Official Title of Study:

Phase I/II Pharmacokinetic Multi-Tumor Study of Subcutaneous Formulation of Nivolumab Monotherapy

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CLINICAL PROTOCOL CA2098KX

Phase I/II pharmacokinetic multi-tumor study of subcutaneous formulation of nivolumab monotherapy

Protocol Amendment 05

Incorporates Administrative Letter 06

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 05	08-Sep-2021	The primary purpose for the amendment is to [redacted] collect additional pharmacokinetic (PK) samples of nivolumab at steady state in Part E of the study (600 mg subcutaneous (SC) Q2W coformulated with rHuPH20). Exclusion criteria were clarified [redacted]. Updated study personnel.
Administrative Letter 06	26-May-2021	Updated study personnel.
Protocol Amendment 04	02-Apr-2021	Changes were made to the protocol to add a new cohort (Part E) with a 600 mg Q2W regimen of subcutaneous (SC) nivolumab coformulated with recombinant human hyaluronidase PH20 (rHuPH20), administered manually by syringe. Approximately 36 participants with advanced/metastatic tumors, including approximately 10 participants with metastatic urothelial carcinoma (mUC), will be enrolled in Part E. Updated to incorporate modified background information and safety information (including contraceptive requirements) for nivolumab. Aligned dose modification criteria with Common Terminology Criteria for Adverse Events (CTCAE) v5. Included considerations in the context of the coronavirus disease 2019 (COVID-19) pandemic. Updated study personnel.
Revised Protocol 03	25-Oct-2019	Updated to increase participant number in Part D, and to identify the dose of SC nivolumab to be used for Parts C and D.
Administrative Letter 05	06-May-2019	Updating study personnel
Administrative Letter 04	24-Apr-2019	Confirming the **Part B** Cycle 1 dose of 960mg for Group 3 and Group 4
Administrative Letter 03	26-Feb-2019	Updating study personnel

Document	Date of Issue	Summary of Change
Revised Protocol 02	11-Dec-2018	Changes from Administrative Letter 02. Assignment (n = 10) / randomization (n = 20) of participants in Part B after dosing in Part A. Inclusion/Exclusion criteria only assessed during screening visit. Removed requirement for exclusion of participants based on positive urine screen for drugs of abuse. In Part B, other solid tumor types may be considered for enrollment at the discretion of the Medical Monitor. Updated frequency of scans for response/survival follow-up. Timing, method, and type of tumor tissue specimens from biopsy defined, including exceptions for participants who had a biopsy in the preceding 12 months. Added criteria to the following sections takes into account anticipated compromise of baseline liver function in participants with HCC: • Inclusion/exclusion criteria • Criteria for dose delay, dose resumption, and dose discontinuation • Management of hepatic adverse events • Drug-induced liver injury Further characterized the Evaluable PK Participants population and defined what is considered an inadequate PK profile. Removed reference to number of interim analyses to allow for greater flexibility to add additional analyses if necessary. Updated required language for the Appendix 3. Added language for subcutaneous administration of nivolumab alone to Appendix 10. Minor formatting and typographical corrections. Minor clarifications throughout document for consistency across sections.
Administrative Letter 02	15-Oct-2018	The purpose of this letter is to: a) Inclusion of the standard exclusion of any patient who tests positive for hepatitis B or hepatitis C virus indicating presence of virus. b) Notify of New Medical Monitor/Study Director
Revised Protocol 01	05-Jul-2018	Removal of SC nivolumab Process D drug substance from the study. Participants in Part D will receive SC nivolumab + rHuPH20 manually by syringe beginning at Cycle 1. Procedures and inclusion criteria were updated to include assessment of tumor PD-L1 expression measured by IHC prior to treatment and to require results for participants in Part A to be available prior to opening Part B for enrollment. [redacted] Each treatment group [redacted] or prior documented MSI-H/dMMR status (for CRC). Additional biomarker and pharmacodynamic assessments added.
Original Protocol	13-Jun-2018	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 05:

The primary purpose for the amendment is to [redacted] collect additional pharmacokinetic (PK) samples of nivolumab at steady state in Part E of the study (600 mg subcutaneous [SC] Q2W coformulated with recombinant human hyaluronidase PH20 [rHuPH20]). Additionally, exclusion criteria were clarified [redacted], and study personnel were updated.

This amendment incorporates the changes from the approved Administrative Letter 06, which are detailed in the Document History but not listed in the Summary of Key changes below. Other edits were made throughout the protocol to fix minor errors, to add clarity, and for consistency.

Revisions apply to future participants enrolled in the study and, where applicable, to all participants currently enrolled.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated study personnel.	To provide current study personnel.
5.1 Overall Design 9.5.1 Pharmacokinetics and Anti-drug Antibody Sample Collection and Processing	Added additional PK sampling for Part E. [redacted]	[redacted] to include additional PK samples of nivolumab at steady state after multiple doses for adequate steady-state PK characterization of SC nivolumab at 600 mg Q2W.
6.2 Exclusion Criteria	Criterion 1) Medical Conditions, o) was clarified to indicate the criterion is only applicable to first-in-human (Parts A-D) and not applicable for Part E [redacted]	Originally included for first-in-man protocol requirement. However, treatment with nivolumab does not require baseline multigated acquisition (MUGA)/ transthoracic echocardiogram (TTE) based on the well characterized safety profile of nivolumab. Thus, no longer required for Part E.
6.2 Exclusion Criteria	Criterion 1) Medical Conditions, r) eligibility determination was clarified [redacted]	For clarification of decisions regarding eligibility for participants who received the COVID-19 vaccine or who are in a COVID-19 interventional trial.

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: Phase I/II pharmacokinetic multi-tumor study of subcutaneous formulation of nivolumab monotherapy

Study Phase: Phase 1/Phase 2

Rationale: This Phase 1/2 study will characterize the pharmacokinetics (PK), safety, and tolerability of high-concentration subcutaneous (SC) nivolumab (BMS-986298) with or without recombinant human hyaluronidase PH20 (rHuPH20), in participants with tumor types in which the effects on nivolumab clearance are similar.

Parts A-E will evaluate the PK, safety, and tolerability of SC nivolumab (± rHuPH20) in participants with 1 of the following tumor types approved for, or currently being investigated for, treatment with nivolumab monotherapy: non-small cell lung cancer (NSCLC); renal cell carcinoma (RCC); unresectable or metastatic melanoma; hepatocellular carcinoma (HCC); or colorectal cancer (CRC) (microsatellite instability-high [MSI-H] or mismatch repair-deficient [dMMR]). For Part B only, addition of other solid tumors were considered, where nivolumab PK was well characterized and discussed with the Sponsor. In addition to the above tumors, Part E will also include participants with metastatic urothelial carcinoma (mUC).

The initial SC dosing regimen was selected as SC nivolumab (BMS-986298) 720 mg once every 4 weeks (Q4W) based on extrapolated bioavailability models for SC administration of biologics (with and without rHuPH20). Based on extrapolated bioavailability models and preliminary PK from Part A, this study proceeded with a dose of 960 mg Q4W for Part B (Groups 3 & 4).

