h for the remaining time points following 24 hours after dose.

[e] For the measurement of irinotecan and its metabolite SN-38.

[f] For the measurement of BMS-813160 and the metabolite BMS-939429 (M1). Samples should only be drawn from participants receiving BMS-813160 in Cohorts 1a and 1b of Arm A, and Cohort 3a of Arm B.

[g] Participants are required to fast for at least 8 hours prior to the C2D1, 0 hour (pre-dose) PK sample collections.

[h] End of infusion (EOI) samples should be taken as close to end of the infusion of irinotecan or nab-paclitaxel as possible (preferably within 2 minutes before the end of the infusion) on the contralateral arm (ie, the arm not used for the infusion).

Table 9.5.4-2: Sparse Pharmacokinetic Sampling Schedule for BMS 813160 and Nivolumab for Arms A and B (Part 2) - Remaining Participants and All Participants in Cohort 3b (Arm B)

Sample Collection Time		Time (Relative to Dosing) Hour: Min[b,c]	BMS-813160 PK Plasma Sample[d] (Cohorts 1a & 1b of Arm A; Cohorts 3a & 3b of Arm B)	Nivolumab PK Serum Sample[e] (Cohort 3b of Arm B only)	Nivolumab Immunogenicity Serum Sample[e] (Cohort 3b of Arm B only)
Study Cycle[a]/Day	Time (Event)				
Cycle 1 Day 1	0 h (pre-dose)	00:00 (pre-dose)	X	X	X
		2:00	X	X	
Cycle 1 Day 15	0 h (pre-dose)	00:00	X	X	
Cycle 2 Day 1	0 h (pre-dose)	00:00 (pre-dose)	X	X	
		2:00	X	X	
Cycle 3 Day 1	0 h (pre-dose)	00:00	X	X	X
		2:00	X		
Cycle 5 Day 1	0 h (pre-dose)	00:00	X	X	X
Cycle 9 Day 1	0 h (pre-dose)	00:00		X	X

[a] 1 cycle = 4 weeks.

[b] Pre-dose samples should be taken just prior to the administration of the first drug (preferably within 30 minutes) during that day. If BMS-813160 dose or the infusion is delayed and a pre-dose sample is already collected, there is no need to collect an additional pre-dose sample. Sampling time other than pre-dose sample is relative to the dosing for the PK sample being collected (ie, sample for BMS-813160 or nivolumab). BMS-813160 should be administered at the start of irinotecan, nab-paclitaxel, or nivolumab infusion.

[c] ± 2 days for sparse sampling or as noted in the protocol.

[d] For the measurement of BMS-813160 and the metabolite BMS-939429 (M1). BMS-813160 PK samples should only be drawn from participants receiving BMS-813160 in Cohorts 1a and 1b of Arm A, and in Cohorts 3a and 3b of Arm B.

[e] Nivolumab PK and immunogenicity samples should only be drawn from participants receiving nivolumab in Cohort 3b of Arm B.

9.5.5 Pharmacokinetic Sample Analyses

The plasma and urine samples will be analyzed for BMS-813160 and BMS-939429 by a validated LC-MS/MS assay and for NMN and creatinine (MATE-renal transporter biomarkers) with a qualified LC-MS/MS method. Serum samples will be analyzed for nivolumab by a validated assay. Plasma samples will be analyzed for irinotecan, SN-38, and nab-paclitaxel by a validated LC-MS/MS assay.

In addition, after the scheduled analyses are complete, plasma and urine samples will be archived for potential analysis of BMS-813160 metabolites, analysis of co-administered drugs and their metabolites, and/or biomarker analyses related to MATE function, if the need arises and to the extent possible.

Detailed instructions for the PK blood collection, labeling, processing, storage, and shipping will be provided to the site in the procedure manual.

9.6 Pharmacodynamics

The effect of dosing regimen on pharmacodynamics of BMS-813160 will be assessed via comparison of the modulation of CCR2 and CCR5 activity, including changes of intra-tumor markers (eg, Treg, TAM or MDSC), and/or changes of peripheral markers (eg, MCP-1, monocyte count, and CCR5 phosphorylation) in the different doses of BMS-813160 being investigated in this study. Data from this study may be pooled with that from other studies to perform PK/pharmacodynamic analyses. Results of PK/ pharmacodynamic analyses will be reported separately if performed.

Pharmacodynamic measures (in the form of biomarker assessments) may be assessed for associations with clinical outcomes. There will be various types of specimens obtained for biomarker testing: whole blood, plasma, serum, peripheral blood monocytes, tumor tissue, and stool sample. The sample subtypes and testing plans associated with each are described in Section 9.8. Complete instructions on the collection, processing, handling, and shipment of all samples described herein will be provided in a separate Laboratory Procedures Manual.

9.7 Pharmacogenomics

The final disposition of samples will be conducted per local regulations.

9.7.1 Whole Blood DNA Sampling

A 6-mL whole blood sample will be drawn at screening (refer to Whole Blood DNA collection in Table 9.8-1 and Table 9.8-2) for potential analysis of DNA variants in ADME-related genes (see Appendix 12 which contains the lists of ADME-related genes from http://pharmaadme.org) and genes related to MATE1 and MATE2-K transporters (SLC47A1 and SLC47A2, respectively). Further details of blood collection and processing will be provided to the site in the procedure manual.

9.8 Biomarkers

Tumor, blood, and stool samples will be drawn at the times indicated in Table 9.8-1 (Part 1) and Table 9.8-2 (Part 2) for biomarker analyses. Blood and urine samples will be drawn during the BMS-813160 monotherapy period in conjunction with the sampling for PK assessments (See Section 9.5.1, Table 9.5.1-1) for NMN and creatinine (MATE-renal transporter biomarkers). Further details of sample collection and processing for these biomarkers will be provided to the site in the procedure manual.

Table 9.8-1: Biomarker Sampling Schedule - Part 1

Sample Collection Time[a]			Whole Blood Sample					
Study Cycle[b] / Day	Time (Event) Hour	Tumor	SNP[c]	Immuno-Phenotyping	Phospho-CCR5	Serum Cytokine Analysis	Plasma Sample for ctDNA	Stool
Screening		X[d]	X				X	X
Cycle 0 Day 1	0 h (pre-dose)			X	X	X	X	
	2 h			X	X	X		
	4 h			X	X	X		
	8 h			X	X	X		
Cycle 0 Day 2	0 h			X	X	X		
Cycle 0 Day 7	0 h (pre-dose)			X		X	X	
Cycle 0 Day 14	0 h (pre-dose)	X[e] (Arms A, B, and C)		X	X	X		
	2 h				X	X		
	4 h				X	X		
	8 h			X	X	X		
Cycle 1 Day 1	0 h (pre-dose)			X		X	X	
Cycle 1 Day 15	0 h (pre-dose)	X (Arm C only)		X		X	X	
Cycle 2 Day 1	0 h (pre-dose)			X		X	X	
Cycle 3 Day 1	0 h (pre-dose)			X		X	X	
Cycle 5 Day 1	0 h (pre-dose)			X		X	X	
Q8W following C5D1[f]				X		X	X	
EOT/Disease progression[g]		X[g]		X		X	X	

Abbreviations: C5D1 = Cycle 5, Day 1; CCR5 = cysteine-cysteine chemokine receptor 5; ctDNA = circulating tumor deoxyribonucleic acid; EOT = end of treatment; MDSC = myeloid-derived suppressor cells; Q8W = every 8 weeks; SNP = single nucleotide polymorphism; Treg = regulatory T cells

[a] All biomarker samples should be obtained at treatment visits corresponding to the indicated time points.

[b] 1 cycle = 4 weeks, except for Cycle 0 (2 weeks).

[c] Whole Blood DNA collection. Genotyping sample will be collected.

[d] Pre-treatment biopsy can be collected during screening or in the preceding 90 days (refer to Section 6.1 for inclusion criteria).

[e] Tumor biopsy (fresh) is mandatory (– 3 day window).

[f] This would align with the response assessment Q8W beginning on C5D1.

[g] Biopsies upon disease progression are optional but encouraged.

Table 9.8-2: Biomarker Sampling Schedule - Part 2 (Including Cross Over)

Sample Collection Time[a]		Tumor IHC WES/GEP	Whole Blood Sample			Serum Cytokine Analysis	Plasma Sample for ctDNA	Stool
Study Cycle[b] / Day	Time (Event) Hour		SNP[c]	Immuno-Phenotyping	GEP, TCR			
Screening		X[d]	X				X	X
Cross-over Baseline		X[e]					X	X
Cycle 1 Day 1	0 h (pre-dose)			X	X	X	X	
	4 h			X		X		
	6 h			X		X		
Cycle 1 Day 15	0 h (pre-dose)			X		X		
Cycle 1 Day 28[f]	0 h (pre-dose)	X[g]		X	X	X	X	
	4-6 h			X		X		
Cycle 3 Day 1	0 h (pre-dose)			X	X	X	X	
Cycle 5 Day 1	0 h (pre-dose)			X	X	X	X	
Q8W following C5D1[h]	0 h (pre-dose)			X	X	X	X	
Pre-Cross Over/ EOT/Disease progression[i]				X	X	X	X	
EOT/Disease progression[j]		X[k]		X	X	X	X	

Abbreviations: C5D1 = Cycle 5, Day 1; CCR5 = cysteine-cysteine chemokine receptor 5; ctDNA = circulating tumor deoxyribonucleic acid; EOT = end of treatment; GEP = gene expression profile; IHC = immunohistochemistry; Q8W = every 8 weeks; SNP = single nucleotide polymorphism; TCR = T-cell repertoire (T-cell receptor clonality); WES = whole-exome sequencing

[a] All biomarker samples should be obtained at treatment visits corresponding to the indicated time points.

[b] 1 cycle = 4 weeks

[c] Whole Blood DNA collection. Genotyping sample will be collected.

[d] Pre-treatment biopsy can be collected during screening or in the preceding 90 days (refer to Section 6.1 for inclusion criteria).

[e] Participants in cross-over cohort will be required to undergo a pre-treatment biopsy.

[f] Whole blood, serum, and plasma samples can be collected on C2D1 instead of C1D28. Pre-dose and 4-6 hour post dose samples will be collected with respect to irinotecan in Cohort 1c and nab-paclitaxel in Cohort 3c. In all other cohorts, samples are collected prior to and 4-6 hour post BMS-813160 administration.

[g] Tumor biopsy is mandatory (– 3 day window).

[h] This will align with the response assessment Q8W beginning on C5D1.

[i] Cohort 1c cross-over participants only.

[j] All participants including cross-over participants at the time of subsequent progression.

[k] Biopsies upon disease progression are optional, but encouraged for all combination therapy arms.

For PD-L1 and biomarker research testing, tumor tissue (FFPE archival or recent acquisition) must be obtained during the screening period. If PD-L1 results are available, assay conditions and results will be collected. (Note: Fine needle aspiration and bone metastases samples are not acceptable for submission.)

Detailed immune and tumor phenotyping will be pursued to build clinical data to support the clinical findings. The biomarker analyses will include but are not limited to the following:

1) Systemic immune monitoring on circulating immune cells (eg, MDSC) and secreted cytokines (in particular, CCL2 and CCL5), chemokines, and other related soluble factors.
2) Examination of tumor-associated immune cells and microenvironment, through proteomics, histopathology (eg, CCR2, CCR5, MDSC, TAM, Treg, and CTL), next generation sequencing (NGS) and expression (mRNA) profiling.
3) Genomic analyses (DNA and/or RNA) on tumor, whole blood/PBMC, and cell-free DNA, for assessing tumor mutation burden, T-cell repertoire (TCR), dominant tumor clone(s), and gene-expression analyses.
4) Stool samples for microbiota analysis.
5) Plasma circulating tumor DNA (ctDNA) analysis.

Next generation DNA sequencing (testing may include but is not limited to whole exome and/or whole genome) may be performed on DNA isolated from peripheral genomic analysis of tumor samples at the time of enrollment and during the study, and association with ctDNA tested via established methods in plasma samples collected during treatment, may be tested for identification of tumor mutations. Blood samples will be drawn at the time points indicated in Table 9.8-1 and Table 9.8-2. RNA sequencing or other methods for gene expression profiling will also be utilized in blood and tumor samples.

The presence of cell-free DNA in circulating blood is a well-documented phenomenon.[38] Fragments of DNA are shed into the blood stream from dividing cells during cell proliferation or cell death. In subjects with cancer, a fraction of this circulating DNA is derived from tumor and is termed ctDNA.[39] Albeit small, fragments of DNA averaging between 800 to 200 base pairs and covering specific genomic regions can be amplified with PCR. Moreover, several studies have detected mutations in ctDNA that exactly correspond to mutations from the parent tumor.[40,41]

9.8.1 Additional Research Collection

This protocol will include residual sample storage for additional research (AR).

For All US sites:

Additional research is required for all study participants, except where prohibited by IRB/ethics committees, or academic/institutional requirements. Where 1 or more of these exceptions occurs,

participation in the additional research should be encouraged but will not be a condition of overall study participation.

- If the IRB/ethics committees and site agree to the mandatory additional research retention and /or collection, then the study participant must agree to the mandatory additional research as a requirement for inclusion in the study.
- If optional participation is permitted and approved, then the study participants may opt out of the additional research retention and /or collection.

For non-US Sites

Additional research is optional for all study participants, except where retention and/or collection is prohibited by local laws or regulations, ethics committees, or institutional requirements.

This collection for additional research is intended to expand the translational research and development (R&D) capability at BMS, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression, and response to treatment etc.

Sample Collection and Storage

All requests for access to samples or data for additional research will be vetted through a diverse committee of the study sponsor's senior leaders in Research and Development (or Designee) to ensure the research supports appropriate and well-defined scientific research activities.

Residual tumor tissue and blood samples from biomarker collection and PK collections (see Table 9.8.1-1) will also be retained for additional research purposes.

Table 9.8.1-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Time Point
Tumor biopsy and blood collection	Screening, on-treatment, and at disease progression (if available)
Residual serum and plasma	All biomarker collections and all PK collection

Note: If a biopsy has been performed and tissue is available, participants are requested to submit fresh tumor tissue at disease progression for biomarker research. Tissue submission is optional and biopsy is not required by protocol.

Samples kept for future research will be stored at the BMS Biorepository in [redacted] USA or an independent, BMS approved storage vendor.

- The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than fifteen (15) years after the end of the study or the maximum allowed by applicable law.

- Transfers of samples by research sponsor to third parties will be subject to the recipient's agreement to establish similar storage procedures.

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key is securely held by the Investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

Additional research samples will be retained for 15 years or the maximum allowed by applicable law. No additional sampling is required for residual collections.

Further details of sample collection and processing will be provided to the site in the procedure manual.

9.8.2 Immunogenicity Assessments

Blood samples for nivolumab immunogenicity analysis will be collected from Arm B (Cohort 3b, Part 2) and Arm C (Part 1 and Part 2) participants at time points specified in Table 9.5.3-1, Table 9.5.4-1, and Table 9.5.4-2. Serum will be analyzed by validated immunogenicity assays. All on-treatment immunogenicity sampling time points are intended to align with days on which study treatment is administered, if dosing occurs on a different day, the sampling should be adjusted accordingly. Selected serum samples may be analyzed by an exploratory method that measures anti-drug antibodies for technology exploration purposes; exploratory results will not be reported. In addition, serum samples designated for PK or biomarker assessments may also be used for immunogenicity analysis if required (eg, insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity-related AEs).

9.9 Health Economics OR Medical Resource Utilization and Health Economics

Not applicable.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

This study will start with three treatment arms: BMS-813160 in combination with either FOLFIRI (Arm A), Gem + nab-paclitaxel (Arm B), or nivolumab (Arm C) in participants with advanced CRC or pancreatic cancer. Each arm consists of a Phase 1b treatment (Part 1) and a Phase 2 efficacy expansion for combination treatments (Part 2).

In Part 1 of treatment Arms A, B and C, approximately 6-9 evaluable participants per dose level per arm will be treated. This sample size provides each dose arm with about 80% probability to detect any AE with event rate of 24%. Approximately 6 additional participants may be added to each dose in each treatment arm or lower doses of BMS-813160 (150 mg QD and 300 mg QD).

In Part 2, the efficacy expansion phase of Arm A includes three cohorts (Cohorts 1a, 1b, and 1c) consisting of 2L CRC, the expansion phase of Arm B continues to focus on 1L pancreatic cancer (Cohorts 3a, 3b, and 3c), and the expansion of Arm C includes 2 cohorts (Cohorts 4 [**closed per Revised Protocol 06**] and 5): 2L pancreatic cancer and 2/3L CRC (MSS), respectively.

Approximately 35 evaluable participants per cohort will be treated in Arms A and B, and approximately 31 evaluable participants per cohort will be treated in Arm C. Arm D (BMS-813160 monotherapy, opens only if an ORR of approximately 15% or durable responses are observed in Arm C) will include approximately 18 evaluable 2L pancreatic (Cohort 7) or 2/3L CRC MSS (Cohort 8) participants. Each disease cohort expansion will be handled independently and there will be no multiplicity adjustment. The number of participants will be continuously monitored such that the number of evaluable participants in Part 2 will not exceed 40 evaluable participants in any cohort. With regard to sample size, participants who are reassigned to a different study treatment following treatment in another cohort will be counted once for each assignment.

Design operating characteristics for each of the Cohorts 4 (**closed per Revised Protocol 06**), 5, 7, and 8 are given in Table 10.1-1, which includes the sample size, the assumptions of historic ORR and true (target) ORR, the associated Type I error, power, and other applicable operating characteristics, although this is not used for statistical hypothesis testing.

With a one-sided exact test at significance level 0.1, data from approximately 18 participants for Cohort 7 and Cohort 8 will provide 72% power to detect a target ORR of 20% against a reference ORR of 5% for Cohort 5 of Arm D. In addition, if 3 responses are observed in either cohort, (eg, 17% observed response rate), the lower limit of the 90% one-sided CI using Clopper-Pearson method for the ORR is 6% (higher than historical ORR of 5%) and the distance to the point estimate is approximately 11%. If the assumed true response rate is 20%, there is a 73% probability of observing at least 3 responses; and the probability is only 6% if the true response rate is only 5% rather than 20%.

The Fleming 2-stage design framework will be used as a guide for Cohorts 4 **(closed per Revised Protocol 06**) and 5 of Arm C.[42,43] The assumed historic and target response rates may change over time and may need to be adjusted by the time of response data from this study are available. Using a 2-stage design provides an option for futility as well as preliminary antitumor activity for strong-go early on. Enrollment may continue into stage 2 while the planned number of participants for Stage 1 are reached for efficacy evaluable tumor assessments. There will be no stopping of a disease cohort for efficacy, although early plan for the next stage of clinical development may be initiated.

As an example, guided by Table 10.1-1, approximately 18 3L CRC participants in Cohort 5, for example, will be treated in Arm C (BMS-813160 + nivolumab) in Stage 1. Assuming the true response rate is 20% in this population when treated with BMS-813160 + nivolumab if there are 3 or more responses in 18 participants, it may trigger to plan early further clinical development after careful evaluation of all available data including duration of response and safety profile. The probability to observe such favorable response is approximately 73% if in fact the treatment is efficacious. If there are no responses in 18 treated participants, the cohort may be stopped for futility. The probability of early stopping for futility is approximately 40% if in fact the treatment is inefficacious, eg, 5%. If the number of responses are at least 1, an additional 13 participants may be treated to collect more data. At the end of Stage 2, if there are 3 or fewer responses, it may not warrant further clinical development. If there are 4 or more responses it may show evidence of treatment efficacy.

Sample sizes for cohorts in Arms A and B are determined based on 1:1:1 randomization. Historical rates for the 2L colorectal and 1L pancreatic cohorts are approximately 15% and 25%, respectively.[11,44,45,46,47,48] To facilitate clinical evaluation of data, point estimate and 80% 1-sided CI *(or 60% 2-sided)* for the difference between treatments will be assessed, and totality of the data will be used for decision-making. With 35 participants randomized to each of the treatments, the expected half-width of an 80% confidence interval for the difference in response rates between experimental and control is expected to be approximately 10% (eg, if the observed difference in rates [experimental - control] is 10%, then a difference less than 0% could be ruled out with 80% confidence). No adjustment has been made to reflect multiple comparisons. If results are sufficiently promising, then the protocol may be amended to expand the cohort to allow comparison between treatments with higher confidence.

Table 10.1-1: Example of Design Characteristics

Treatment Cohort (Indication)	Historic/ Target Rate (%)	Stage	Cumulative Sample Size	Conclude Inefficacy if R[a]	Conclude Efficacy if R[a]	PET[b] for Futility (%)	PEE[c] for Efficacy (%)	Type I Error	Power
One-Sample Fixed Design									
Arm D: Cohort 7 (2L pancreatic) Arm D: Cohort 8 (2/3L CRC [MSS])	5/20		18					0.1	0.72
Fleming's Two-Stage Design									
Arm C: Cohort 4 (2L pancreatic) (Closed per Revised Protocol 06)	5/20	1	18	≤ 0	≥ 3	40	73	0.09	0.9
		2	31	≤ 3	≥ 4				
Arm C: Cohort 5 (2/3L CRC [MSS])	5/20	1	18	≤ 0	≥ 3	40	73	0.09	0.9
		2	31	≤ 3	≥ 4				

[a] R is the cumulative number of responses at the end of stage

[b] Probability of early termination (PET) if the historic rate is true

[c] Probability of early efficacy (PEE) signal if the target rate is true

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent and were registered into the IRT
Treated	All participants who take at least 1 dose of study treatment
Response-evaluable	All treated participants with measurable disease at baseline and one of the following: 1) at least one post-baseline tumor assessment, 2) clinical progression, or 3) death
Pharmacokinetic	All treated participants who have evaluable concentration-time data
Immunogenicity	All nivolumab treated participants who have baseline and at least one post baseline immunogenicity assessment
Biomarker	All treated participants with available biomarker data

10.3 Statistical Analyses

The statistical analysis plan (SAP) 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 the statistical output reported, including subgroup of age, gender, and race.

10.3.1 Efficacy Analyses

The primary efficacy analyses will be performed on treated 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 on censoring scheme on time-to-event endpoints such as duration of response (DOR) and PFS will be described in the SAP. Participants reassigned into Arm C cohorts following treatment in another cohort, will be combined with participants originally assigned in these cohorts for efficacy analysis. A sensitivity analysis excluding these participants may be performed, and details will be included in statistical analysis plan if applicable.

Endpoint	Statistical Analysis Methods
ORR is defined as the proportion of all treated participants whose best overall response (BOR) is either CR or PR. BOR for a participant will be assessed per RECIST v1.1 by investigator.	Estimate of ORR and corresponding two-sided exact 95% CI using the Clopper-Pearson method (stratified by tumor sidedness in Arm A and by prior neoadjuvant or adjuvant therapy in Arm B in Part 2; stratification was removed per Revised Protocol 06) by treatment for each tumor type Estimate of difference in ORR between each treatment cohort and the control cohort of Arm A and Arm B and corresponding two-sided exact 95% CI (stratified by tumor sidedness in Arm A and by prior neoadjuvant or adjuvant therapy in Arm B in Part 2; stratification was removed per Revised Protocol 06) by treatment for each tumor type
Median DOR 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 per RECIST v1.1 or death, whichever occurs first.	Median duration of response using the Kaplan-Meier method and corresponding two-sided 95% CI using Brookmeyer and Crowley methodology (using log-log transformation) [stratified by tumor sidedness in Arm A and by prior neoadjuvant or adjuvant therapy in Arm B in Part 2; stratification was removed per Revised Protocol 06] by treatment for each tumor type
PFSR at 24 weeks PFS for a participant is defined as the time from the first dosing date to the date of first objectively documented disease progression or death due to any cause, whichever occurs first.	Estimate by the Kaplan-Meier method and corresponding 95% CI will be derived based on Greenwood formula (stratified by tumor sidedness in Arm A and by prior neoadjuvant or adjuvant therapy in Arm B in Part 2; stratification was removed per Revised Protocol 06) by treatment for each tumor type.

10.3.2 Safety Analyses

All safety analyses will be performed on the treated population.

Endpoint	Statistical Analysis Methods
Incidence of DLTs (Part 1 and Cohort 3b of Part 2 only), AEs, SAEs, AEs leading to discontinuation, deaths AEs will be graded according to CTCAE v4.03.	DLT rate by dose level/arm (Part 1 and Cohort 3b in Part 2). Frequency distribution of treated participants with AE using the worst CTC grade. Participants will only be counted (1) once at the preferred term (PT) level, (2) once at the system organ class (SOC) level, and (3) once in the 'Total subject' row at their worst CTC grade, regardless of SOC or PT.
Summary measures of vital signs and lab clinical test results Lab abnormalities Laboratory values will be graded according to CTCAE v4.03.	Vital signs and clinical laboratory test results will be listed and summarized Lab shift table using the worst CTC grade on treatment per participant

10.3.3 Pharmacokinetic Analyses

Endpoint	Statistical Analysis Methods
Cmax, Tmax, AUC(0-8), AUC(0-24), C24, CLT/F, AI_AUC, AI_Cmax, MR_Cmax, MR_AUC(0-24), %UR, CLR	Summary statistics: geometric means and coefficients of variation
Tmax	Summary statistics: medians and ranges
Ctrough	Summary statistics to assess attainment of steady state: geometric means and coefficients of variation; plots vs time by dose

Pharmacokinetic time-concentration data may be pooled with data from other studies for population PK analysis, which will be presented in a separate report.

10.3.3.1 BMS-813160 in Monotherapy Phase

Summary statistics will be tabulated for the PK parameters by dose and study day, for each analyte. Geometric means and coefficients of variation will be presented for Cmax, AUC(0-8), AUC(0-24), C24, CLT/F, CLR, and AI for BMS-813160. In addition, geometric means and coefficients of variation of MR_Cmax and MR_AUC(0-24) will be presented for metabolite, if data permit. Geometric means and coefficients of variation of %UR and CLR will be presented for BMS-813160. Medians and ranges will be presented for Tmax. Means and standard deviations will be presented for other PK parameters.

Summary statistics will also be tabulated for trough plasma concentrations by study day, for each analyte. Geometric mean trough plasma concentrations will be plotted by study day for each analyte.

10.3.3.2 BMS-813160 in Combination Phase

To assess the effect of Gem/nab-paclitaxel or FOLFIRI on the PK of BMS-813160, point estimates and 90% confidence intervals will be calculated for the geometric mean ratios of Cmax, and AUC(0-24)/AUC(0-8) with chemotherapy treatment (combination phase) and without chemotherapy (monotherapy phase) in each arm. These estimates will be based on the results of a linear mixed model analysis for each arm on log(Cmax), and log(AUC(0-24))/ log(AUC(0-8)) with treatment (with/without chemotherapy) as a fixed effect and subject as repeated measurement.

Plasma concentration data will be tabulated using summary statistics. These data, together with data from the monotherapy, may also be pooled with other datasets for PPK analysis, which will be presented in a separate report.

10.3.3.3 Nivolumab in Combination Phase

End-of-infusion and trough (Ctrough) concentrations for nivolumab will be tabulated using summary statistics. These data may also be pooled with other datasets from nivolumab studies for PPK analysis, which will be presented in a separate report.

10.3.4 Irinotecan and Nab-Paclitaxel in Combination Phase (Part 2)

Summary statistics will be provided for the PK parameters of nab-paclitaxel, irinotecan and SN-38, by chemotherapy treatment group. Geometric means and coefficients of variation will be presented for Cmax, AUC(0-24), and Ctrough for nab-paclitaxel, irinotecan, and SN-38. Medians and ranges will be presented for Tmax. These PK parameters will be compared with the historical data to assess if BMS-813160 has any effect on the PK of nab-paclitaxel and irinotecan.

10.3.5 Immunogenicity Analyses

Endpoint	Statistical Analysis Methods
Incidence of ADA to nivolumab Baseline ADA-positive participant is defined as a participant who has an ADA detected sample at baseline.[a] ADA-positive participant is a participant with at least 1 ADA-positive sample relative to baseline after initiation of the treatment	Frequency distribution of baseline ADA-positive participants and ADA-positive participants after initiation of the treatment

[a] Baseline sample is the last sample before initiation of the treatment

A listing of all available immunogenicity data will be provided by dose, and immunogenicity status. The frequency of participants with a baseline and/or at least 1 positive ADA assessment of nivolumab will be summarized.

10.3.6 Biomarker Analyses

Endpoint	Statistical Analysis Methods
Summary measures of change (or % change) from baseline in various biomarkers in the tumor (such as Treg & TAM) and peripheral blood	Summary statistics by planned study day and dose in each arm; Plots of the time course of biomarkers
Summary measures of RO level	Summary statistics/plots by planned study day and dose in each arm

10.3.7 ECG Analyses

All ECG data analyses including summaries of each ECG parameter, frequency distribution of participants' maximum values/changes, and scatter plots will be performed following the current practice of ECG data analysis. Concentration-response analysis may be performed using a mixed effect model, if appropriate and applicable. The details of ECG data analysis will be provided in the SAP.

10.3.8 Other Analyses

The exploratory objective related to OS will be assessed by OS rate at certain time points (eg, 1 year and 2 years) by the Kaplan-Meier method and corresponding 95% CI will be derived based on Greenwood formula by study treatment for each tumor type. OS rate is defined as the proportion of participants who are alive at the time point. OS for a participant is defined as the time from the first dosing date to the date of death due to any cause.

PD biomarker exploratory analyses will be described in detail in the SAP finalized before database lock. The PPK analysis and PD analysis may be presented separately from the main clinical study report.

DNA variants in ADME-related genes from the Core and Extended ADME gene lists (see Appendix 12 which contains ADME gene lists from http://pharmaadme.org) as well as genes related to MATE1 and MATE2-K transporters (SLC47A1 and SLC47A2, respectively), will be determined, if deemed necessary.

10.3.9 Interim Analyses

Expansion phase of Arm C employs a 2-stage design framework and, therefore, there will be interim analysis as planned when adequate number of participants have response-evaluable data. Additional interim analyses may also 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
%UR	percent urinary recovery over dosing interval; percent urinary recovery over 24 hours corrected for molecular weight
1L	first line
2L	second line
3L	third line
5-FU	5-fluorouracil
ADA	anti-drug antibody
AE	adverse event
AI	accumulation index, calculated based on ratio of AUC(TAU) and Cmax at steady state to after the first dose
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
AUC(0-8)	area under the concentration-time curve from time 0 to 8 hours post dose
AUC(0-24)	area under the plasma concentration-time curve from time zero to 24 hours post dose
AUC(0-T)	area under the plasma concentration-time curve from time zero to the time of last quantifiable plasma concentration
AUC(INF)	area under the plasma concentration-time curve from time zero extrapolated to infinite time
AUC(TAU)	area under the concentration-time curve in 1 dosing interval
BICR	blinded independent central review
BID	twice per day
BMI	body mass index
BMS	Bristol-Myers Squibb Company
BP	blood pressure
BOR	best overall response
BUN	blood urea nitrogen
C24	observed plasma concentration at 24 hours post dose
Cavgss	average steady-state concentrations

Term	Definition
C-C	cysteine-cysteine
CCL2	chemokine (C-C motif) ligand 2
CCL5	chemokine (C-C motif) ligand 5
CCR1	cysteine-cysteine (C-C) chemokine receptor 1
CCR2	cysteine-cysteine (C-C) chemokine receptor 2
CCR4	cysteine-cysteine (C-C) chemokine receptor 4
CCR5	cysteine-cysteine (C-C) chemokine receptor 5
cHL	classical Hodgkin lymphoma
CI	confidence interval
CL	clearance
CLR	renal clearance
CLT/F	apparent total body clearance
Cmax	maximum observed plasma concentration
Cmaxss	maximum observed plasma concentration at steady state
Cminss	trough concentration at steady state
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRC	colorectal cancer
CRF	case report form
CrCL	creatinine clearance
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTLA-4	cytotoxic T-lymphocyte antigen-4
Ctrough	trough observed plasma concentration
CXCR2	C-X-C chemokine receptor 2
CXCR3	C-X-C chemokine receptor 3
CXCR5	C-X-C chemokine receptor 5
CYP	cytochrome P450

Term	Definition
DDI	drug-drug interaction
DILI	drug induced liver injury
DKD	diabetic kidney disease
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
EC50	50% of the maximal response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
EOI	end of infusion
EOT	end of treatment
EU	European Union
F	oral bioavailability
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
FOLFIRI	FOL (folinic acid [leucovorin]) F (fluorouracil [5-fluorouracil]) IRI (irinotecan [CAMPTOSAR])
FOLFOX	FOL (folinic acid [leucovorin]) F (fluorouracil [5-fluorouracil]) OX (oxaliplatin [ELOXATIN])
FSH	follicle stimulating hormone
FU	follow up
Gem	gemcitabine
GEP	gene expression profiling
GFR	glomerular filtration rate
GI	gastrointestinal
GPCR	G protein-coupled receptor
GPVE	Global Pharmacovigilance and Epidemiology