Revised Protocol 03

PK results from Parts A and B of this study and the breadth of data from population PK analyses with nivolumab IV across the clinical program were used to establish an SC dose of nivolumab with rHuPH20 to be administered every 4 weeks that is expected to provide comparable exposure (Cavgd28) to the IV nivolumab. PK data for SC and IV nivolumab from this study were combined with existing IV nivolumab PK data to identify a dose expected to provide PK exposures that are non-inferior to the initially approved dosing regimen, IV nivolumab 3 mg/kg Q2W.

[redacted]

Protocol Amendment 04

To support characterization of Q2W dosing of SC nivolumab and to provide dosing optionality for participants, 600 mg Q2W coformulated with rHuPH20 will be investigated in Part E. For Parts A-D, SC nivolumab and rHuPH20 were mixed at the site pharmacy (coadministration) prior

to study drug administration. As of Protocol Amendment 04, coformulated drug product (SC nivolumab and rHuPH20 solutions pre-mixed in 1 vial with the same dose ratio) will be introduced for Part E. In addition, all ongoing participants in Parts C & D may switch to the coformulated drug product.

In Part E, approximately 36 participants in total will be enrolled. In addition to participants with the tumor types described for Parts A-D, approximately 10 participants with mUC will be included. The clinical benefit of IV nivolumab has been demonstrated in mUC, and Part E will provide preliminary PK data for SC nivolumab in this tumor type.

Study Population:

The study population will include participants with 1 of the following advanced or metastatic tumors approved for treatment with nivolumab monotherapy: non-small cell lung cancer (NSCLC); renal cell carcinoma (RCC); unresectable or metastatic melanoma; hepatocellular carcinoma (HCC); microsatellite instability-high or mismatch repair-deficient colorectal cancer (MSI-H/dMMR CRC); or metastatic urothelial carcinoma (mUC [Part E only]).

Objectives and Endpoints:

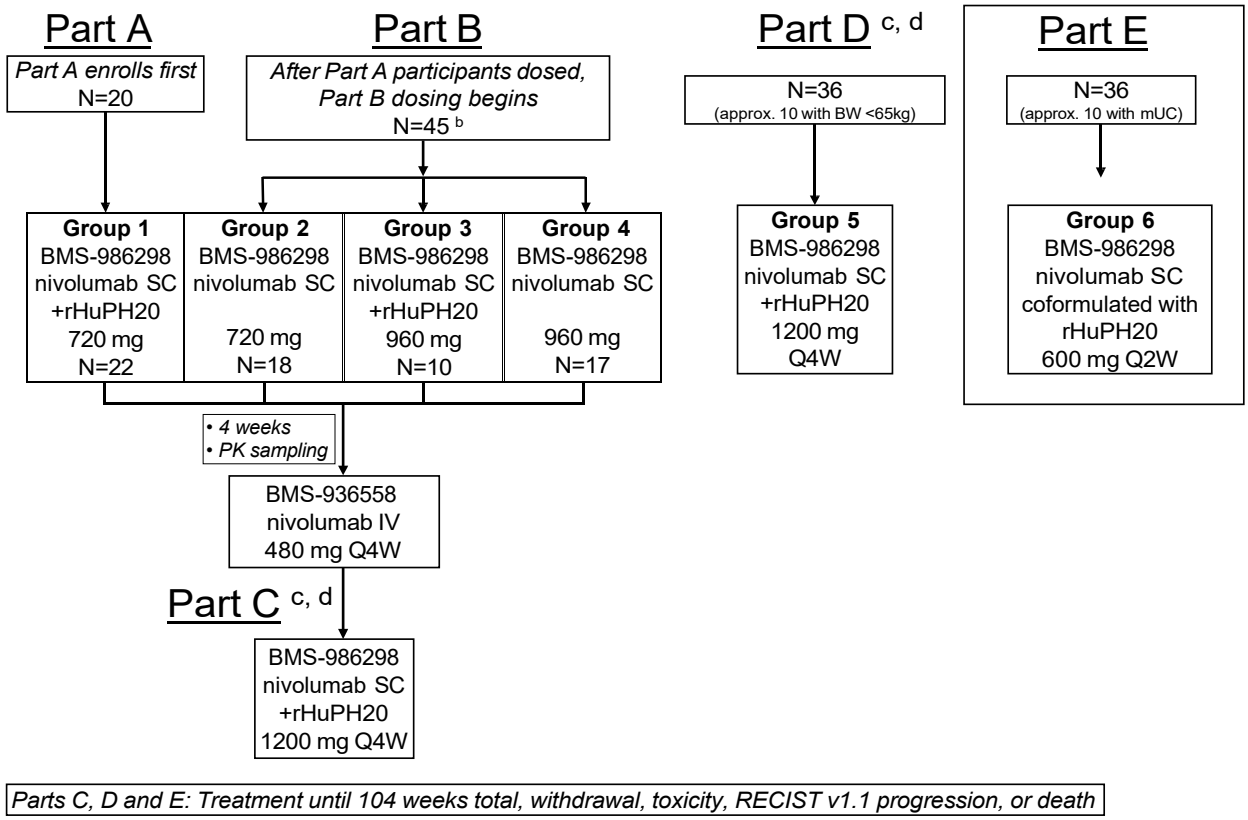
Objectives	Endpoints
Primary Parts A- D: To describe the pharmacokinetics of nivolumab administered subcutaneously, with or without rHuPH20 Part E: To evaluate the pharmacokinetics of SC nivolumab 600 mg Q2W coformulated with rHuPH20	• Serum nivolumab Parts A, B, D, and E: – Cmax – Tmax – AUC(TAU) – Ctau • Serum nivolumab Part C: – Ctrough
Secondary To assess the safety profile of SC nivolumab.	• Incidences of AEs, TRAEs, SAEs, TRSAEs, AEs/TRAEs leading to discontinuation, deaths, and laboratory abnormalities.
To evaluate incidence of AEs in the broad standardized MedDRA query (SMQ) of Anaphylactic Reaction and the select AE hypersensitivity/infusion reaction category.	• Incidence of AEs in the broad SMQ of Anaphylactic Reaction occurring within 2 days after study drug administration • Incidence of events within the hypersensitivity/infusion reaction select AE category occurring within 2 days after study drug administration.
To assess the immunogenicity of nivolumab	• Incidence of anti-nivolumab antibodies and neutralizing antibodies, if applicable
Exploratory To evaluate preliminary efficacy in all participants	• ORR, PFS, and OS
To characterize biomarker measures [redacted]	• Including, but not limited to: summary measures of change (or % change) from baseline in various biomarkers and molecular characteristics of the tumor (Parts A-D, and based on tissue availability for Part E)/blood
To assess the immunogenicity of rHuPH20	• Incidence of anti-rHuPH20 antibodies and neutralizing antibodies, if applicable
To assess the preliminary participant experience and preference for SC or IV administration of nivolumab.	• Patient experience and preference questionnaire • Qualitative Patient Interviews

Abbreviations: AE = adverse event; AUC(TAU) = area under the concentration-time curve over the dosing interval; Cmax = maximum observed serum nivolumab concentration; Ctau = observed serum nivolumab concentration at the end of the dosing interval; Ctrough = trough observed serum nivolumab concentration; IV = intravenous; MedDRA = Medical Dictionary for Regulatory Activities; ORR= objective response rate; OS = overall survival; PFS = progression-free survival; Q2W = every 2 weeks; rHuPH20 = recombinant human hyaluronidase PH20; SAE = serious adverse event; SC = subcutaneous; SMQ = standardized MedDRA queries; TRAE = treatment-related adverse event; TRSAE = treatment-related serious adverse event.

Overall Design:

Study CA2098KX is a multicenter, randomized, open-label, multi-tumor Phase 1/2 study that will evaluate the PK, safety, and tolerability of nivolumab administered subcutaneously with and without rHuPH20 in participants with 1 of the following advanced or metastatic tumor types: non-small cell lung cancer (NSCLC); renal cell carcinoma (RCC); unresectable or metastatic melanoma; hepatocellular carcinoma (HCC); or colorectal cancer (CRC) (microsatellite instability-high [MSI-H] or mismatch repair deficient [dMMR]). For Part B only, addition of other solid tumors were considered, where nivolumab PK was well characterized and discussed with the Sponsor. In addition to the above tumors, Part E will also include participants with metastatic urothelial carcinoma (mUC). The study is divided into the following periods: a Screening period; a Treatment period consisting of Part A, Part B, Part C, Part D, and Part E; and a Safety Follow-up period.

Figure 1: CA2098KX Study Schematic[a]



Abbreviations: BW = body weight; IV = intravenous; PK = pharmacokinetic; Q4W = every 4 weeks; mUC = metastatic urothelial carcinoma; rHuPH20 = recombinant human hyaluronidase PH20; Q2W = every 2 weeks; Q4W = every 4 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SC = subcutaneous.

[a] Schema represent the actual numbers of participants enrolled for Parts A, B, and D.

[b] Actual enrollment: The first 10 participants were assigned to Group 3. The next 35 participants were randomized 1:1 into Group 2 (n=18) and Group 4 (n=17).

[c] Crossover into Part C and dosing in Part D (Group 5) will begin after the SC nivolumab (BMS-986298) dosing regimen is identified from analysis of PK data from Parts A & B. At the time of Protocol Amendment 04, enrollment for Part D has completed and actual enrollment was 36 participants.
Note: Group 2 and Group 4 will receive SC nivolumab (BMS-986298) by syringe pump without rHuPH20.

[d] Any ongoing participants on SC nivolumab + rHuPH20 treatment may switch over to nivolumab coformulated with rHuPH20 drug product.

Number of Participants:

Approximately 139 total participants will receive study treatment as follows (also see study design schematic in Figure 1).

- In Part A, 22 participants received 720 mg SC nivolumab (BMS-986298) manually by syringe with rHuPH20.
- In Part B, 45 participants were dosed. The first 10 participants were assigned to Group 3. The next 35 participants were randomized 1:1 into Group 2 (n=18) and Group 4 (n=17).
- In Part D, approximately 36 participants (approximately 10 with baseline BW < 65 kg) will receive nivolumab (BMS-986298) 1200 mg with rHuPH20 administered SC manually by syringe every 4 weeks.
- In Part E, approximately 36 participants, including approximately 10 participants with mUC, will receive nivolumab (BMS-986298) 600 mg coformulated with rHuPH20 administered SC manually by syringe every 2 weeks.

Additional participants may have been assigned/randomized to study treatment for each participant who was unable to complete one of the following:

- Planned Cycle 1 (SC study treatment) and/or Cycle 2 (IV nivolumab) treatments and PK sampling in Part A
- Planned Cycle 1 (SC study treatment) and/or Cycle 2 (IV nivolumab) treatments and PK sampling in Part B
- Planned Cycle 1 and/or Cycle 2 treatments and PK sampling in Part D

For Part E, additional participants may be assigned for each participant who was unable to complete the first dose and up to [redacted] of PK sampling.

Each treatment group in Part A, Part B, and Part D [redacted] by IHC or with MSI-H/dMMR (for CRC). For Part E, tissue PD-L1 assessment is optional.

Randomization - where applicable - will not be stratified by tumor type or by any demographic or disease characteristic.

Treatment Arms and Duration:

Approximately 139 total participants with any of included advanced or metastatic tumor types will receive study treatment as follows:

- **Part A/B:**
  - **Part A**
    - Group 1: Single dose of nivolumab (BMS-986298) 720 mg administered SC with rHuPH20 manually by syringe (n=22)

  - **Part B** After participants are dosed in Part A, 45 participants were dosed in Part B. The first 10 participants were assigned to Group 3. The next 35 participants were randomized 1:1 into Group 2 (n=18) and Group 4 (n=17):
    - Group 2: Single dose of nivolumab (BMS-986298) 720 mg administered SC without rHuPH20 by syringe pump
    - Group 3: Single dose of nivolumab (BMS-986298) 960 mg administered SC with rHuPH20 manually by syringe
    - Group 4: Single dose of nivolumab (BMS-986298) 960 mg administered SC without rHuPH20 by syringe pump
  - Four (4) weeks after the single SC nivolumab (BMS-986298) dose, all participants in Part A and Part B received IV nivolumab (BMS-936558) 480 mg Q4W dosing until Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 progression, unacceptable toxicity, withdrawal of consent, completion of 104 weeks of treatment, cross over to SC nivolumab dosing in Part C, or study termination by the Sponsor, whichever occurs first.
- **Part C:** Participants in Part A and Part B will cross over from nivolumab (BMS-936558) IV dosing (four [4] weeks after last IV dose) to nivolumab (BMS-986298) 1200 mg administered SC with rHuPH20 manually by syringe every 4 weeks.
- **Part D** (Approximately 36; of which approximately 10 with baseline BW < 65 kg): On Day 1 of each treatment cycle, SC nivolumab (BMS-986298) 1200 mg administered SC with rHuPH20 manually by syringe every 4 weeks.
- **Part E** (Approximately 36; of which approximately 10 with mUC): nivolumab (BMS-986298) 600 mg coformulated with rHuPH20 administered SC manually by syringe every 2 weeks.

For Parts A-D, SC nivolumab and rHuPH20 were mixed at the site pharmacy (coadministration) prior to study drug administration. As of Protocol Amendment 04, coformulated drug product (SC nivolumab and rHuPH20 solutions pre-mixed in 1 vial with the same dose ratio) will be introduced for Part E. In addition, all ongoing participants in Parts C & D may switch to the coformulated drug product.

Parts A, B and D: Each treatment group in Part A, Part B, and Part D [redacted] by IHC or with MSI-H/dMMR (for CRC).

Part E: Tissue PD-L1 assessment is optional.

Doses for Part B (Group 3 & 4) were adjusted based on PK and safety information from Part A to be 960 mg Q4W and confirmed by an administrative letter to the investigators.