Term	Definition
GTP-γS	guanosine 5'-3-O-[thio]triphosphate
HCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HLM	human liver microsomes
hPBMC	human peripheral blood mononuclear cell
IB	Investigator's Brochure
IC50	50% inhibition concentration
IC90	90% inhibition concentration
ICF	informed consent form
IFNγ	interferon gamma
IgG4	immunoglobulin G4
IHC	immunohistochemistry
INFγ	interferon gamma
IP/IMP	Investigational [Medicinal] Product
IRB/IEC	institutional review board / independent ethics committee
IRT	Interactive Response Technologies
IV	intravenous
Kd	dissociation constant
KI	knock in
LC−MS/MS	liquid chromatography-tandem mass spectrometry
LDH	lactate dehydrogenase
M1	metabolite number 1
MATE	multidrug and toxin extrusion protein
MCP-1	monocyte chemotactic protein-1
MDSC	myeloid-derived suppressor cells
MR_AUC(0-24)	ratio of metabolite AUC(0-24) to parent AUC(0-24), corrected for molecular weight
MR_Cmax	ratio of metabolite Cmax to parent Cmax, corrected for molecular weight
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid

Term	Definition
MRI	magnetic resonance imaging
MSI-H	microsatellite instability high
MSS	microsatellite stable
NCI	National Cancer Institute
NGS	next generation sequencing
NMN	N-methylnicotinamide
Non-IP/Non-IMP	Non-investigational [Medicinal] Product
NSCLC	nonsmall cell lung cancer
NTCP	sodium-taurocholate cotransporting polypeptide
OATP	organic anion transporting polypeptide
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death-1 (receptor)
PD-L1	programmed death-ligand 1
PE	physical exam
PEE	probability of early efficacy
PET	positron emission tomography
PET	probability of early termination
PFS	progression free survival
PFSR	progression free survival rate
P-gp	P glycoprotein
PID	participant identification number
PK	pharmacokinetic(s)
PPK	population PK analysis
PO	by mouth; orally
PR	partial response
PT	preferred term

Term	Definition
Q2W	every 2 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks
Q12W	every 12 weeks
QD	once per day
QTcF	QT corrected for heart rate using Fridericia's method
R&D	research and development
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SMT	Safety Management Team
SNP	single nucleotide polymorphism
SOC	system organ class
SUSAR	suspected, unexpected serious adverse reaction
T3	triiodothyronine
T4	thyroxine
TAM	tumor-associated macrophage
TCR	T-cell repertoire / T-cell receptor clonality
TG	thioglycollate
T-HALF	apparent terminal phase half-life
Tmax	time of maximum observed plasma concentration
TME	tumor microenvironment
Treg	regulatory T cells
TSH	thyroid stimulating hormone

Term	Definition
UGT	uridine 5'-diphospho-glucuronosyltransferase
UGT1A1	5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
US	United States
USA	United States of America
VEGF	vascular endothelial growth factor
Vss	volume of distribution at steady state
Vz	volume of distribution of terminal phase
WBC	white blood cell
WES	whole-exome sequencing
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 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 will receive approval/favorable opinion by 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 one 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 date). 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 local health authority) except where necessary to eliminate an 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 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 to subjects/participants, 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 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 participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent 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 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 hand-written 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 medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of 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 (or 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 • nonstudy disposition (e.g., 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 dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable

If	Then
commercial supply, or a specialty pharmacy)	under law and the 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 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 tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If 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, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet Sponsor or designee training requirements and must only access the BMS electronic data capture 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, 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, 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 treatments containers must be immediately destroyed as required for safety, or to meet 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 treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, 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 drug.
- 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 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 Monitor to review throughout the clinical trial period.

It is the investigator's or designee's responsibility to arrange for disposal of all empty 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, is solely the responsibility of the investigator or designee.

For this study, study treatments (those supplied by BMS or its vendors) such as full or partially used study treatment containers, vials, syringes cannot be destroyed on-site.

It is however, the investigator's or designee's responsibility to arrange for disposal of all empty study treatment containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of full or partially used study treatments supplied by BMS or its vendors will be arranged by the responsible Study Monitor.

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:

- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Other criteria (as determined by the study team)

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 (CTAg) governing [Study site or Investigator] 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 CTAg.

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. This includes worsening of an abnormal baseline result. 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

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 • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) • medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases • admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
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 one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) 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 SAES 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 back-up 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 paper 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 post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

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

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

- Postmenopausal female
  - A postmenopausal state is defined as 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 period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels.

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

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 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 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.

METHODS OF CONTRACEPTION

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 and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] – oral (birth control pills) – intravaginal (vaginal birth control suppositories, rings, creams, gels) – transdermal • Combined (estrogen- and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy
• Progestogen-only hormonal contraception associated with inhibition of ovulation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] – oral – injectable • Progesterone-only hormonal contraception must begin at least 30 days prior to initiation of study therapy
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b,c] • Bilateral tubal occlusion
• Vasectomized partner *Having 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.*

A vasectomy is a highly effective contraception method provided that the participant 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.* • Continuous abstinence must begin at least 30 days prior to initiation of study therapy • 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 • Periodic abstinence (including but not limited to calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study.
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 drug, 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] Intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices 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 (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

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 end of relevant systemic exposure defined as 7 months after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in 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 study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study 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 1.1) guideline 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 one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

10 mm by CT/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 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 solid tumor. Nodal size is normally reported as two 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 measures is the short axis. For example, an abdominal node which 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 short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

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 < 10mm 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 skin or lung, abdominal masses/abdominal organomegaly identified by physical exam 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, 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 one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

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

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

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 on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered 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 one or more target lesions cannot be measured or adequately assessed as either fully resolved or 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 Progressive Disease 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 below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if 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 very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure 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 measure, 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 (< 10mm short axis).
- **Non-CR/Non-PD:** Persistence of one 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 presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy A modest 'increase' in the size of one 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 has only 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 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 diameter in a measurable lesion). Examples include, an increase in lymphangitic disease from localized to widespread, or may 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 pre-existing 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 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 Progressive Disease (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 the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline. A lesion identified on Chest X-Ray that was not present in prior CT can be considered a new lesion and will result in Progressive Disease (PD).

If a new lesion is equivocal, for example because of its small size, continued follow-up evaluation will clarify if it represents truly 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 FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly 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 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 pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not 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 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	Not evaluated	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, PR = partial response, SD = stable disease, PD = progressive disease and NE = inevaluable

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]

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease and NE = inevaluable		

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

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 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 stable disease 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 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 'zero' 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 minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE

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**
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable		

[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 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 one (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 progressive disease.

REFERENCES

[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 MANAGEMENT ALGORITHMS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

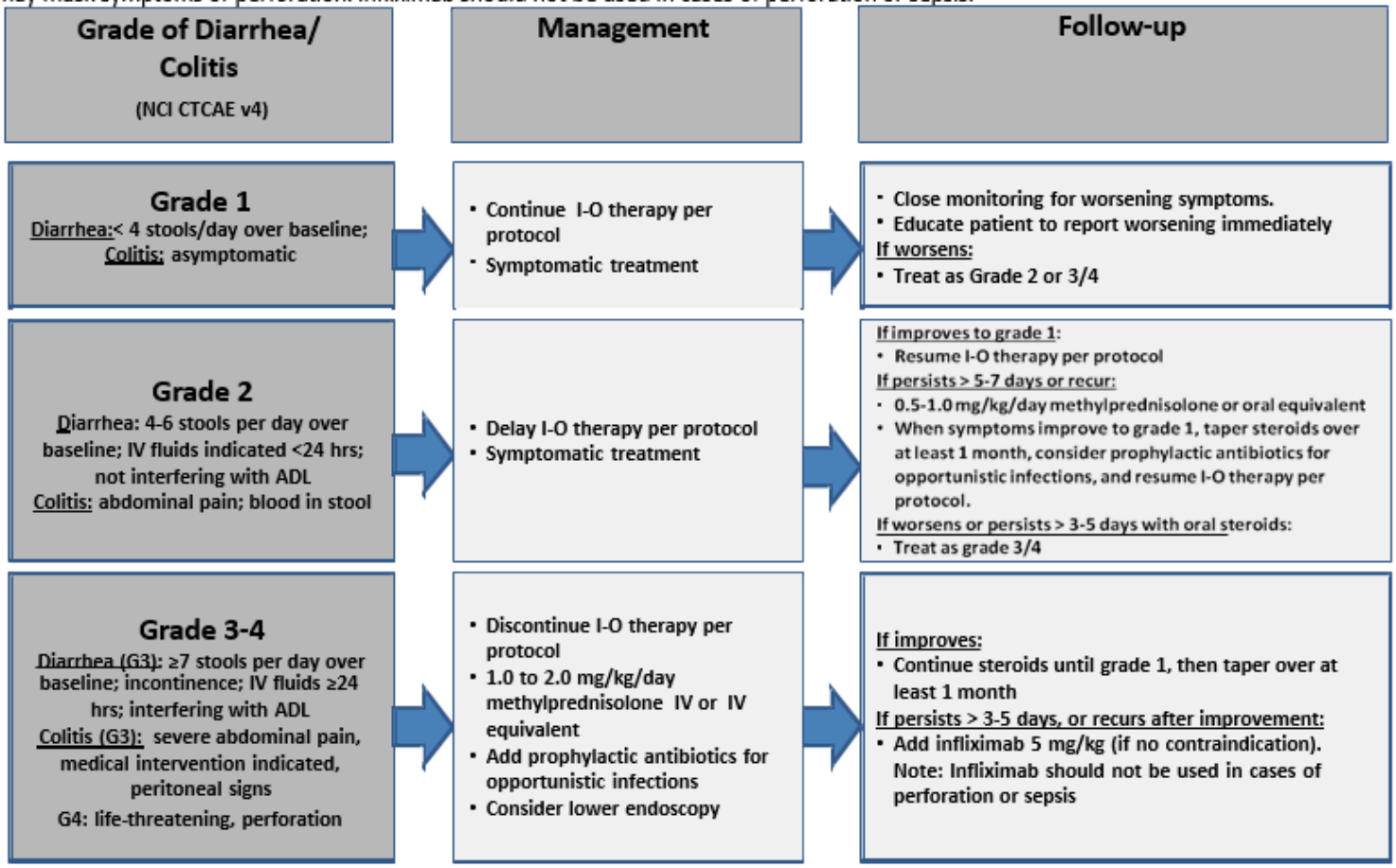
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