Parts A & B: Four weeks after the SC dose of study treatment (ie, Study Day 29), participants received 480 mg IV nivolumab (BMS-936558) Q4W until Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 progression, unacceptable toxicity, withdrawal of consent, completion of 104 weeks of treatment, cross over to SC nivolumab dosing in Part C, or study termination by the Sponsor, whichever occurs first. For each participant who was unable to complete the planned Cycle 1 (SC study treatment) and Cycle 2 (IV nivolumab) treatments and PK sampling, an additional participant was assigned.

Parts C & D: An outline of the considerations for Part C and Part D dose selection is presented in Section 10.3.8 (Interim Analyses).

Part E: The dose in Part E is 600 mg SC nivolumab coformulated with rHuPH20 Q2W. [redacted] For each participant who is unable to complete the planned study treatments and PK sampling following the first dose, an additional participant may be assigned via interactive response technology (IRT).

Dosing in the study will continue until RECIST v.1.1 progression, unacceptable toxicity, withdrawal of consent, completion of 104 weeks of total treatment, or study termination by the Sponsor, whichever occurs first.

Study Treatment:

Study Drug for CA2098KX		
Medication	**Potency**	**IP/Non-IP**
Nivolumab (BMS-986298) Solution for SC Injection	960 mg (120 mg/mL)	IP
Nivolumab and rHuPH20 (BMS-986298) Solution for SC Injection	600 mg ([redacted] mg/mL) and [redacted] units (2000 units/mL)	IP
Nivolumab (BMS-936558-01) Solution for IV Injection	100 mg (10 mg/mL) and 40 mg (10 mg/mL)	IP
[redacted] Drug Product (rHuPH20)[a]	[redacted] Units/mL ([redacted] mg/mL)	IP[b]

Abbreviations: EU = European Union; IP = investigational product; IV = intravenous; rHuPH20 = recombinant human hyaluronidase PH20; SC = subcutaneous; US = United States.

[a] [redacted] is a formulation containing the enzyme rHuPH20 and is referred as rHuPH20 in the protocol.

[b] rHuPH20 is classified as an IP per local guidelines (as an active ingredient in the US, and as an excipient in the EU).

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA2098KX) - Parts A-D

Procedure	Screening Visit	Notes Screening assessments must be performed within 28 days prior to the first dose in the study.
Eligibility Assessments		
Informed Consent	X	A participant is considered enrolled only when a protocol-specific informed consent is signed.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed and confirmed prior to first dose. See Sections 6.1 and 6.2.
Medical History	X	Include any toxicities or allergy related to previous treatments including prior anticancer/radiotherapy, smoking history (including electronic cigarettes), and alcohol history.
ECOG	X	Within 14 days prior to first dose. See Appendix 7.
Register participant in IRT	X	IRT contact must occur for IVRS participant number assignment at the time when informed consent is obtained.
Microsatellite instability and mismatch repair status	X	Confirm documentation of prior local testing (high microsatellite instability [MSI-H] and/or mismatch repair deficient [dMMR]) for participants with colorectal cancer (CRC).
Tumor Tissue Sample	X	Sufficient tumor tissue obtained up to 12 months prior to first study treatment in the metastatic setting or from an unresectable site (block [redacted] is requested, obtained from core needle biopsy, excisional, or incisional biopsy). For fresh samples, the tumor should be amenable to biopsy and the 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. Participants should not have received any systemic anticancer therapy after the date that the submitted tumor tissue was obtained. Up to 5 participants from each part of the trial (part A & B) and approximately 15 participants in Part D, who do not meet tissue requirements may be allowed treatment after discussion with the Medical Monitor. [redacted] Assessment of tumor-cell PD-L1 expression by IHC must be performed centrally using pre-treatment tissue sample. [redacted] must be collected for all participants in Part A prior to initiation of Part B. For participants with CRC, assessment of tumor PD-L1 expression is not required, since documentation of MSI-H/dMMR status is required.

Table 2-1: Screening Procedural Outline (CA2098KX) - Parts A-D

Procedure	Screening Visit	Notes Screening assessments must be performed within 28 days prior to the first dose in the study.
Safety Assessments		
Assessment of Signs and Symptoms	X	After obtaining informed consent, assess all signs and symptoms within 14 days prior to first dose.
Physical Examination (PE)	X	Within 14 days of first dose. If the screening PE is performed within 24 hours prior to dosing on Day 1 then a single examination may count as both the screening and predose evaluation.
Physical Measurements	X	Within 14 days of first dose. Include height and weight.
Vital Signs	X	Includes body temperature, respiratory rate, and seated BP and HR. BP and HR should be measured after participant has been resting quietly for ≥5 minutes. Consider alternate position(s) for vital sign collection.
Pulse Oximetry	X	Oxygen saturation at rest. Perform within 14 days prior to first dose.
Concomitant Medication Use	X	Within 14 days of first dose
Electrocardiogram (ECG)	X	12-lead ECGs should be recorded after the participant has been supine for at least 5 minutes.
Serious Adverse Event (SAE)	X	Serious adverse event collection from signing of informed consent.
Laboratory Tests		
Serology	X	See Section 9.4.4.
Hematology	X	To be performed locally within 14 days prior to first dose. See Section 9.4.4.
Liver Function Tests	X	To be performed locally within 14 days prior to first dose. See Section 9.4.4
Chemistry	X	To be performed locally within 14 days prior to first dose. See Section 9.4.4.
Thyroid Function Test	X	To be performed locally within 14 days prior to first dose. TSH with free triiodothyronine (T3) and free thyroxine (T4), or equivalent. See Section 9.4.4.
Coagulation Panel	X	For participants with HCC only: prothrombin time (PT)/international normalized ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen. To be performed locally within 14 days prior to first dose. If screening labs are drawn within 4 days of first treatment then these will also qualify as Day 1 (pre-dose).
Pregnancy Test	X	For WOCBP only. Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done at screening visit and within 24 hours prior to first dose. See Section 9.4.4.

Table 2-1: Screening Procedural Outline (CA2098KX) - Parts A-D

Procedure	Screening Visit	Notes Screening assessments must be performed within 28 days prior to the first dose in the study.
Efficacy Assessments		
Body Imaging	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. See Section 9.1.1.1.
Brain Imaging	X	MRI of the brain without and with contrast is required for participants with known or suspected brain metastases, unless participant has completed an imaging study of the brain within 30 days of study drug administration. CT of the brain without and with contrast can be performed if MRI is contraindicated.
Disease Assessments	X	For participants with HCC only: serum alpha fetoprotein (AFP)

Abbreviations: AFP = alpha fetoprotein; aPTT = activated partial thromboplastin time; BP = blood pressure; CRC = colorectal cancer; CT = computed tomography; dMMR = mismatch repair deficient; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HCC = hepatocellular carcinoma; HCG = human chorionic gonadotropin; HR = heart rate; IHC = immunohistochemistry; INR = international normalized ratio; IRT = Interactive Response Technology; MRI = magnetic resonance imaging; MSI-H = high microsatellite instability; PD-L1 = programmed death ligand 1; PE = physical examination; PT = prothrombin time; SAE = serious adverse event; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; WOCBP = women of childbearing potential.