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

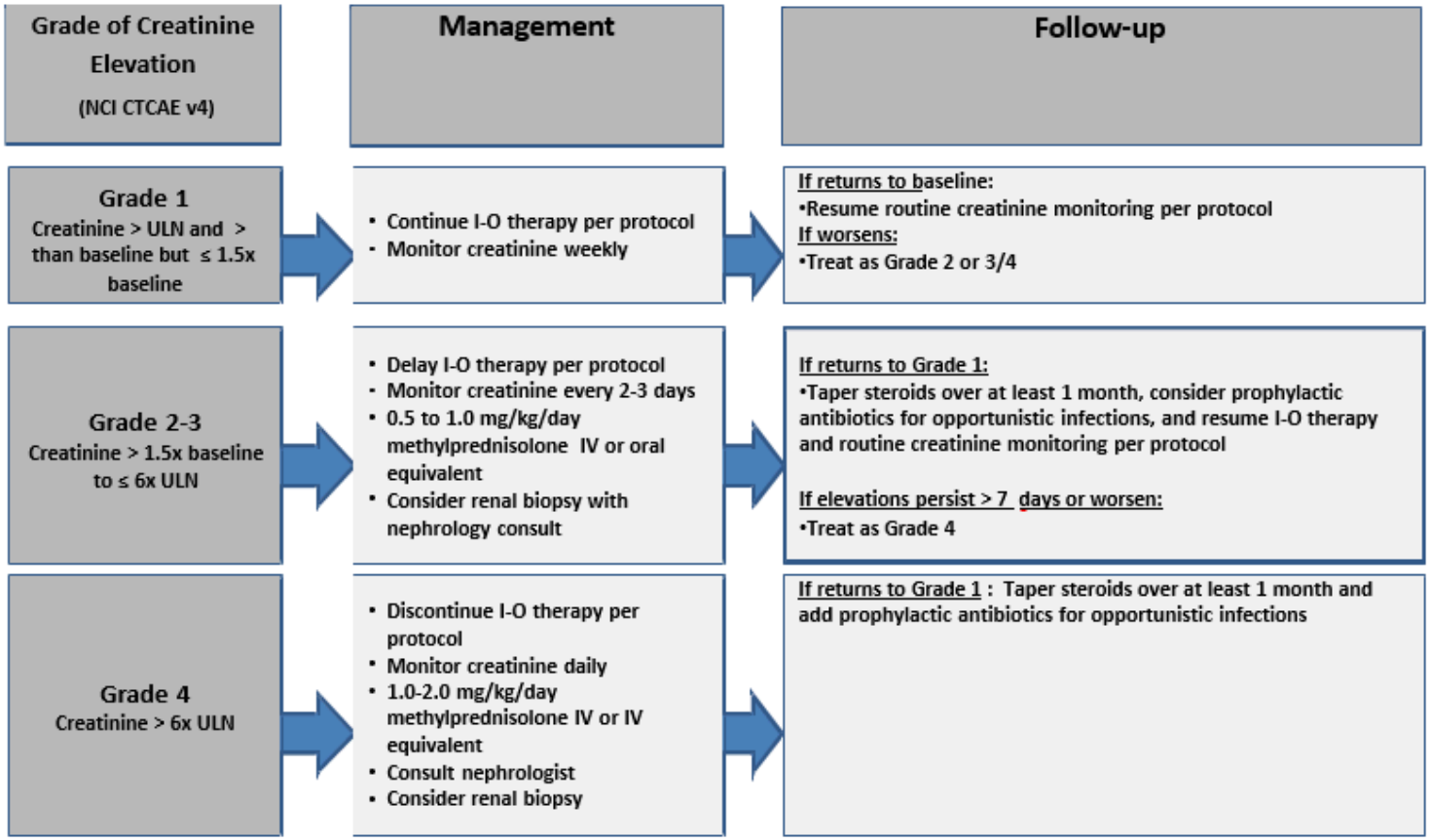


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

Renal Adverse Event Management Algorithm

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

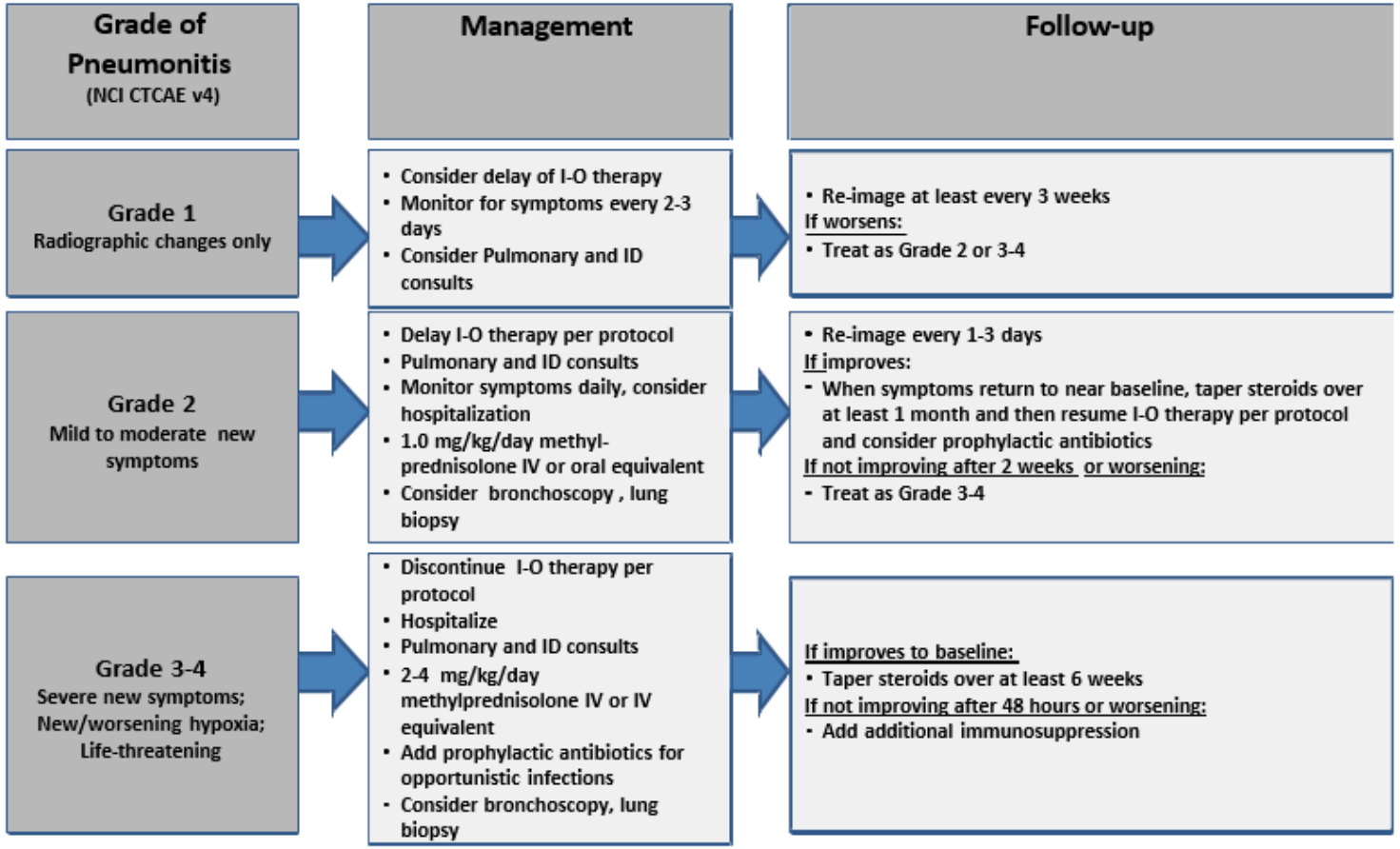


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

Pulmonary Adverse Event Management Algorithm

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

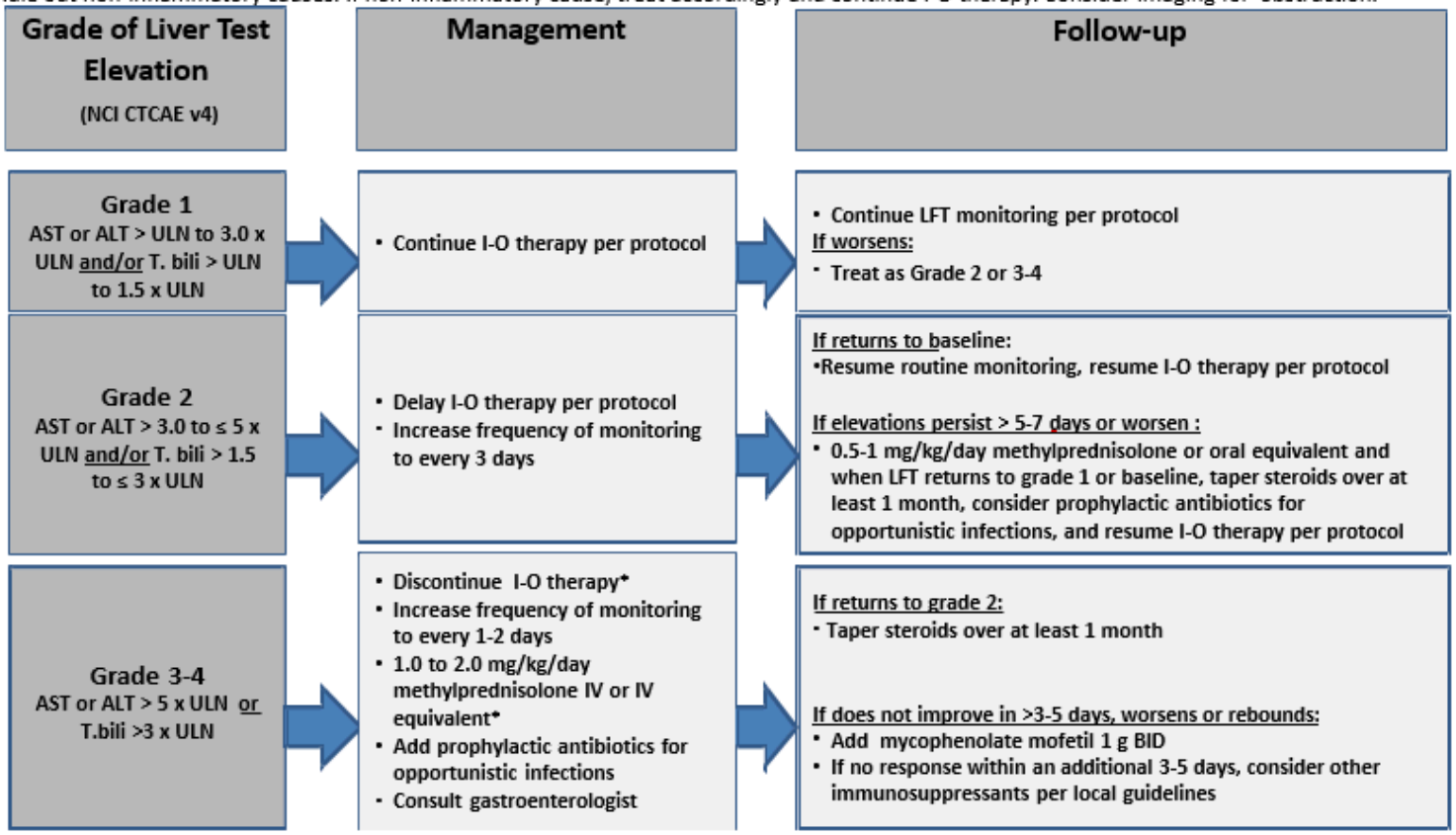


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

Hepatic Adverse Event Management Algorithm

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



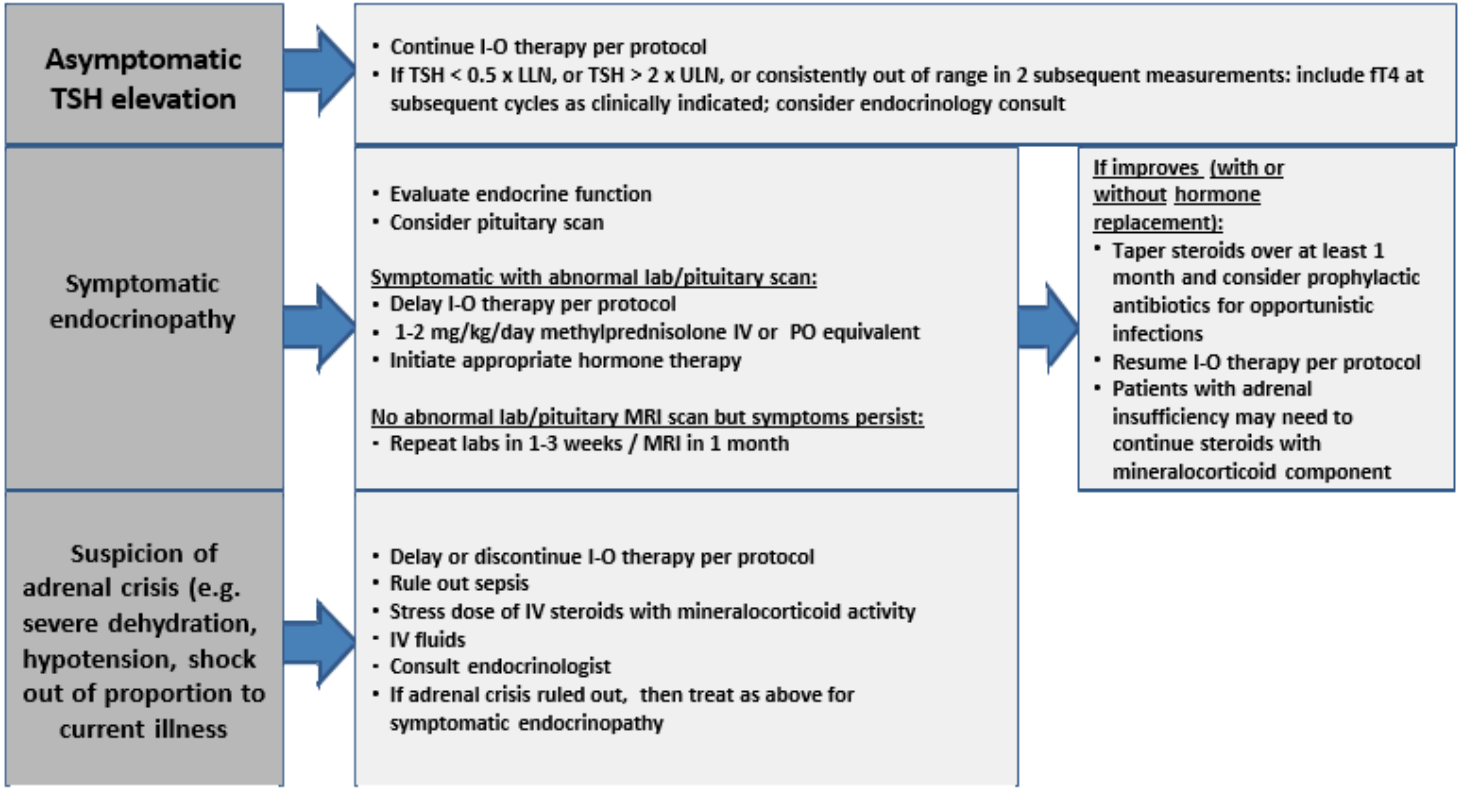
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

27-Jun-2019

Endocrinopathy Adverse Event Management Algorithm

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

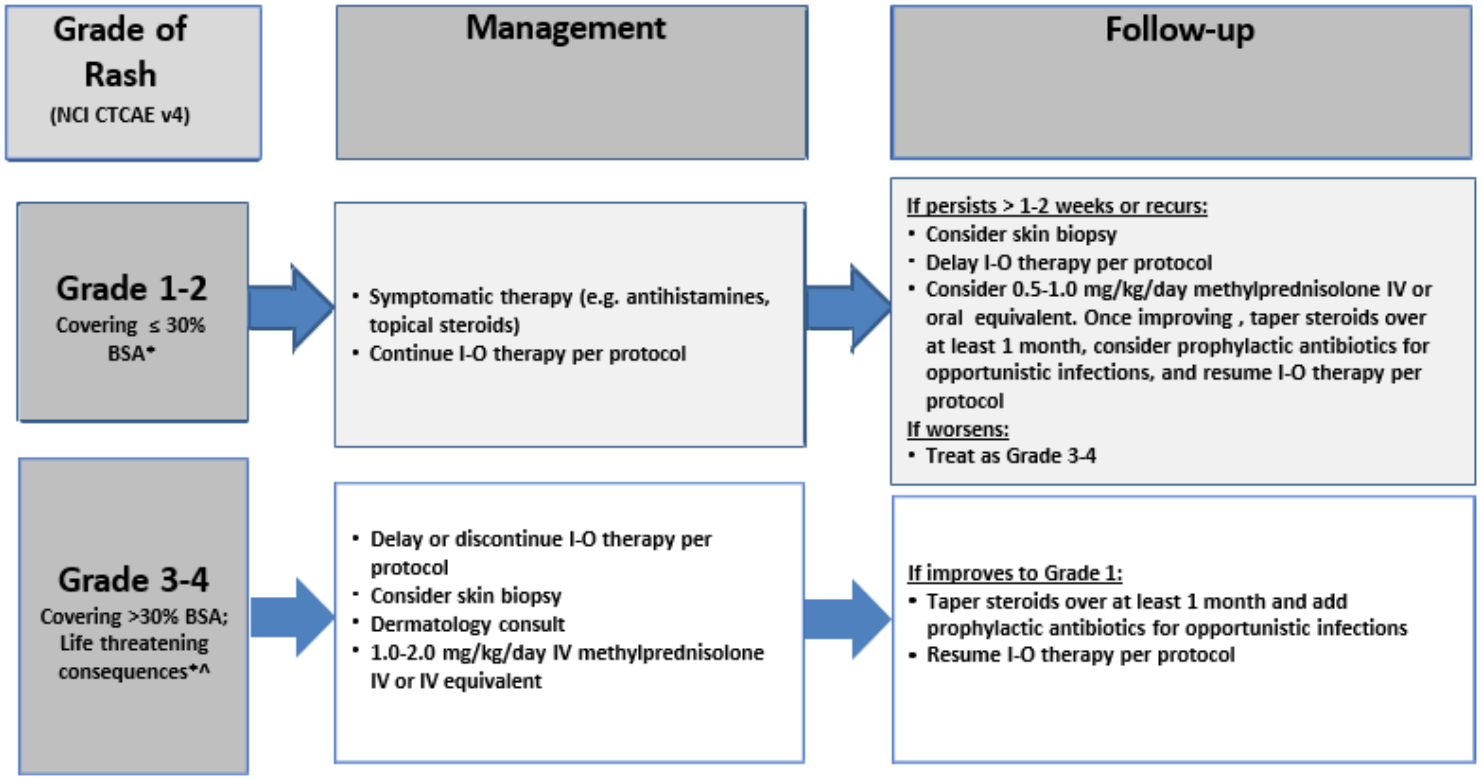


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

Skin Adverse Event Management Algorithm

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



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

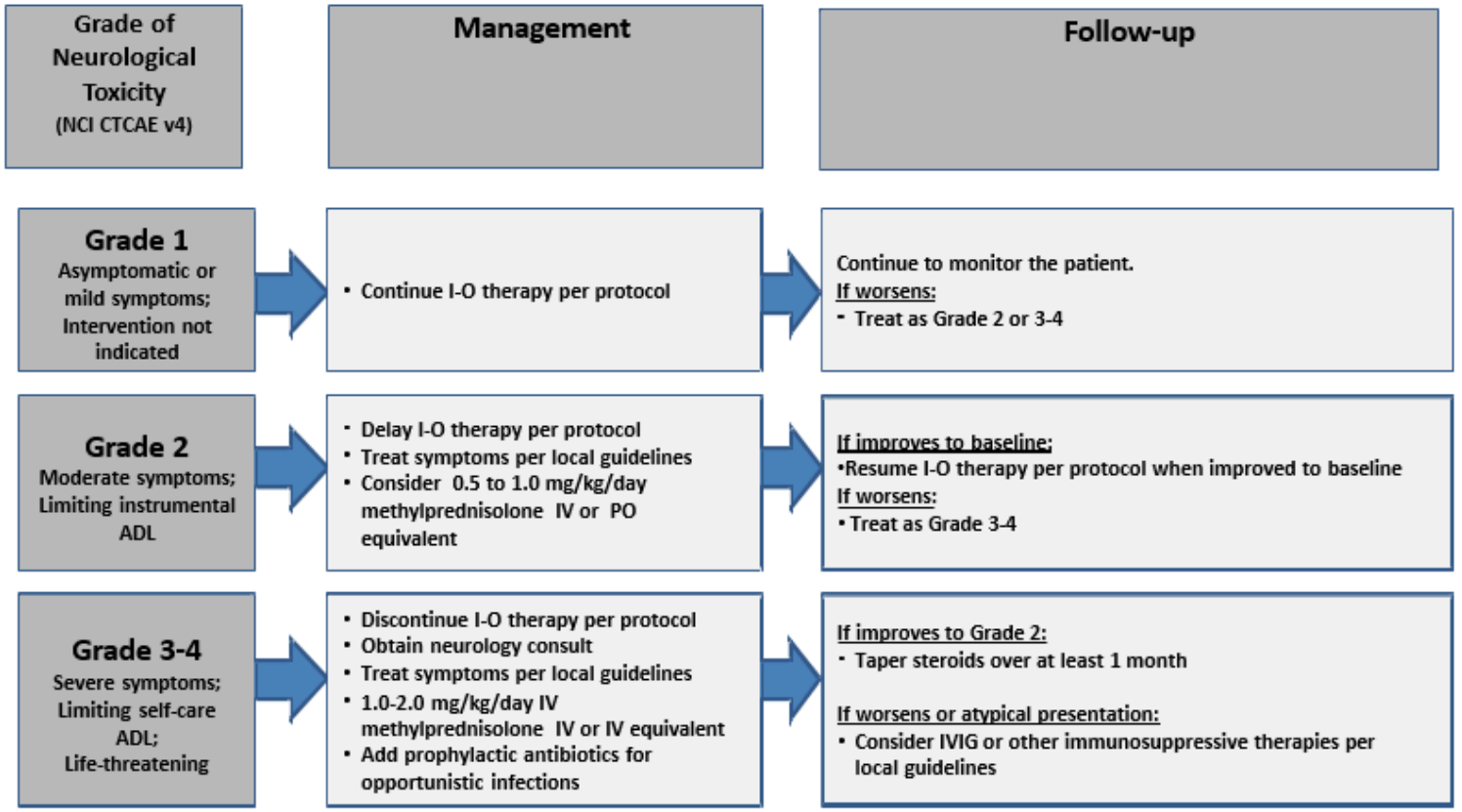
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