Table 2-2: Screening Procedural Outline (CA2098KX) - Part E

Procedure	Screening Visit	Notes[a] Screening assessments must be performed within 28 days prior to the first dose in the study.
Eligibility Assessments		
Informed Consent	X	Must be obtained prior to performing any screening procedures. Study allows for re-enrollment of a participant that has discontinued the study as a pre-treatment failure. If re-enrolled, the participant must be re-consented and assigned a new participant number from IRT.
Inclusion/Exclusion Criteria	X	Must be confirmed prior to the first dose of study drug.
Medical History	X	All medical history relevant to the disease under study.
Contact IRT	X	Register in Interactive Response system to obtain participant number.
Microsatellite instability and mismatch repair status	X	Confirm documentation of prior local testing (high microsatellite instability [MSI-H] and/or mismatch repair deficient [dMMR]) for participants with colorectal cancer (CRC).
Tumor Sample Submission	See Notes	Tumor tissue sample submission is highly recommended, but optional for participants in Part E. For all participants in Part E, including mUC participants, submission of an archival FFPE tissue block (preferred) or unstained slides of tumor tissue from core biopsy, excisional biopsy, or surgical specimen obtained within 12 months of enrollment is highly recommended. For fresh samples, the tumor should be amenable to biopsy and the 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. Fine needle aspirates or other cytology samples are not acceptable. Tumor PD-L1 expression by IHC is an optional assessment for participants in Part E. [redacted] Please refer to Section 9.8 for additional information.
Baseline Tumor Assessment	X	Must be performed within 28 days prior to the first dose of study drug. Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease. See Section 9.1.1.1. MRI of the brain without and with contrast is required for participants with known or suspected brain metastases, unless participant has completed an imaging study of the brain within 28 days of study drug administration. CT of the brain (with and without contrast) can be performed if MRI is contraindicated. See Section 9.1.1.1.
Disease Assessments	X	For participants with HCC only: serum alpha fetoprotein (AFP)

Table 2-2: Screening Procedural Outline (CA2098KX) - Part E

Procedure	Screening Visit	Notes[a] Screening assessments must be performed within 28 days prior to the first dose in the study.
Safety Assessments		
Assessment of Signs and Symptoms	X	Within 14 days prior to the first dose of study drug.
Physical Examination, Measurements, Vital Signs, and Performance Status	X	Height, weight, performance status (Appendix 7), BP, HR, temperature and oxygen saturation by pulse oximetry at screening only. Must be collected within 14 days prior to the first dose of study drug.
Concomitant Medication Collection	X	Within 14 days prior to the first dose of study drug. Vaccine use within 30 days prior to first study treatment. See Section 6.2.
Electrocardiogram (ECG)	X	At rest. Within 14 days prior to the first dose of study drug.
Serious Adverse Event (SAE)	X	Serious adverse event collected from signing of informed consent. COVID-19 or positive SARS-CoV-2 test results should be reported to BMS within 24 hours regardless of the seriousness criteria. All AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infection collected from time of consent. See Section 9.2.1.
Laboratory Tests		
Clinical Laboratory Assessments	X	On-site/local laboratory tests must be performed within 14 days prior to the first dose of study drug. Viral testing to be completed within 28 days prior to the first dose of study drug. For HIV: testing at sites where locally mandated; see Appendix 8. Refer to Section 9.4.4 for list of laboratory tests to conduct.

Table 2-2: Screening Procedural Outline (CA2098KX) - Part E

Procedure	Screening Visit	Notes[a] Screening assessments must be performed within 28 days prior to the first dose in the study.
Coagulation Panel	X	For participants with HCC only: prothrombin time (PT)/international normalized ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen. To be performed locally within 14 days prior to first dose. If screening labs are drawn within 4 days of first treatment then these will also qualify as Day 1 (pre-dose).
Pregnancy Test (Women of Childbearing Potential [WOCBP] Only)	X	Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done at screening visit and repeated within 24 hours prior to first dose of study treatment. See Section 9.4.4.

Abbreviations: AE = adverse event; AFP = alpha fetoprotein; aPTT = activated partial thromboplastin time; BMS = Bristol-Myers Squibb; BP = blood pressure; COVID-19 = coronavirus disease 2019; CRC = colorectal cancer; CRF = case report form; CT = computed tomography; dMMR = mismatch repair deficient; ECG = electrocardiogram; FFPE = formalin-fixed paraffin-embedded; HCC = hepatocellular carcinoma; HCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; HR = heart rate; IHC = immunohistochemistry; INR = international normalized ratio; IRT = Interactive Response Technology; MRI = magnetic resonance imaging; MSI-H = high microsatellite instability; PD-L1 = programmed death ligand 1; PT = prothrombin time; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

[a] Some of the assessments referred to in this section may not be captured as data in the CRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations and should be documented in the patient's source notes.

Table 2-3: On-treatment Procedural Outline (CA2098KX) - Parts A-E

Procedure	Parts A-D: Day 1 of each treatment cycle (Cycle = 28 days) Part E: [redacted] of each treatment cycle [a] (Cycle = 28 days)	Timepoints Relative to Dosing Schedule	Notes[b]
Randomization			
Randomization (Part B, Group 2 and 4)	X		Once participant eligibility has been confirmed, randomization can be performed.
Eligibility Assessments			
ECOG Performance Status	X		Predose (Appendix 7)
Safety Assessments			
Physical Examination	X		Predose
Physical Measurements	X		Predose. Weight only
Vital Signs	X		Predose.
Pulse Oximetry	X		Predose. Oxygen saturation at rest.
Child-Pugh Score	X		Participants with HCC only. Predose. See Appendix 9.
Concomitant Medication Assessment	Continuously		Review prior to each dosing.

Table 2-3: On-treatment Procedural Outline (CA2098KX) - Parts A-E

Procedure	Parts A-D: Day 1 of each treatment cycle (Cycle = 28 days) Part E: [redacted] of each treatment cycle [a] (Cycle = 28 days)	Timepoints Relative to Dosing Schedule	Notes[b]
Adverse Event Assessment and Serious Adverse Events (SAE)	Continuously assessed using NCI CTCAE v.5		Non-serious AEs will be collected starting with the first dose of the study drug and through 100 days after discontinuation of dosing. All SAEs must be collected which occur within 100 days of discontinuation of dosing or completion of the participant's participation in the study if the last scheduled visit occurs at a later time, except in cases where a study participant has started a new anti-neoplastic therapy. However, any SAE occurring after the start of a new treatment that is suspected to be related to study treatment by the investigator will be reported. See Section 9.2. All AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, the condition stabilizes, or is deemed irreversible, or until the participant is lost to follow-up (as defined in Section 8.3). For suspected cases, participants should be followed until SARS-CoV-2 infection is ruled out as per institutional policy on SARS-CoV-2. COVID-19 or positive SARS-CoV-2 test results should be reported to BMS within 24 hours regardless of the seriousness criteria.
Assessment of post-SC injection reaction		X	**Parts A-D:** Perform on Day 2 of each cycle of SC treatment. **Part E:** Participants are contacted approximately 24 hours after the first 2 SC manual injections for reporting of any injection-site reactions. See Section 9.4.7.

Table 2-3: On-treatment Procedural Outline (CA2098KX) - Parts A-E

Procedure	Parts A-D: Day 1 of each treatment cycle (Cycle = 28 days) Part E: [redacted] of each treatment cycle [a] (Cycle = 28 days)	Timepoints Relative to Dosing Schedule	Notes[b]
Laboratory Tests			**Parts A-D** Cycle 1 and Cycle 2: The laboratory tests may be performed within 48 hours prior to the first and second doses in the study. Cycle 3 and beyond: The laboratory tests may be performed within 72 hours prior to dosing. Pregnancy testing must be performed within 24 hours prior to dosing. **Part E** Perform on site/local laboratory testing within 72 hours prior to each dose. For the first treatment visit, labs need not be repeated if they were performed within 72 hours and the results are available and have been reviewed for eligibility. Refer to Section 9.4.4 for the list of laboratory tests to be conducted.
Chemistry Complete Blood Count with Differential and Platelets Thyroid Function Tests	X		Predose. See Section 9.4.4.
Coagulation panel	X		For participants with HCC only. Within 72 hours of dosing. Including PT/INR, aPTT, and fibrinogen.
Pregnancy Test (WOCBP only)		X	Serum or urine (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG) within 24 hours prior to administration of first dose of study treatment and then every 4 weeks (± 7 days) regardless of dosing schedule.

Table 2-3: On-treatment Procedural Outline (CA2098KX) - Parts A-E

Procedure	Parts A-D: Day 1 of each treatment cycle (Cycle = 28 days) Part E: [redacted] of each treatment cycle [a] (Cycle = 28 days)	Timepoints Relative to Dosing Schedule	Notes[b]
Pharmacokinetic and Immunogenicity Assessments			
PK and Immunogenicity Blood Sampling	[redacted]		
Biomarker Assessments			
Exploratory Biomarker Assessments	See Section 9.8 and sampling schedule in Table 9.8-1 and Table 9.8-2.		
Additional Research Sampling	See Section 9.8.4 and Table 9.8.4-1.		
[redacted]			

Table 2-3: On-treatment Procedural Outline (CA2098KX) - Parts A-E

Procedure	Parts A-D: Day 1 of each treatment cycle (Cycle = 28 days) Part E: [redacted] of each treatment cycle [a] (Cycle = 28 days)	Timepoints Relative to Dosing Schedule	Notes[b]
Efficacy Assessments			
Body Imaging		X	Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should first occur at Week 12 (±7 days) starting from first dose date. Imaging should then occur every 8 weeks (±7 days) before the subsequent dose (namely within 7 days of dosing on Day 22 in treatment Cycles 5, 7, 9, etc.) until investigator-assessed disease progression or treatment discontinuation (including treatment beyond progression), whichever occurs later. See Section 9.1.1.1 for further details.
Brain Imaging		X	Participants with a history of brain metastasis should have a surveillance MRI approximately every 12 weeks, or sooner if clinically indicated.
Disease assessment - AFP	X		Participants with HCC only.
Clinical Drug Supplies			
Study Drug Administration	X **Part A/B:** Day 1 Cycle 1: SC dose Day 1 Cycle ≥2: IV dosing **Part C:** Day 1 of each cycle: SC dosing manually by syringe **Part D:** Day 1 of each cycle: SC dosing manually by syringe		The first dose must be administered within 3 calendar days following treatment assignment/randomization.[c] For Parts A-D, drug administration must occur on Day 1 of Cycle 1 and Cycle 2. For Cycle 3 and beyond, drug administration is ±3 days but no less than 21 days from the previous dose. Study drug infusion start and stop times will be recorded for SC and IV administration. **Part A and Part B** All assigned/randomized participants receive SC nivolumab (BMS-986298) on Cycle 1 Day 1. On Day 1 of Cycle 2 and each cycle thereafter, all participants in treatment Groups 1, 2, 3, and 4 receive IV nivolumab (BMS-936558) every 4 weeks (Q4W).

Table 2-3: On-treatment Procedural Outline (CA2098KX) - Parts A-E

Procedure	Parts A-D: Day 1 of each treatment cycle (Cycle = 28 days) Part E: [redacted] of each treatment cycle [a] (Cycle = 28 days)	Timepoints Relative to Dosing Schedule	Notes[b]
	Part E: [redacted] of each cycle: SC dosing manually by syringe		**Part C** Upon approval of revised protocol 03, Participants in Part A and Part B will cross over to Part C to receive 1200 mg SC nivolumab (BMS-986298) with rHuPH20 manually by syringe on Day 1 of each treatment cycle. **Part D** All assigned participants in Group 5 receive SC nivolumab (BMS-986298) with rHuPH20 manually by syringe on Day 1 of each cycle. **Part E** All assigned participants in Group 6 receive 600 mg SC nivolumab (BMS-986298) coformulated with rHuPH20 manually by syringe on [redacted] of each cycle. For Part E, participants may be dosed [redacted] from the previous dose. All participants in the study will be treated for a maximum of 104 weeks total (nivolumab IV or/and SC) or until confirmed progression, unacceptable toxicity, withdrawal of informed consent, or discontinuation of the study by the Sponsor. Treatment for all participants can continue beyond initial investigator-assessed progression until a maximum of 104 weeks total (nivolumab IV or/and SC) (see Section 8.1.2).

Table 2-3: On-treatment Procedural Outline (CA2098KX) - Parts A-E

Procedure	Parts A-D: Day 1 of each treatment cycle (Cycle = 28 days) Part E: [redacted] of each treatment cycle [a] (Cycle = 28 days)	Timepoints Relative to Dosing Schedule	Notes[b]
Outcomes Research Assessments			
Patient Experience and Preference Questionnaire	See Section 9.10.1 for further details.		
Qualitative Patient Interviews	See Section 9.10.2 for further details.		

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; BMS = Bristol-Myers Squibb; COVID-19 = coronavirus disease 2019; CRF = case report form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; HCC = hepatocellular carcinoma; HCG = human chorionic gonadotropin; IgG = immunoglobulin G; INR = international normalized ratio; IV = intravenous; MRI = magnetic resonance imaging; NCI CTCAE v.5 = National Cancer Institute Common Terminology Criteria for Adverse Events version 5; PT = prothrombin time; Q4W = every 4 weeks; rHuPH20 = recombinant human hyaluronidase PH20; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus disease 2; SC = subcutaneous; WOCBP = women of childbearing potential.

[a] If a dose is delayed, the procedures schedule for that same time point must also be delayed to coincide with when that time point's dosing actually occurs, with the exception of tumor assessments which must occur as scheduled.

[b] Some of the assessments referred to in this section may not be captured as data in the CRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations and should be documented in the patient's source notes.

[c] Randomization/treatment assignment = randomization (Part B Groups 2, 4) /treatment assignment (Part A, Part B Group 3, Parts C, D, and E).