27-Jun-2019

Neurological Adverse Event Management Algorithm

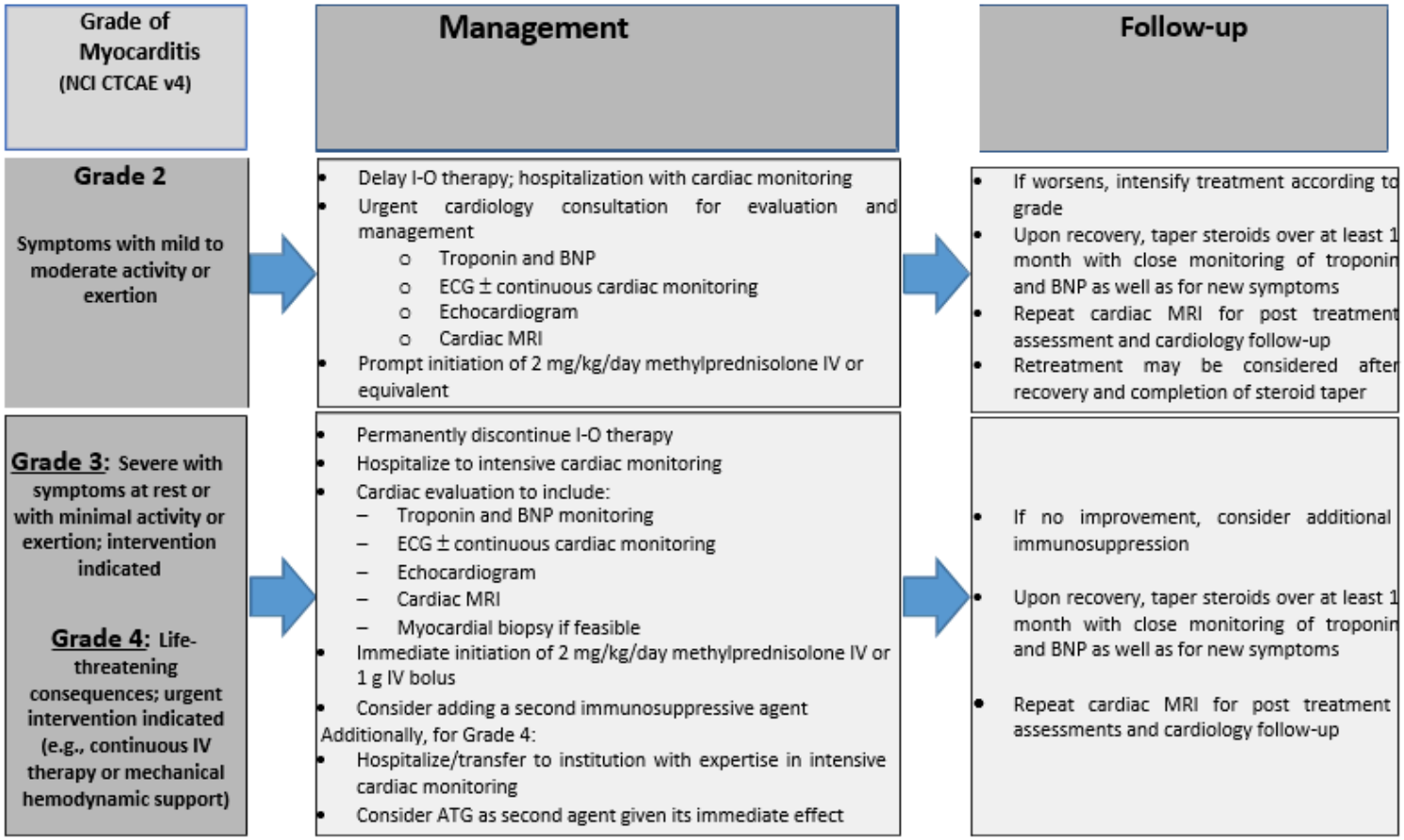
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

27-Jun-2019

Myocarditis Adverse Event Management Algorithm



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.

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

27-Jun-2019

APPENDIX 7 ECOG PERFORMANCE STATUS SCALE

STATUS	ECOG SCALE
Normal activity	0
Symptoms, but fully ambulatory	1
Symptomatic, but in bed < 50% of the day.	2
Needs to be in bed > 50% of the day, but not bedridden	3
Unable to get out of bed	4
Dead	5

APPENDIX 8 CYP3A4 AND P-GP GUIDANCE

The lists below are not meant to be all inclusive. Please consult individual drug labels for further information. Additional information is also available at:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Table 1: Classification of In Vivo Inhibitors of CYP Enzymes

CYP Enzymes	Strong Inhibitors[a] ≥ 5-fold Increase in AUC or > 80% Decrease in CL	Moderate Inhibitors[b] ≥ 2 but < 5-fold Increase in AUC or 50-80% Decrease in CL	Weak Inhibitors[c] ≥ 1.25 but < 2-fold Increase in AUC or 20-50% Decrease in CL
CYP3A	Boceprevir, clarithromycin, conivaptan, grapefruit juice,[d] indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil,[e] nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice,[d] imatinib, verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo,[f] goldenseal,[f] isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton

Please note that this is not an exhaustive list.

[a] A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by equal or more than 5-fold.

[b] A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold.

[c] A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-fold but equal to or more than 5-fold.

[d] The effect of grapefruit juice varies widely among brands and is concentration, dose, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).

[e] Withdrawn from the United States market because of safety reasons.

[f] Herbal product.

Abbreviations: AUC = area under the concentration-time curve; CYP = cytochrome P450.

Table 2: Classification of In Vivo Inducers of CYP Enzymes

CYP Enzymes	Strong Inducers ≥ 80% Decrease in AUC	Moderate Inducers 50-80% Decrease in AUC	Weak Inducers 20-50% Decrease in AUC
CYP3A	Avasimibe,[a] carbamazepine, phenytoin, rifampin, St. John's wort[b]	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, echinacea,[c] pioglitazone, prednisone, rufinamide

Please note that this is not an exhaustive list.

[a] Not a marketed drug.

[b] The effect of St. John's wort varies widely and is preparation dependent.

[c] Herbal product.

Abbreviations: AUC = area under the concentration-time curve; CYP = cytochrome P450.

Table 3: Examples of clinical inhibitors for transporters

Transporter	Inhibitors ≥2 fold increase in digoxin AUC with co-administration
P-gp	Amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil

Please note that this is not an exhaustive list.

Abbreviations: AUC = area under the concentration-time curve

APPENDIX 9 MATE INHIBITORS GUIDANCE

The list below is not meant to be all inclusive. Please consult individual drug labels for further information.

Table 1: Examples of clinical inhibitors for MATE

Transporter	Inhibitors
MATE	Cimetidine, famotidine, cetirizine, cephalexin, cephradine,imatinib, indinavir, ritonavir,ondansetron, pyrimethamine, mitoxantron, topotecan,zafirlukast, corticosterone, chlorpheniramine,dasatinib, erlotinib,nilotinib,disopyramide,procainamide,diphenylhydramine,desipramine,imipramine,diltiazem, quinidine, verapamil, metformin, pramipexol, talipexol, ranitidine,trimethoprim

Please note that this is not an exhaustive list.

APPENDIX 10 UGT1A1 GUIDANCE

The list below is not meant to be all inclusive. Please consult individual drug labels for further information.

Table 1: Examples of clinical inhibitors for UGT1A1

Transporter	Inhibitors
UGT1A1	atazanavir, gemfibrozil and indinavir, ketoconazole, diclofenac, probenecid, silibinin, tacrolimus

Please note that this is not an exhaustive list.

APPENDIX 11 MATE SUBSTRATES GUIDANCE

The list below is not meant to be all inclusive. Please consult individual drug labels for further information.

Table 1: Examples of clinical substrates for MATE

Transporter	substrates
MATE	Metformin, cisplatin, oxaliplatin, ganciclovir, acyclovir, procainamide, captopril, quinine

Please note that this is not an exhaustive list.

APPENDIX 12 CORE AND EXTENDED ADME GENE LIST

Core ADME Gene List:

Gene Symbol	Full Gene Name	Class
ABCB1	ATP-binding cassette, sub-family B (MDR/TAP), member 1	Transporter
ABCC2	ATP-binding cassette, sub-family C (CFTR/MRP), member 2	Transporter
ABCG2	ATP-binding cassette, sub-family G (WHITE), member 2	Transporter
CYP1A1	cytochrome P450, family 1, subfamily A, polypeptide 1	Phase I
CYP1A2	cytochrome P450, family 1, subfamily A, polypeptide 2	Phase I
CYP2A6	cytochrome P450, family 2, subfamily A, polypeptide 6	Phase I
CYP2B6	cytochrome P450, family 2, subfamily B, polypeptide 6	Phase I
CYP2C19	cytochrome P450, family 2, subfamily C, polypeptide 19	Phase I
CYP2C8	cytochrome P450, family 2, subfamily C, polypeptide 8	Phase I
CYP2C9	cytochrome P450, family 2, subfamily C, polypeptide 9	Phase I
CYP2D6	cytochrome P450, family 2, subfamily D, polypeptide 6	Phase I
CYP2E1	cytochrome P450, family 2, subfamily E, polypeptide 1	Phase I
CYP3A4	cytochrome P450, family 3, subfamily A, polypeptide 4	Phase I
CYP3A5	cytochrome P450, family 3, subfamily A, polypeptide 5	Phase I
DPYD	dihydropyrimidine dehydrogenase	Phase I
GSTM1	glutathione S-transferase M1	Phase II
GSTP1	glutathione S-transferase pi	Phase II
GSTT1	glutathione S-transferase theta 1	Phase II
NAT1	N-acetyltransferase 1 (arylamine N-acetyltransferase)	Phase II
NAT2	N-acetyltransferase 2 (arylamine N-acetyltransferase)	Phase II
SLC15A2	solute carrier family 15 (H+/peptide transporter), member 2	Transporter
SLC22A1	solute carrier family 22 (organic cation transporter), member 1	Transporter
SLC22A2	solute carrier family 22 (organic cation transporter), member 2	Transporter
SLC22A6	solute carrier family 22 (organic anion transporter), member 6	Transporter
SLCO1B1	solute carrier organic anion transporter family, member 1B1	Transporter
SLCO1B3	solute carrier organic anion transporter family, member 1B3	Transporter
SULT1A1	sulfotransferase family, cytosolic, 1A, phenol-preferring, member 1	Phase II
TPMT	thiopurine S-methyltransferase,	Phase II
UGT1A1	UDP glucuronosyltransferase 1 family, polypeptide A1	Phase II
UGT2B15	UDP glucuronosyltransferase 2 family, polypeptide B15	Phase II
UGT2B17	UDP glucuronosyltransferase 2 family, polypeptide B17	Phase II
UGT2B7	UDP glucuronosyltransferase 2 family, polypeptide B7	Phase II

Extended ADME Gene List:

Gene Symbol	Full Gene Name	Class
ABCB8	ATP-binding cassette, sub-family B (MDR/TAP), member 8	Transporter
ABCC12	ATP-binding cassette, sub-family C (CFTR/MRP), member 12	Transporter
ABCC3	ATP-binding cassette, sub-family C (CFTR/MRP), member 3	Transporter
ABCC4	ATP-binding cassette, sub-family C (CFTR/MRP), member 4	Transporter
AHR	aryl hydrocarbon receptor	Modifier
ALDH4A1	aldehyde dehydrogenase 4 family, member A1	Phase I
ALDH5A1	aldehyde dehydrogenase 5 family, member A1	Phase I
ALDH6A1	aldehyde dehydrogenase 6 family, member A1	Phase I
CES1	carboxylesterase 1 (monocyte/macrophage serine esterase 1)	Phase I
CES2	carboxylesterase 2 (intestine, liver)	Phase I
CYP7A1	cytochrome P450, family 7, subfamily A, polypeptide 1	Phase I
EPHX1	epoxide hydrolase 1, microsomal (xenobiotic)	Phase I
FMO3	flavin containing monooxygenase 3	Phase I
GSTA1	glutathione S-transferase A1	Phase II
GSTA2	glutathione S-transferase A2	Phase II
GSTA3	glutathione S-transferase A3	Phase II
GSTA4	glutathione S-transferase A4	Phase II
GSTA5	glutathione S-transferase A5	Phase II

Gene Symbol	Full Gene Name	Class
GSTM2	glutathione S-transferase M2 (muscle),glutathione S-transferase M4	Phase II
GSTM3	glutathione S-transferase M3 (brain)	Phase II
GSTM4	glutathione S-transferase M4	Phase II
GSTO1	glutathione S-transferase omega 1,glutathione S-transferase omega 2	Phase II
GSTO2	glutathione S-transferase omega 2	Phase II
GSTT2	glutathione S-transferase theta 2	Phase II
SLC10A1	solute carrier family 10 (sodium/bile acid cotransporter family), member 1	Transporter
SLC15A1	solute carrier family 15 (oligopeptide transporter), member 1	Transporter
SLC22A11	solute carrier family 22 (organic anion/cation transporter), member 11	Transporter
SLC22A8	solute carrier family 22 (organic anion transporter), member 8	Transporter
SLC7A5	solute carrier family 7 (cationic amino acid transporter, y+ system), member 5	Transporter
SLCO1A2	solute carrier organic anion transporter family, member 1A2	Transporter
SLCO2B1	solute carrier organic anion transporter family, member 2B1	Transporter
SULT1A2	sulfotransferase family, cytosolic, 1A, phenol-preferring, member 2	Phase II
SULT1A3	sulfotransferase family, cytosolic, 1A, phenol-preferring, member 3	Phase II
SULT1B1	sulfotransferase family, cytosolic, 1B, member 1	Phase II
UGT1A3	UDP glucuronosyltransferase 1 family, polypeptide A3	Phase II
UGT1A6	UDP glucuronosyltransferase 1 family, polypeptide A6	Phase II
UGT1A7	UDP glucuronosyltransferase 1 family, polypeptide A7	Phase II

Gene Symbol	Full Gene Name	Class
UGT1A8	UDP glucuronosyltransferase 1 family, polypeptide A8	Phase II
UGT1A9	UDP glucuronosyltransferase 1 family, polypeptide A9	Phase II
UGT2A1	UDP glucuronosyltransferase 2 family, polypeptide A1	Phase II
UGT2B11	UDP glucuronosyltransferase 2 family, polypeptide B11	Phase II
UGT2B28	UDP glucuronosyltransferase 2 family, polypeptide B28	Phase II
UGT2B4	UDP glucuronosyltransferase 2 family, polypeptide B4	Phase II
ABCA1	ATP-binding cassette, sub-family A (ABC1), member 1	Transporter
ABCA4	ATP-binding cassette, sub-family A (ABC1), member 4	Transporter
ABCB11	ATP-binding cassette, sub-family B (MDR/TAP), member 11	Transporter
ABCB4	ATP-binding cassette, sub-family B (MDR/TAP), member 4	Transporter
ABCB5	ATP-binding cassette, sub-family B (MDR/TAP), member 5	Transporter
ABCB6	ATP-binding cassette, sub-family B (MDR/TAP), member 6	Transporter
ABCB7	ATP-binding cassette, sub-family B (MDR/TAP), member 7	Transporter
ABCC1	ATP-binding cassette, sub-family C (CFTR/MRP), member 1	Transporter
ABCC10	ATP-binding cassette, sub-family C (CFTR/MRP), member 10	Transporter
ABCC11	ATP-binding cassette, sub-family C (CFTR/MRP), member 11	Transporter
ABCC5	ATP-binding cassette, sub-family C (CFTR/MRP), member 5	Transporter
ABCC6	ATP-binding cassette, sub-family C (CFTR/MRP), member 6	Transporter
ABCC8	ATP-binding cassette, sub-family C (CFTR/MRP), member 8	Transporter