Table 2-4: Safety Follow Up Procedural Outline (CA2098KX) - Parts A-E

Procedure	Follow-up Visit 1 and Visit 2	Survival Follow-up	Notes[a] **Follow-up Visit 1 = 30 days from last dose ±7 days, or may be on date of discontinuation if the date of discontinuation is more than 30 days after last dose.** **Follow-up Visit 2 = approximately 100 days (± 7 days) from last dose.**
Targeted Physical Examination	X		Weight, BP, HR, temperature, ECOG performance status
Vital Signs	X		See note in screening procedures.
Serious and Non-serious Adverse Event Assessment	X	X*	*Beyond 100 days from the last dose of study therapy, participants will be followed for drug-related AEs until AE resolves, returns to baseline, or is deemed irreversible, or until the participant is lost to follow-up or withdraws study consent. All AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, the condition stabilizes, or is deemed irreversible, or until the participant is lost to follow-up (as defined in Section 8.3). For suspected cases, participants should be followed until SARS-CoV-2 infection is ruled out as per institutional policy on SARS-CoV-2. COVID-19 or positive SARS-CoV-2 test results should be reported to BMS within 24 hours regardless of the seriousness criteria.
Laboratory Tests	X		To be performed at Follow-up Visit 1, repeat at Follow-up Visit 2 if study drug-related toxicity persists. See Section 9.4.4.
Review of Concomitant Medications	X		
Subsequent Cancer Therapy	X	X	Include documentation of subsequent cancer therapy (ie, systemic therapy, tumor-directed surgery, or radiation therapy).
Pregnancy Test	X		Serum or urine

Table 2-4: Safety Follow Up Procedural Outline (CA2098KX) - Parts A-E

Body Imaging	X	X	Participants who discontinue treatment for reasons other than tumor progression should continue to have tumor assessments: contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 12 weeks (±1 week) until investigator-assessed disease progression or withdrawal of consent, whichever occurs first. Radiographic assessments should not be delayed until follow-up Visit 1 or Visit 2. See Section 9.1.1.1 for further details on imaging assessments.
Brain Imaging	X	X	Participants with a history of brain metastasis or symptoms should have surveillance MRIs per standard of care (approximately every 12 weeks) or sooner if clinically indicated.
Collection of Survival Information		X	Every 3 months (± 14 days) from Follow-up Visit 2 until death, lost to follow-up, or withdrawal of study consent for up to 5 years following start of therapy. May be performed by phone contact or office visit. BMS may request that survival data be collected on all treated participants outside of the 3-month specified window. At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact.
PK and Immunogenicity Blood Sampling	X		[redacted]
Biomarker Assessment			
[redacted]			

Abbreviations: AE = adverse event; BMS = Bristol-Myers Squibb; BP = blood pressure; CRF = case report form; COVID-19 = coronavirus disease 2019; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; HR = heart rate; MRI = magnetic resonance imaging; PK = pharmacokinetics; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] Some of the assessments referred to in this section may not be captured as data in the CRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulation and should be documented in the patient's source notes.

3 INTRODUCTION

In the last decade, there have been accelerated advances in our understanding of the role of the immune system and interplay with diseases, such as cancer. Research with agents that modulate the immune system, such as nivolumab, has transformed cancer therapeutics with notable clinical benefit observed across several tumors. Nivolumab has demonstrated durable responses as monotherapy and in combination with ipilimumab in several tumor types, including NSCLC, melanoma, RCC, cHL, SCLC, gastric cancer, SCCHN, urothelial cancer, HCC, and CRC. In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in participants with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or recurrent or metastatic SCCHN. Nivolumab in combination with ipilimumab improved progression-free survival (PFS) and objective response rate (ORR) over ipilimumab alone in participants with unresectable or metastatic melanoma.

Research with this pillar of therapy known as immuno-oncology (IO), of which nivolumab belongs to, continues with combination approaches and movement into earlier lines of therapy in tumors where nivolumab has been established. Due to this evolution with nivolumab and the treatment paradigm with IO, Bristol-Myers Squibb (BMS) is committed to improve the conditions for use of nivolumab, to meet the needs of patients, caregivers and health care practitioners (HCPs).

Currently, nivolumab treatment as monotherapy or in combination with ipilimumab is administered via intravenous (IV) infusion over 30 to 60 minutes. As an alternative to IV infusion, BMS is evaluating SC administration of a high-concentration nivolumab with or without rHuPH20, a recombinant human hyaluronidase PH20 enzyme. The addition of rHuPH20 to nivolumab is to enhance permeation of high-volume fluids and allows for reduced administration times of less than five minutes.

SC dosing incorporating a flat dose of a biologic drug product provides several potential advantages to HCPs that include reducing dosing errors; decreasing the time needed for dose preparation and administration; and alleviating IV infusion center occupancy. For the patient, this could also improve the drug administration experience by shortening injection time, and alleviating the need for IV infusion port (particularly if nivolumab is given as monotherapy or in combination with oral or SC drug regimens). Given the broadening use of nivolumab across various tumors, as monotherapy and in combination with other therapeutic agents, a quick subcutaneous injection has the potential to improve conditions for administering HCPs, caregivers and ultimately the patients. Additionally, the coronavirus disease 2019 (COVID-19) pandemic has caused significant disruptions to delivery of cancer care, with dose delays and discontinuation and a negative impact on patient quality of life.[1] This disruption has heightened the criticality of providing alternative routes of cancer treatment, such as oral or SC delivery, as options for patients and providers.

3.1 Study Rationale

This Phase 1/2 study will characterize the PK, safety, and tolerability of high–concentration SC nivolumab (BMS-986298) with or without recombinant human hyaluronidase PH20 (rHuPH20), in participants with tumor types in which the effects on nivolumab clearance are similar.

Parts A-E will evaluate the PK (pharmacokinetics), safety, and tolerability of SC nivolumab (± rHuPH20) in participants with 1 of the following tumor types approved for, or currently being investigated for, treatment with nivolumab monotherapy : non-small cell lung cancer (NSCLC); renal cell carcinoma (RCC); unresectable or metastatic melanoma; hepatocellular carcinoma (HCC); or colorectal cancer (CRC) (microsatellite instability-high [MSI-H] or mismatch repair-deficient [dMMR]).[7,8] For Part B only, addition of other solid tumors were considered, where nivolumab PK was well characterized and discussed with the Sponsor. In addition to the above tumors, Part E will also include participants with metastatic urothelial carcinoma (mUC).

The initial SC dosing regimen was selected as SC nivolumab (BMS-986298) 720 mg once every 4 weeks (Q4W) based on extrapolated bioavailability models for SC administration of biologics (with and without rHuPH20). Based on extrapolated bioavailability models and preliminary PK from Part A, this study proceeded with a dose of 960 mg Q4W for Part B (Groups 3 & 4).

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PK results from Parts A and B of this study and the breadth of data from population PK analyses with nivolumab IV across the clinical program were used to establish an SC dose of nivolumab with rHuPH20 to be administered every 4 weeks that is expected to provide comparable exposure (Cavgd28) to the IV nivolumab. PK data for SC and IV nivolumab from this study were combined with existing IV nivolumab PK data to identify a dose expected to provide PK exposures that are non-inferior to the initially approved dosing regimen, IV nivolumab 3 mg/kg Q2W.