Gene Symbol	Full Gene Name	Class
ABCC9	ATP-binding cassette, sub-family C (CFTR/MRP), member 9	Transporter
ABCG1	ATP-binding cassette, sub-family G (WHITE), member 1	Transporter
ADH1A	alcohol dehydrogenase 1A (class I), alpha polypeptide	Phase I
ADH1B	alcohol dehydrogenase IB (class I), beta polypeptide	Phase I
ADH1C	alcohol dehydrogenase 1C (class I), gamma polypeptide	Phase I
ADH4	alcohol dehydrogenase 4 (class II), pi polypeptide	Phase I
ADH5	alcohol dehydrogenase 5 (class III), chi polypeptide,methionyl aminopeptidase 1	Phase I
ADH6	alcohol dehydrogenase 6 (class V)	Phase I
ADH7	alcohol dehydrogenase 7 (class IV), mu or sigma polypeptide	Phase I
ALDH1A1	aldehyde dehydrogenase 1 family, member A1	Phase I
ALDH1A2	aldehyde dehydrogenase 1 family, member A2	Phase I
ALDH1A3	aldehyde dehydrogenase 1 family, member A3	Phase I
ALDH1B1	aldehyde dehydrogenase 1 family, member B1	Phase I
ALDH2	aldehyde dehydrogenase 2 family (mitochondrial)	Phase I
ALDH3A1	aldehyde dehydrogenase 3 family, memberA1	Phase I
ALDH3A2	aldehyde dehydrogenase 3 family, member A2	Phase I
ALDH3B1	aldehyde dehydrogenase 3 family, member B1	Phase I
ALDH3B2	aldehyde dehydrogenase 3 family, member B2	Phase I
ALDH7A1	aldehyde dehydrogenase 7 family, member A1	Phase I

Gene Symbol	Full Gene Name	Class
ALDH8A1	aldehyde dehydrogenase 8 family, member A1	Phase I
ALDH9A1	aldehyde dehydrogenase 9 family, member A1	Phase I
AOX1	aldehyde oxidase 1	Phase I
ARNT	aryl hydrocarbon receptor nuclear translocator	Modifier
CBR1	carbonyl reductase 1	Phase I
CBR3	carbonyl reductase 3	Phase I
CDA	cytidine deaminase	Modifier
CYB5R3	cytochrome b5 reductase 3	Phase I
CYP11A1	cytochrome P450, family 11, subfamily A, polypeptide 1	Phase I
CYP11B1	cytochrome P450, family 11, subfamily B, polypeptide 1	Phase I
CYP11B2	cytochrome P450, family 11, subfamily B, polypeptide 2	Phase I
CYP17A1	cytochrome P450, family 17, subfamily A, polypeptide 1	Phase I
CYP1B1	cytochrome P450, family 1, subfamily B, polypeptide 1	Phase I
CYP20A1	cytochrome P450, family 20, subfamily A, polypeptide 1	Phase I
CYP20A1	cytochrome P450, family 20, subfamily A, polypeptide 1	Phase I
CYP21A2	cytochrome P450, family 21, subfamily A, polypeptide 2	Phase I
CYP24A1	cytochrome P450, family 24, subfamily A, polypeptide 1	Phase I
CYP26A1	cytochrome P450, family 26, subfamily A, polypeptide 1	Phase I
CYP27A1	cytochrome P450, family 27, subfamily A, polypeptide 1	Phase I

Gene Symbol	Full Gene Name	Class
CYP2A13	cytochrome P450, family 2, subfamily A, polypeptide 13	Phase I
CYP2A7	cytochrome P450, family 2, subfamily A, polypeptide 7	Phase I
CYP2C18	cytochrome P450, family 2, subfamily C, polypeptide 18	Phase I
CYP2F1	cytochrome P450, family 2, subfamily F, polypeptide 1	Phase I
CYP2J2	cytochrome P450, family 2, subfamily J, polypeptide 2	Phase I
CYP39A1	cytochrome P450, family 39, subfamily A, polypeptide 1	Phase I
CYP3A43	cytochrome P450, family 3, subfamily A, polypeptide 43	Phase I
CYP3A7	cytochrome P450, family 3, subfamily A, polypeptide 7	Phase I
CYP4B1	cytochrome P450, family 4, subfamily B, polypeptide 1	Phase I
CYP4F11	cytochrome P450, family 4, subfamily F, polypeptide 11	Phase I
CYP51A1	cytochrome P450, family 51, subfamily A, polypeptide 1	Phase I
EPHX2	epoxide hydrolase 2, cytoplasmic	Phase I
FMO1	flavin containing monooxygenase 1	Phase I
FMO2	flavin containing monooxygenase 2	Phase I
FMO4	flavin containing monooxygenase 4	Phase I
FMO5	flavin containing monooxygenase 5	Phase I
GPX2	glutathione peroxidase 2 (gastrointestinal)	Phase I
GPX3	glutathione peroxidase 3 (plasma)	Phase I
GPX7	glutathione peroxidase 7	Phase I

Gene Symbol	Full Gene Name	Class
GSR	glutathione reductase	Phase I
GSTK1	glutathione S-transferase kappa 1	Phase II
GSTM5	glutathione S-transferase M5	Phase II
GSTZ1	glutathione transferase zeta 1 (maleylacetoacetate isomerase)	Phase II
NNMT	nicotinamide N-methyltransferase	Phase II
NR1I2	nuclear receptor subfamily 1, group I, member 2	Modifier
NR1I3	nuclear receptor subfamily 1, group I, member 3	Modifier
PNMT	phenylethanolamine N-methyltransferase	Phase II
PON1	paraoxonase 1	Phase I
PON2	paraoxonase 2	Phase I
PON3	paraoxonase 3	Phase I
POR	P450 (cytochrome) oxidoreductase	Modifier
PPARD	peroxisome proliferative activated receptor, delta	Modifier
PPARG	peroxisome proliferative activated receptor, gamma	Modifier
RXRA	retinoid X receptor, alpha	Modifier
SLC10A2	solute carrier family 10 (sodium/bile acid cotransporter family), member 2	Transporter
SLC13A1	solute carrier family 13 (sodium/sulfate symporters), member 1	Transporter
SLC13A2	solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 2	Transporter
SLC13A3	solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 3	Transporter

Gene Symbol	Full Gene Name	Class
SLC16A1	solute carrier family 16 (monocarboxylic acid Transporter), member 1	Transporter
SLC19A1	solute carrier family 19 (folate transporter), member 1	Transporter
SLC22A10	solute carrier family 22 (organic anion/cation transporter), member 10	Transporter
SLC22A12	solute carrier family 22 (organic anion/cation transporter), member 12	Transporter
SLC22A13	solute carrier family 22 (organic cation transporter), member 13	Transporter
SLC22A14	solute carrier family 22 (organic cation transporter), member 14	Transporter
SLC22A15	solute carrier family 22 (organic cation transporter), member 15	Transporter
SLC22A16	solute carrier family 22 (organic cation transporter), member 16	Transporter
SLC22A17	solute carrier family 22 (organic cation transporter), member 17	Transporter
SLC22A18	solute carrier family 22 (organic cation transporter), member 18	Transporter
SLC22A18AS	solute carrier family 22 (organic cation transporter), member 18 antisense	Transporter
SLC22A3	solute carrier family 22 (extraneuronal monoamine transporter), member 3	Transporter
SLC22A4	solute carrier family 22 (organic cation transporter), member 4	Transporter
SLC22A5	solute carrier family 22 (organic cation transporter), member 5	Transporter
SLC22A7	solute carrier family 22 (organic anion transporter), member 7	Transporter
SLC22A9	solute carrier family 22 (organic anion/cation transporter), member 9	Transporter
SLC27A1	solute carrier family 27 (fatty acid transporter), member 1	Transporter
SLC28A1	solute carrier family 28 (sodium-coupled nucleoside transporter), member 1	Transporter
SLC28A2	solute carrier family 28 (sodium-coupled nucleoside transporter), member 2	Transporter

Gene Symbol	Full Gene Name	Class
SLC28A3	solute carrier family 28 (sodium-coupled nucleoside transporter), member 3	Transporter
SLC29A1	solute carrier family 29 (nucleoside Transporter), member 1	Transporter
SLC29A2	solute carrier family 29 (nucleoside Transporter), member 2	Transporter
SLC2A4	solute carrier family 2 (facilitated glucose transporter), member 4	Transporter
SLC2A5	solute carrier family 2 (facilitated glucose/fructose transporter), member 5	Transporter
SLC5A6	solute carrier family 5 (sodium-dependent vitamin transporter)	Transporter
SLC6A6	solute carrier family 6 (neurotransmitter transporter, taurine), member 6	Transporter
SLC7A8	solute carrier family 7 (cationic amino acid transporter, y+ system), member 8	Transporter
SLCO1C1	solute carrier organic anion transporter family, member 1C1	Transporter
SLCO2A1	solute carrier organic anion transporter family, member 2A1	Transporter
SLCO3A1	solute carrier organic anion transporter family, member 3A1	Transporter
SLCO4A1	solute carrier organic anion transporter family, member 4A1	Transporter
SLCO4C1	solute carrier organic anion transporter family, member 4C1	Transporter
SLCO5A1	solute carrier organic anion transporter family, member 5A1	Transporter
SLCO6A1	solute carrier organic anion transporter family, member 6A1	Transporter
SULT1C1	sulfotransferase family, cytosolic, 1C, member 1	Phase II
SULT1C2	sulfotransferase family, cytosolic, 1C, member 2	Phase II
SULT1E1	sulfotransferase family 1E, estrogen-preferring, member 1	Phase II
SULT2A1	sulfotransferase family, cytosolic, 2A, DHEA preferring, member 1	Phase II

Gene Symbol	Full Gene Name	Class
SULT2B1	sulfotransferase family, cytosolic, 2B, member 1	Phase II
TAP1	transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)	Transporter
UGT1A10	UDP glucuronosyltransferase 1 family, polypeptide A10	Phase II
UGT1A4	UDP glucuronosyltransferase 1 family, polypeptide A4	Phase II
UGT1A5	UDP glucuronosyltransferase 1 family, polypeptide A5	Phase II
UGT2B10	UDP glucuronosyltransferase 2 family, polypeptide B10	Phase II
ABCC13	ATP-binding cassette, sub-family C (CFTR/MRP), member 13	Transporter
ARSA	arylsulfatase A	Modifier
CAT	catalase	Modifier
CHST8	carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 8	Phase II
CYP19A1	cytochrome P450, family 19, subfamily A, polypeptide 1	Phase I
CYP26C1	cytochrome P450, family 26, subfamily C, polypeptide 1	Phase I
CYP27B1	cytochrome P450, family 27, subfamily B, polypeptide 1	Phase I
CYP2R1	cytochrome P450, family 2, subfamily R, polypeptide 1	Phase I
CYP2S1	cytochrome P450, family 2, subfamily S, polypeptide 1	Phase I
CYP46A1	cytochrome P450, family 46, subfamily A, polypeptide 1	Phase I
CYP4A11	cytochrome P450, family 4, subfamily A, polypeptide 11	Phase I
CYP4F12	cytochrome P450, family 4, subfamily F, polypeptide 12	Phase I
CYP4F2	cytochrome P450, family 4, subfamily F, polypeptide 2	Phase I

Gene Symbol	Full Gene Name	Class
CYP4F3	cytochrome P450, family 4, subfamily F, polypeptide 3	Phase I
CYP4F8	cytochrome P450, family 4, subfamily F, polypeptide 8	Phase I
CYP4Z1	cytochrome P450, family 4, subfamily Z, polypeptide 1	Phase I
CYP7B1	cytochrome P450, family 7, subfamily B, polypeptide 1	Phase I
CYP8B1	cytochrome P450, family 8, subfamily B, polypeptide 1	Phase I
DHRS13	dehydrogenase/reductase (SDR family) member 13	Phase I
DHRS2	dehydrogenase/reductase (SDR family) member 2	Phase I
GPX1	glutathione peroxidase 1	Phase I
GPX4	glutathione peroxidase 4 (phospholipid hydroperoxidase)	Phase I
GPX5	glutathione peroxidase 5 (epididymal androgen-related protein)	Phase I
GPX6	glutathione peroxidase 6 (olfactory)	Phase I
GSS	glutathione synthetase	Phase I
GSTCD	glutathione S-transferase, C-terminal domain containing	Phase II
HNF4A	hepatocyte nuclear factor 4, alpha	Modifier
HNMT	histamine N-methyltransferase	Phase II
HSD11B1	hydroxysteroid (17-beta) dehydrogenase 11	Phase I
HSD17B11	hydroxysteroid (17-beta) dehydrogenase 11	Phase I
HSD17B14	hydroxysteroid (17-beta) dehydrogenase 14	Phase I
LOC731356	similar to dehydrogenase/reductase (SDR family) member 4 like 2	Phase I

Gene Symbol	Full Gene Name	Class
MGST1	microsomal glutathione S-transferase 1	Phase II
MGST2	microsomal glutathione S-transferase 2	Phase II
MGST3	microsomal glutathione S-transferase 3	Phase II
MPO	myeloperoxidase	Modifier
NOS1	nitric oxide synthase 1 (neuronal)	Phase I
NOS2A	nitric oxide synthase 2A (inducible, hepatocytes)	Phase I
NOS3	nitric oxide synthase 3 (endothelial cell)	Phase I
PPARA	peroxisome proliferator-activated receptor alpha	Modifier
SERPINA7	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 7	Modifier
SLC7A7	solute carrier family 7 (cationic amino acid transporter, y+ system), member 7	Transporter
SOD1	superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))	Modifier
SOD2	superoxide dismutase 2, mitochondrial	Modifier
SOD3	superoxide dismutase 3, extracellular precursor	Modifier
SULF1	sulfatase 1	Phase I
SULT4A1	sulfotransferase family 4A, member 1	Phase II
TAP2	transporter 2, ATP-binding cassette, sub-family B (MDR/TAP)	Transporter
UGT8	UDP glycosyltransferase 8 (UDP-galactose ceramide galactosyltransferase)	Phase II
XDH	xanthine dehydrogenase	Phase I
ADHFE1	alcohol dehydrogenase, iron containing, 1	Phase I

Gene Symbol	Full Gene Name	Class
CHST1	carbohydrate (keratan sulfate Gal-6) sulfotransferase 1	Phase II
CHST10	carbohydrate sulfotransferase 10	Phase II
CHST11	carbohydrate (chondroitin 4) sulfotransferase 11	Phase II
CHST12	carbohydrate (chondroitin 4) sulfotransferase 12	Phase II
CHST13	carbohydrate (chondroitin 4) sulfotransferase 13	Phase II
CHST2	carbohydrate (N-acetylglucosamine-6-O) sulfotransferase 2	Phase II
CHST3	carbohydrate (chondroitin 6) sulfotransferase 3	Phase II
CHST4	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 4	Phase II
CHST5	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 5	Phase II
CHST6	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 6	Phase II
CHST7	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 7	Phase II
CHST9	carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 9	Phase II
CYP2D7P1	cytochrome P450, family 2, subfamily D, polypeptide 7 pseudogene 1	Phase I
DDO	D-aspartate oxidase	Phase I
DHRS1	dehydrogenase/reductase (SDR family) member 1	Phase I
DHRS12	dehydrogenase/reductase (SDR family) member 12	Phase I
DHRS3	dehydrogenase/reductase (SDR family) member 3	Phase I
DHRS4	dehydrogenase/reductase (SDR family) member 4	Phase I
DHRS4L1	dehydrogenase/reductase (SDR family) member 4 like 1	Phase I

Gene Symbol	Full Gene Name	Class
DHRS4L2	dehydrogenase/reductase (SDR family) member 4 like 2	Phase I
DHRS7	dehydrogenase/reductase (SDR family) member 7	Phase I
DHRS7B	dehydrogenase/reductase (SDR family) member 7B	Phase I
DHRS7C	dehydrogenase/reductase (SDR family) member 7C	Phase I
DHRS9	dehydrogenase/reductase (SDR family) member 9	Phase I
DHRSX	dehydrogenase/reductase (SDR family) X-linked	Phase I
DPEP1	dipeptidase 1 (renal)	Phase I
FMO6P	flavin containing monooxygenase 6	Phase I
HAGH	hydroxyacylglutathione hydrolase	Phase I
IAPP	islet amyloid polypeptide	Modifier
KCNJ11	potassium inwardly-rectifying channel, subfamily J, member 11	Modifier
LOC728667	similar to dehydrogenase/reductase (SDR family) member 2 isoform 1	Phase I
LOC731931	similar to dehydrogenase/reductase (SDR family) member 2 isoform 1	Phase I
MAT1A	methionine adenosyltransferase I, alpha	Modifier
METAP1	methionyl aminopeptidase 1	Phase I
PDE3A	phosphodiesterase 3A, cGMP-inhibited	Phase I
PDE3B	phosphodiesterase 3B, cGMP-inhibited	Phase I
PLGLB1	plasminogen-like B1	Phase I
ATP7A	ATPase, Cu++ transporting, alpha polypeptide (Menkes syndrome)	Modifier

Gene Symbol	Full Gene Name	Class
ATP7B	ATPase, Cu++ transporting, beta polypeptide	Modifier
CFTR	cystic fibrosis transmembrane conductance regulator	Modifier

APPENDIX 13 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 05, 12-Dec-2019

The revised protocol incorporates additional clarity regarding the recommended dose of BMS-813160 used for Part 2 of the study, adds 75-mg and 300-mg BMS-813160 tablets to the study formulary, adds exclusions and restrictions on participants receiving live / attenuated vaccines, adds clinical guidance on the treatment of treatment-related infusion reactions, and provides updates to Appendix 2, Appendix 3, and Appendix 6.

Summary of key changes for Revised Protocol 05

Section Number & Title	Description of Change	Brief Rationale
Title Page; 1: Synopsis	Short Title added.	Short Title added for clarity and alignment with Short Title provided on ClinicalTrials.gov.
1: Synopsis; 3.3: Benefit/Risk Assessment; 5.1: Overall Design; 5.1.3: Treatment Period (Part 2); 7.2: Method of Treatment Assignment	Statements related to a BMS-813160 dose found to be safe in Part 1 were replaced with a dose of BMS-813160 300 mg BID. The dose and schedule of BMS-813160 in Part 2 of the study was clarified as 300 mg BID, except for Cohort 1b (150 mg QD).	Clarification of the dose and schedule of BMS-813160 in Part 2 of the study.
1: Synopsis; 5.1: Overall Design	The study design schematic (Part 2) of the combination therapy expansion, illustrated in Figure 1-2 and Figure 5.1-2, was modified to clearly state the recommended doses and schedules of BMS-813160.	Clarification of the dose and schedule of BMS-813160 in Part 2 of the study.
1: Synopsis; 5.1.3: Treatment Period (Part 2)	Treatment Period (Part 2) statements modified to be read as: "The doses of BMS-813160 in Part 2 **were** chosen based on safety, PK, and PD available data from Part 1 of the study. **Based on these considerations, BMS-813160 300 mg BID dosing regimen was selected for primary investigation in this study. A regimen of BMS-813160 150 mg QD in combination with FOLFIRI will also be evaluated in Arm A.**"	The phrase in bold was added to clarify the dose and schedule of BMS-813160 in Part 2 of the study.
1: Synopsis; 7: Treatment; 7.1: Treatments Administered	Addition of tablet dosage form of BMS-813160 to the study. • Table 1-3 and Table 7-1: Study Treatments for CV202103. • Table 1-4 and Table 7.1-1: Selection and Timing of Dose.	Study formulary updated with the addition of 75-mg and 300-mg BMS-813160 tablets.

Summary of key changes for Revised Protocol 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
3.1.7: Rationale for Testing BMS-813160 in Combination with Nivolumab, Gemcitabine, and Nab-Paclitaxel	The following statement was added, "Based on the data available, the safety profile of BMS-813160 is manageable with either the 300 mg BID or 600 mg QD dose in combination with gemcitabine and nab-paclitaxel or nivolumab."	Statement added based on safety data available from Part 1 of the study.
3.1.8: Rationale for Exploring Monotherapy in Arm D	Section was reorganized and modified.	Clarification.
3.2.1.3: Clinical Pharmacokinetics of BMS-813160	Preliminary PK evaluation in participants with advanced solid tumors receiving 300 mg BID or 600 mg QD monotherapy dose (Study CV202103) was added.	Section updated based on preliminary PK data available from Part 1 of the study.
5.4.6: Rationale for Using BMS-813160 Tablet	Section added describing the rationale for the addition of tablet dosage form of BMS-813160 to the study.	Study formulary updated with the addition of 75-mg and 300-mg BMS-813160 tablets.
5.5.1: Rationale for Dose Selection of BMS-813160	The following paragraph was added: "The selection of the Part 2 dose for BMS-813160 in CV202103 is primarily based on available data from Part 1 of CV202103. At 300 mg BID, preliminary PK data suggested similar average plasma levels of BMS-813160 in cancer patients relative to that in healthy subjects. Based on the higher Cmax at steady state with the 600 mg QD dose and the lack of apparent difference in PD or safety between the 300 mg BID and 600 mg QD dose, 300 mg BID has been chosen as the primary dose to be evaluated in Part 2 of the study."	Rationale for the selection of BMS-813160 300 mg BID dosing regimen for primary investigation in Part 2 of the study.
6.1: Inclusion Criteria, 2), b), *i*), 3 and 2), b), *ii*), 10	Criteria statements modified to be read as: "Participants must have received an oxaliplatin-containing regimen and an irinotecan- containing regimen (or a combined oxaliplatin- and irinotecan-containing regimen) **but no more than 2 lines of systemic chemotherapy for metastatic disease**."	The phrase in bold was added to clarify the number of previous treatments permitted in Arms C and D of the study.
6.2: Exclusion Criteria, 2), r)	Participants who have received a live / attenuated vaccine within 30 days of first treatment.	Alignment with Nivolumab Investigator Brochure.

Summary of key changes for Revised Protocol 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
7.7.1: Prohibited and/or Restricted Treatments	Any live / attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose.	Alignment with Nivolumab Investigator Brochure.
7.4.4: BMS-813160 Dose Modifications	First bullet modified to be read as "..., Type 2 second or third-degree heart block will require dose interruption and restarting at one dose level lower **when ECG changes resolve to baseline**." Table 7.4.4-1 was modified to add BMS-813160 75 mg BID as a dose reduction for the BMS-813160 150 mg QD starting dose.	The phrase in bold was added for clarification. A dose regimen of 75 mg QD using 75-mg BMS-813160 tablet can be used as an alternative the 150 mg QOD dose reduction.
7.4.7: Nivolumab Dose Modifications	Section updated to include text and link to Section 7.4.7.4, *Treatment of Treatment-related Infusion Reactions*.	Management of infusion reactions added to the protocol.
7.4.7.1: Dose Delays in Nivolumab (Cohort 3b of Arm B and All Cohorts of Arm C)	Criteria for treatment delays were updated.	Criteria were updated to align with nivolumab dose delay.
7.4.7.4: Treatment of Treatment-related Infusion Reactions	Section added describing treatment-related infusion reactions and clinical guidance.	Section added to provide guidance on the treatment of nivolumab treatment reactions.
7.7.3: Permitted Therapy	Second bullet modified to add statement, "Corticosteroids are allowed for prophylaxis in the chemotherapy arms if clinically indicated as part of standard of care."	Modified to allow prophylactic treatment with corticosteroids in the chemotherapy arms where appropriate.
8.4: Study Termination	Section added to describe the evaluation of benefit/risk leading to termination of all or part of the study.	Criteria added for study termination.
9.1: Efficacy Assessments	Section updated to provide guidance on unscheduled tumor assessments.	Clarification on submitting unscheduled imaging.
10.1: Sample Size Determination	Arm C: Cohort 5 (2/3L CRC [MSS]) in Table 10.1-1 was reorganized for clarity.	Clarification of 2- stage design for Cohorts 4 and 5.
Appendix 2: Study Governance Considerations	Modified Good Clinical Practice section to: • Add bullet to clarify that the study will also be conducted in accordance with ethical principles derived from international guidelines, including	Modified text to align with statement in the informed consent form and TransCelerate Common Protocol Template.

Summary of key changes for Revised Protocol 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
	the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines Good Clinical Practice. • Align with revised definition of serious breach to Regulation No 536/2014 of the European Parliament and of the Council.	
Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up and Reporting	Events Meeting the AE Definition: • "...medical and scientific judgement 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**." • "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**." • 6th bulleted statement and last paragraph were deleted. Events NOT Meeting the AE Definition: • Previous text was deleted with the exception of the 3rd and 4th bulleted statements. 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."	Text was modified and phrase in bold was added to clarify the need to report abnormal lab tests or other safety assessments when the final diagnosis is not available. Text was modified and phrase in bold was added to clarify the need for the investigator to report the specific term of "intentional overdose" as an AE term. All other types of overdose should NOT be reported as an AE but should be recorded elsewhere on the CRF. There are no changes to the reporting of AEs associated with any type of overdose. Text deleted to clarify that disease related events and events associated with lack of efficacy will need to continue to be reported as AEs if the event meets the criteria of an AE. Text deleted to clarify that disease related events and events associated with lack of efficacy will need to continue to be reported as AEs if the event meets the criteria of an AE. Text was deleted to clarify that disease related events and events associated with lack of efficacy will need to continue to be reported as AEs if the event meets the criteria of an AE.

Summary of key changes for Revised Protocol 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 6: Management Algorithms, 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.	Language was modified to align protocol with current Nivolumab Investigator Brochure and nivolumab program safety parameters.
All	Minor formatting and typographical corrections.	

Overall Rationale for the Revised Protocol 04, 12-Jul-2018

The revised protocol adds a new table to Section 2, Schedule of Activities, clarifying the procedures needed for participants in Part 2 of the study to cross over from Cohorts 1c and 3c to Cohorts 5 and 4, respectively. Additional revisions include reordering the inclusion criteria from Revised Protocol 03, clarifying the biomarker sample collections for cross-over participants, and some administrative changes.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
2: Schedule of Activities	Mandatory pre-treatment biopsy assessments in Table 2-1 and Table 2-2 were clarified to describe sufficient tumor tissue as 3 to 4 blocks or minimum of 30 slides. Section was updated to include Table 2-2, Baseline for Cross-Over Procedural Outline - Cohort 1c to Cohort 5 - Cohort 3c to Cohort 4 - Part 2. Table 2-7, Follow-up Procedural Outline, was modified to include cross-over, follow-up safety assessments.	Clarification. Table 2-2 and Table 2-7 were added and modified, respectively, to clarify the procedures needed for participants in Part 2 of the study to cross over from Cohorts 1c and 3c to Cohorts 5 and 4, respectively.
6.1: Inclusion Criteria	• Criterion 2), iii) was moved back to its original number as per Protocol Revision 02, criterion 2), b). • The Protocol Revision 02 Part 2 criteria 2), b), ii), 1 through 6 are not applicable as per Protocol Revision 03. • The Protocol Revision 03 Part 2 criteria 2), a), ii), 1, 2, 3, and 4 are renumbered as 2), b), ii), 7, 8, 9, and 10, respectively.	The study inclusion criteria were reordered to facilitate the transfer of this information in the electronic data capture system (RAVE). An edit check in RAVE will ensure that the site will select the accurate revised new criteria.
6.2: Exclusion Criteria	Criterion 2), d), iv) is not applicable as per Protocol Revision 04. Criterion 2), o) was clarified to allow Whipple or other upper GI surgery if there is no clinical evidence of malabsorption. Criterion 2), p) is not applicable as per Protocol Revision 04. Criterion 2), q) is not applicable as per Protocol Revision 04.	Clarification.
7.2: Method of Treatment Assignment	Section was updated to clarify that cross-over participants will retain their	Clarification.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	original personal identification numbers throughout the study.	
7.4.4: BMS-813160 Dose Modifications	Table 7.4.4-1, Recommended Dose Modifications for BMS-813160, was updated to include a dose reduction for participants receiving 300 mg QD.	Clarification.
9.8: Biomarkers	Table 9.8-2 was modified to align with the cross-over sample collections in Part 2 of the study. The peripheral blood mononuclear cells (PBMC) sample collections in Table 9.8-2, Biomarker Sampling Schedule - Part 2, were replaced with blood sample collections.	Table was modified to clarify the biomarker sample collections for cross-over participants. Evolving science indicates that the best collection for the peripheral gene expression profiling analysis is whole blood PAXgene® instead of whole blood with isolated PBMC.
10.3.1: Efficacy Analyses	Section updated to clarify that participants reassigned into Arm C cohorts following treatment in another cohort, will be combined with participants originally assigned in these cohorts for efficacy analysis.	Clarification.
All	Minor formatting and typographical corrections.	Clarification.

Overall Rationale for the Revised Protocol 03, 07-May-2018

The revised protocol adds and modifies disease-specific cohorts, study treatments, PK, and biomarker assessments. Additional revisions include clarifying and alignment modifications to the clinical protocol template and some administrative changes.

Summary of key changes for Revised Protocol 03

Section Number & Title	Description of Change	Brief Rationale
1: Synopsis; 3.1.3: Rationale for the Chemotherapy Regimens in Arms A and B; 3.1.4: Rationale for Selecting 2L CRC in Part 2 Arm A; 3.1.5: Rationale for Combining BMS-813160 with Nivolumab in Patients with Advanced Pancreatic and Colorectal Cancers in Arm C; 3.1.6: Rationale for Testing Lower Dose of BMS-813160; 3.1.7: Rationale for Testing BMS-813160 in Combination with Nivolumab, Gemcitabine, and Nab-Paclitaxel; 3.1.8: Rationale for Exploring Monotherapy in Arm D; 5.1: Overall Design; 5.1.3: Treatment Period (Part 2); 5.1.4: Treatment Period (Parts 1 and 2); 7.1: Treatments Administered	Figure 1-2 and Figure 5.1-2, Study Design Schematic (Part 2), modified as follows: • Cohorts 1a, 1b, and 1c (2L CRC) replaced Cohort 1 (1L CRC) and Cohort 2 (3L CRC). Two new treatments were added: Cohort 1b, low dose BMS-813160 + FOLFIRI, and Cohort 1c, FOLFIRI treatment comparator. • Cohort 3 (1L pancreatic) was divided into Cohorts 3a, 3b, and 3c (1L pancreatic). Two new treatments were added: Cohort 3b, BMS-813160 + nivolumab + Gem/nab-paclitaxel, and Cohort 3c, Gem/nab-paclitaxel treatment comparator. • FOLFIRI retreatment (cohort 2) and Colorectal MSI-H (cohort 6 and 9) were removed from Part 2, Arm C and Arm D. Cetuximab and panitumumab treatment options removed as potential additions to FOLFIRI therapy (Part 2) throughout the protocol. Cohort 3b (1L pancreatic), BMS-813160 + nivolumab + Gem/nab-paclitaxel treatment, added with a safety lead-in with staggered dosing (sentinel participant) approach. Study treatment rationale sections added or updated to describe modifications to Part 2 of the study, combination therapy expansion.	• Randomization was added to Part 2 to better evaluate safety and efficacy of the BMS-813160 + chemotherapy combination. A second dose was added to Arm A to test PK, PD, and efficacy of lower dose of BMS-813160 in combination with chemotherapy. • Randomization was added to Part 2 to better evaluate safety and efficacy of BMS-813160 + chemotherapy +/- nivolumab. A combination of BMS-813160 + nivolumab + Gem/nab-paclitaxel combination was added to Arm B to evaluate safety and preliminary efficacy of the combination. • FOLFIRI retreatment and MSI-H post PD-1 cohorts were removed from the study. Bevacizumab can be added to 2L FOLFIRI treatment if appropriate. A staggered dosing (sentinel participant) approach and safety lead in will reduce the number of patients enrolled to the combination if there are any unanticipated toxicities.
1: Synopsis;	Table 1-2 and Table 4-2, Objectives and Endpoints (Part 2), were updated	Study objectives and endpoints were updated to align with revisions to the Part 2 study design.

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
4: Objectives and Endpoints	to include BMS-813160 in combination with nivolumab + Gem + nab-paclitaxel (Arm B) and as monotherapy (Arm D).	
1: Synopsis; 5.5.1: Rationale for the Dose Selection of BMS-813160; 7.1: Treatment Administered; 7.4.4: BMS-813160 Dose Modifications	Treatment Period (Part 1), Table 1-4, Table 7.1-1, Table 7.4.4-1, and section text modified to remove the exploratory BMS-813160 600 mg BID dosing regimen.	The exploratory BMS-813160 600 mg BID dosing regimen was not initiated in Part 1 of the study, and this regimen will not be explored in Part 2.
1: Synopsis; 5.1.4: Treatment Period (Parts 1 and 2)	Treatment Period (Part 2) modified to permit eligible participants in Cohorts 1c and 3c to cross over to Cohorts 5 and 4, respectively, at the time of disease progression. Participants will have to meet all eligibility criteria to re-enter the study.	Eligible participants on the control arms of Arm A and B will be allowed to cross over at the time of PD as they may be eligible for Arm C.
1: Synopsis; 2: Schedule of Activities; 5.1: Overall Design; 8.1.1: Post Study Treatment Study Follow-up	Safety Follow-up Period (Parts 1 and 2), Figure 1-2, Table 2-1, Table 2-3, Table 2-6, and Figure 5.1-2 updated to include participants in Cohort 3b (Arm B, Part 2) to be followed for at least 100 days after last dose of study treatment.	Follow-up period extended to monitor for AEs, accounting for the long half-life of nivolumab.
1: Synopsis; 5.2: Number of Participants	Overall number of participants in Part 2 revised. Participants per cohort in Part 2 updated.	Sections were updated to align with revisions in Part 2 of the study design and Section 10.1, Sample Size Determination.
2: Schedule of Activities	References to PK sampling Table 9.5.2-2 were removed from Table 2-1 to Table 2-5. References to PK sampling Table 9.5.4-2 were added to Table 2-2 and Table 2-3. References to PK sampling Table 9.5.3-1 were added to Table 2-4 and Table 2-5. Reference to Table 9.8-2, Biomarker Sampling Schedule - Part 2, added to Table 2-1 to Table 2-5. Table 2-3, On-treatment Procedural Outline (Arm B), modified with additional study treatment, BMS-	Section 2 timing and events tables were updated to align with revisions in Part 2 of the study design.

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	813160 + Gem/nab-paclitaxel + nivolumab, for Cohort 3b in Part 2. EOT assessments were updated in Table 2-4 and Table 2-5 for Vital Signs, ECOG, 12-Lead ECG.	
3.2.1.4: Clinical Safety of BMS-813160	Section updated with an on-going safety evaluation of BMS-813160 2-week monotherapy lead-in and combination with chemotherapy or nivolumab in Part 1.	On-going clinical safety update of BMS-813160 in Part 1 provided.
3.2.2.2: Clinical Pharmacokinetics of Nivolumab	Section updated with recent US FDA and EU CHMP approvals for nivolumab 480 mg Q4W treatment regimen.	Section updated with recent regulatory approvals.
3.3: Benefit/Risk Assessment	Section updated to include the combination of Gem/nab-paclitaxel, nivolumab, and BMS-813160 (Cohort 3b).	A Gem/nab-paclitaxel, nivolumab, and BMS-813160 combination was added to Arm B to evaluate safety and preliminary efficacy of the combination.
5.1.2: Treatment Period (Part 1)	Section updated to add participants for the PK and PD assessments of lower doses of BMS-813160 in combination with nivolumab.	The Sponsor proposes to add lower doses that provide a trough concentration of 0.3 to 0.5-fold IC90 for inhibiting CCR2/5 function.
5.4.4: Rationale for Control Arms	The control arms for Arm A (FOLFIRI) and Arm B (Gem/nab-paclitaxel) were added.	Control arms were added to better evaluate safety and efficacy of BMS-813160 combined with either FOLFIRI or Gem/nab-paclitaxel ± nivolumab, respectively.
5.5.2: Rationale for Lower Dose of BMS-813160	Lower doses of 150 mg QD and 300 mg QD to be evaluated in the study.	The Sponsor proposes to add lower doses that provide a trough concentration of 0.3 to 0.5-fold IC90 for inhibiting CCR2/5 function.
6.1: Inclusion Criteria, 2), a), *ii*), 1. to 5.	Inclusion criteria modified for disease-specific cohorts. Criterion moved to 2), a), *iii*) from 2), b).	Clarification.
6.2: Exclusion Criteria, 1), b)	Eligibility criteria added for participants with adequately treated CNS metastasis.	Clarification.
6.2: Exclusion Criteria, 5), e), *i*)	New exception, intraventricular conduction delay which is not considered clinically significant, was added to QRS ≥ 120 msec exclusion criterion.	Clarification.
6.2: Exclusion Criteria, 7), a)	Eligibility of prisoners or participants who are involuntarily incarcerated was modified to include prohibitions by local regulations/guidelines/laws.	Clarifications.

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
6.3.1: Meals and Dietary Restrictions	Section was modified to align with intensive PK sampling in Part 2.	Section updated to require fasting on C2D1 for PK characterization.
6.4: Screen Failures	New phrasing added to CONSORT statement.	New phrase added, '...as applicable,...' to CONSORT statement to enable use of the section without change or editing, as it will be applicable to all interventional protocols.
7.4.4: BMS-813160 Dose Modifications	Qualifying phrase, 'unless the delay was from chemotherapy alone or unrelated to study treatment', added to 5th bulleted statement. Two bulleted statements were added regarding participants who miss a dose at the specified time or vomit a dose. Dose Reduction 2 was removed from Table 7.4.4-1. Lower dose BMS-813160 treatment (Cohort 1b) added to the dose modification table to align with revisions in Part 2 of the study design.	Clarification regarding dose modification. Starting doses of BMS-813160 and only one dose reduction added to all doses.
7.4.5: FOLFIRI Dose Modifications	Dose Reduction 2 for Infusion 5-FU in Table 7.4.5-1 reduced to 1600 mg/m^2 from 2000 mg/m^2.	Clarification for dose modification of FOLFIRI.
7.7.3: Permitted Therapy	Section was added to describe qualified therapy with corticosteroids, immunosuppressive agents, and influenza vaccines.	Clarification on permitted therapy while on study.
7.7.4: Palliative Local Therapy	Section was added to describe palliative and supportive care for disease-related symptoms and study documentation.	Clarification allowing palliative and local therapy.
8.1: Discontinuation	Text added to align with TransCelerate clinical protocol template (CPT) and clarify expectations for reporting pregnancy.	Text added to align with TransCelerate CPT and clarify expectations for reporting pregnancy.
9.1: Efficacy Assessments	Text added to align with updated Appendix 5, Response Evaluation Criteria in Solid Tumors Guidelines (Version 1.1) with BMS Modifications.	Appendix was updated to harmonize language for RECIST 1.1 criteria across immuno-oncology program.
9.2.1: Time Period and Frequency for Collecting AE and SAE Information	Text in section is reorganized.	Changes made to clarify timing to start collection of SAE from signing of consent and AE collection from the start of study treatment.
9.2.2: Method of Detecting AEs and SAEs	Section and text added to align with TransCelerate CPT.	Section and text added to align with TransCelerate CPT.

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
9.2.5: Pregnancy	New text added to clarify the circumstances for continuation of study treatment after confirmation of end of pregnancy.	Alignment with Section 8.1, Discontinuation from Study Treatment in Study Protocol.
9.3: Overdose	The requirement to report all occurrences of overdose as SAE is deleted.	Overdoses that meet the regulatory definition of SAE will be reported as an SAE.
9.5: Pharmacokinetics	Subsection headings, table titles, and section text modified to include the revised cohorts in Part 2.	Section updated to align with revisions in Part 2 of the study design.
9.8: Biomarkers	Table 9.8-2, Biomarker Sampling Schedule - Part 2, added with an updated biomarker panel of assessments. Section text modified to include biomarker panel for Part 2.	Section updated to align with revisions in Part 2 of the study design.
10.1: Sample Size Determination	The statistical analyses and participant population in Part 2 of the study were updated.	Section modified to align with revisions in Part 2 of the study design.
10.3: Statistical Analyses	A description of the participant population will be included in the statistical output reported, including subgroup of age, gender, and race.	Sentence added to meet the compliance requirement of the Global Data Privacy Regulation and the MR-001 (for France) for the collection of 'Race.'
10.3.1: Efficacy Analyses	Statistical analysis method updated to include an estimate of difference in ORR between each treatment cohort and the control cohort of Arm A and Arm B and corresponding two-sided exact 95% CI by treatment for each tumor type.	Text added to align with revisions in Part 2 of the study design.
10.3.2: Safety Analyses	Section was updated to include Cohort 3b in Part 2.	Text added to align with revisions in Part 2 of the study design.
Appendix 2: Study Governance Considerations; Good Clinical Practice; 3rd paragraph	Revised definition of serious breach.	Revised definition to serious breach according to REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use.
Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up and Reporting	New sections, *Events Meeting the AE Definition* and *Events NOT Meeting the AE Definition*, and text added. For SAE reporting, deleted cancer, overdose, suspected transmission of an infectious agent. Pregnancy and potential drug-induced liver injury (DILI) statements clarified. *Assessment of Causality* text revised.	New Sections and text added to align with TransCelerate CPT. Align with regulatory definition (EMA GVP Module VI (EMA/873138/2011) and ICH E2A). Clarify the timeline/process for reporting pregnancy and DILI. Assessment of Causality text revised to align with TransCelerate CPT.

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 10: Response Evaluation Criteria in Solid Tumors Guidelines (Version 1.1) with BMS Modifications	Fluid collections (ie, pleural effusions, pericardial effusions and ascites) will not be followed as non-target lesions and will not contribute to response or progression. Removed timeframe for minimum time of study and definition of Day 1 to declare SD since this can vary per study. This is now outlined in the actual body of the protocol and specified per study requirements.	Appendix was updated to harmonize language for RECIST 1.1 criteria across immuno-oncology program.
1: Synopsis	Data Monitoring Committee: No	New field added to align with TransCelerate CPT, and a multi-layered process to ensure safety monitoring is described.
All	Minor formatting and typographical corrections.	Clarification.

Overall Rationale for the Revised Protocol 02, 11-Sep-2017

The revised protocol provides additional survival follow-up, tumor markers, PK sampling of irinotecan and nab-paclitaxel in a subset of participants and some administrative changes.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
1: Synopsis; 4: Objectives and Endpoints	Objectives and Endpoints (Part 1 and Part 2) were updated to include exploratory objectives and endpoints assessing overall survival in treated participants. Objectives and Endpoints (Part 2) were updated to include an exploratory objective and endpoint assessing the effect of irinotecan and nab-paclitaxel in a subset of participants by comparing with historical data.	Overall survival is being added as an exploratory endpoint as a direct measure of clinical benefit. [redacted] pharmacokinetics (PK) samples will be collected to assess the potential for a drug-drug interaction.
1: Synopsis; 2: Schedule of Activities 5.1: Overall Design 5.1.5.2: Survival Follow-up	Section was added to describe a Survival Follow-up period. Survival Follow-up to begin after completion of Safety Follow-up every 12 weeks (Q12W) [± 2 weeks] until 2 years after last dose of study treatment. Table 2-6 was modified to include Survival Follow-up Q12W after Safety Follow-up Phase. Follow-up Period modified in Study Schemes (Figure 5.1-1 and Figure 5.1-2) to include separate safety follow-up and survival follow-up phases.	A Survival Follow-up period was added to the study design and Schedule of Activities to assess the clinical benefit of study treatments.
Section 9.5.4: Pharmacokinetic Assessment of Irinotecan and Nab-Paclitaxel Section 10.3.4: Irinotecan and Nab-Paclitaxel in Combination Phase (Part 2)	Sections added to describe the PK variables and sampling schedule for irinotecan (Arm A, Part 2, Cohort 1 only) and nab-paclitaxel (Arm B, Part 2) combinations therapies.	[redacted] PK samples will be collected to assess the potential for a drug-drug interaction.
Section 9.8: Biomarkers	Section and Table 9.8-1 modified to include circulating tumor DNA (ctDNA) analysis and plasma sample schedule for ctDNA, respectively.	Collection of plasma ctDNA for analysis will enable assessments of tumor mutations, tumor mutation burden, and other biomarkers.
Section 10.3.8: Other Analyses	Section modified to describe analysis of added exploratory objective related to overall survival.	Overall survival is being added as an exploratory endpoint as a direct measure of clinical benefit..

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.4.4: Clinical Safety Laboratory Assessments	List of clinical laboratory assessments modified to include serum testing for amylase.	List of clinical laboratory assessments updated to align with amylase testing described in Nonhepatic Nonhematologic DLT [Section 7.4.1, 3), a), v), (3)] and Guidelines for Permanent Discontinuation in Nivolumab (Arm C) [Section 7.4.7.3, 7), d)].
Section 2: Schedule of Activities	The footnotes for ± 3 day window for chemotherapy and ECG-specified schedules were moved in Tables 2-2 to 2-5 to the table headings and table notes, respectively.	Clarification.
Appendix 2: Study Governance Considerations	Study governance (Appendix 2) updated 01-Aug-2017.	Clarification.
Appendix 4: Women of Childbearing Potential Definitions and Methods of Contraception	WOCBP guidance (Appendix 4) updated 20-Jul-2017.	Clarification.
All	Minor formatting and typographical corrections	Clarification.

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

The revised protocol [redacted] includes administrative changes outlined in the Administrative Letter 01.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
1: Synopsis; 5.1.2: Treatment Period (Part 1); 5.2: Number of Participants; 10.1: Sample Size Determination	Protocol text was modified in order to clearly specify the sample size of every cohort, and statement "Sample sizes may need to be increased in order to explore differential responses between biomarker expressed and non-expressed groups" removed. The number of subjects will be continuously monitored such that the number of evaluable participants in Part 2 will not exceed 40 per cohort for Cohorts 1 to 6 and 12 per cohort for Cohorts 7 to 9.	Number of patients in each cohort specified in Part 1 and 2. The sample sizes for cohorts in Part 2 are based on the number of evaluable participants needed to support a decision whether or not a treatment is effective using target and historic response rates, while controlling Type 1 error.
1: Synopsis; 5.1.3: Treatment Period (Part 2)	Protocol text was modified to clearly state that the BMS-813160 dose in Part 2 will not exceed the dose and schedule determined to be safe in Part 1.	[redacted]
6.1: Inclusion Criteria, 2), b), *ii*), 2.	Inclusion criteria was modified to require a prior oxaliplatin-containing regimen for all Arm A Cohort 2 ("3L Colorectal") metastatic CRC participants.	Inclusion criteria to ensure that patients received appropriate prior therapy.
6.1: Inclusion Criteria, 2), b), *i*), 3.; 6.1: Inclusion Criteria, 2), b), *ii*), 5.	Inclusion criteria for participants with metastatic CRC on Arm C was updated to require prior therapy with an oxaliplatin-containing regimen and an irinotecan-containing regimen in the metastatic setting or a regimen combining oxaliplatin and irinotecan in the metastatic setting.	Inclusion criteria was modified to ensure that participants received appropriate prior therapy.
6.1: Inclusion Criteria, 2), b), *ii*), 6.	Inclusion criteria for participants with metastatic MSI-H CRC on Arm C was updated to also require prior therapy with an oxaliplatin-containing regimen and an irinotecan-containing regimen in the metastatic setting or a regimen combining oxaliplatin and irinotecan in the metastatic setting.	Inclusion criteria was modified to ensure that participants received appropriate prior therapy.
7.4.1: Dose Limiting Toxicity, 3), a), *v*), (1)	The DLT exception of Grade 4 electrolyte or laboratory abnormalities was removed.	Grade 4 laboratory abnormalities will be considered DLT.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
1: Synopsis; 3.1.3: Rationale for the Chemotherapy Regimens in Arms A and B; 7.1: Treatments Administered	Administration of bevacizumab, cetuximab, or panitumumab is allowed but not required as protocol-specified therapy. The biologic will be administered in accordance with local Health Authority approved labeling for these agents.	Administration of biologics was updated to acknowledge different local standard of care practices.
7.4.1.1: Stopping Rules During Part 2	Section added to describe the safety stopping rules during Part 2 of the study.	Safety stopping rules added for Part 2 of the study.
9.4.4: Clinical Safety Laboratory Assessments	List of clinical laboratory assessments modified to include serum testing for hepatitis C antibody.	List of clinical laboratory assessments updated to align with hepatitis C testing described in exclusion criteria (Section 6.2, e, *ii*).
9.8: Biomarkers	Table 9.8-1 modified to remove PBMC sample collections and align tumor sample collection with the on-treatment procedural outlines for Arms A, B, C, and D.	PBMC sample collections are not needed.
2: Schedule of Activities	Table 2-2 modified to align ECG footnote (b) with the on-treatment procedural outlines for Arms B, C, and D.	Correction of error in Table for Arm A.
All	Minor formatting and typographical corrections	Clarification.