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To support characterization of Q2W dosing of SC nivolumab and to provide dosing optionality for participants, 600 mg Q2W coformulated with rHuPH20 will be investigated in Part E. For Parts A-D, SC nivolumab and rHuPH20 were mixed at the site pharmacy (coadministration) prior to study drug administration. As of Protocol Amendment 04, coformulated drug product (SC nivolumab and rHuPH20 solutions pre-mixed in 1 vial with the same dose ratio) will be introduced for Part E. In addition, all ongoing participants in Parts C & D may switch to the coformulated drug product.

In Part E, approximately 36 participants in total will be enrolled. In addition to participants with the tumor types described for Parts A-D, approximately 10 participants with mUC will be included. The clinical benefit of IV nivolumab has been demonstrated in mUC, and Part E will provide preliminary PK data for SC nivolumab in this tumor type.[5,6]

3.1.1 Research Hypothesis

Parts A-D: The purpose of Parts A-D is to characterize the PK, safety, and tolerability of nivolumab administered subcutaneously with and without rHuPH20 in participants with advanced or metastatic tumors.

Part E: The purpose of Part E is to characterize the PK, safety, and tolerability of SC nivolumab 600 mg Q2W coformulated with rHuPH20 in participants with advanced or metastatic tumors, including mUC.

3.2 Background

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses. [7,8,9] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor.[10] Collectively, these signals govern the balance between T-cell activation and tolerance.

3.2.1 Nivolumab Mechanism of Action

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-

antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

Nivolumab (OPDIVO^{TM}) is approved for the treatment of several types of cancer in multiple regions, including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).

3.2.2 Nivolumab Clinical Activity

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy in several tumor types, including NSCLC, melanoma, RCC, cHL, SCLC, gastric cancer, SCCHN, urothelial cancer, HCC, and CRC. In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in patients with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or recurrent or metastatic SCCHN. Details of the clinical activity in these various malignancies are provided in the USPI and SmPC.

3.2.3 Clinical Pharmacology of Nivolumab

Nivolumab PK was assessed using a population PK approach for single-agent nivolumab.

Nivolumab as a single agent: The PK of single-agent nivolumab was studied in patients over a dose range of 0.1 mg/kg to 20 mg/kg administered as a single dose or as multiple doses of nivolumab as a 60-minute infusion every 2 or 3 weeks. Nivolumab clearance (CL) decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of 24.5% (47.6%) resulting in a geometric mean steady state clearance (CLss) (CV%) of 8.2 mL/h (53.9%) in patients with metastatic tumors; the decrease in CLss is not considered clinically relevant. Nivolumab clearance does not decrease over time in patients with completely resected melanoma, as the geometric mean population clearance is 24% lower in this patient population compared with patients with metastatic melanoma at steady state. The geometric mean volume of distribution at steady state (Vss) (%CV) is 6.8 L (27.3%), and geometric mean elimination half-life (t1/2) is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks (Q2W), and systemic accumulation was approximately 3.7-fold. The exposure to nivolumab increases dose proportionally over the dose range of 0.1 mg/kg to 10 mg/kg administered Q2W. The predicted exposure (Cavg and Cmax) of nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion.

Specific Populations: The population PK analysis suggested that the following factors had no clinically important effect on nivolumab CL: age (29 to 87 years), weight (35 to 160 kg), gender, race, baseline LDH, PD-L1 expression, solid tumor type, tumor size, renal impairment, and mild hepatic impairment.

Renal Impairment:

The effect of renal impairment on the clearance of nivolumab was evaluated by a population PK analysis in patients with mild (eGFR 60 to 89 mL/min/1.73 m^2), moderate (eGFR 30 to

59 mL/min/1.73 m^2), or severe (eGFR 15 to 29 mL/min/1.73 m^2) renal impairment. No clinically important differences in the clearance of nivolumab were found between patients with renal impairment and patients with normal renal function.

Hepatic Impairment:

The effect of hepatic impairment on the clearance of nivolumab was evaluated by population PK analyses in patients with HCC and in patients with other tumors with mild hepatic impairment (total bilirubin [TB] less than or equal to the ULN and AST greater than ULN or TB greater than 1 to 1.5 times ULN and any AST) and in HCC patients with moderate hepatic impairment (TB greater than 1.5 to 3 times ULN and any AST). No clinically important differences in the clearance of nivolumab were found between patients with mild/moderate hepatic impairment.

Full details on the clinical pharmacology aspects of nivolumab can be found in the Investigator Brochure and product label.

Nivolumab IV 480 mg Q4W is approved in the following indications: unresectable or metastatic melanoma, adjuvant treatment of melanoma, advanced renal cell carcinoma, classical Hodgkin lymphoma, recurrent or metastatic squamous cell carcinoma of the head and neck, locally advanced or metastatic urothelial carcinoma, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer, hepatocellular carcinoma, and esophageal squamous cell carcinoma, and it was used in Parts A and B of this study.

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Model-based assessment of nivolumab absorption when administered subcutaneously was conducted using population PK (PPK) approach. A previously developed PPK model with IV administration across several tumor types was used to further evaluate the rate (estimated as bioavailability) and extent of absorption. [redacted] All the other PK parameters and the effect of covariates on PK parameters were consistent with those estimated previously with the IV population PK model.

3.2.4 Recombinant Human Hyaluronidase PH20

Recombinant human hyaluronidase PH20 (rHuPH20, Halozyme Therapeutics, Inc.) is a glycosylated 447-amino acid single-chain recombinant human polypeptide that can temporarily depolymerize hyaluronan in the SC space locally at the site of injection. Hyaluronan is a repeating polymer of N-acetyl-glucosamine and glucuronic acid that contributes to the soluble gel-like component of the extracellular matrix of the skin. Depolymerization of hyaluronan results in a transient reduction in the viscosity of the gel-like phase of the extracellular matrix and increased hydraulic conductance that facilitates the dispersion and absorption of injected drugs (see rHuPH20 Investigator's Brochure).[11] This facilitates administration of greater volumes via the SC route as compared to SC administration without rHuPH20. rHuPH20 enables the delivery of large volumes for rapid SC injections, may shorten dose administration time, may reduce administration frequency, and may enable potential improvements to the PK profiles of co-administered drugs,

including improved absorption, increased bioavailability, accelerated Tmax, increased Cmax, and decreased PK variability.

3.2.4.1 Nonclinical Toxicity of Recombinant Human Hyaluronidase PH20

General toxicity studies were performed in cynomolgus monkeys, and a developmental and reproductive toxicity program was performed in mice (see rHuPH20 IB). In a 39-week toxicity study in monkeys, rHuPH20 was well-tolerated, and 2 mg/kg administered SC weekly (~1,000,000 U for a 5 kg monkey), which was the highest dose tested, was determined to be the no-observed-adverse-effect level (NOAEL). In mice, at very high doses (≥ 9 mg/kg/day SC) of rHuPH20, embryo-fetal toxicity consisted of reduced fetal weights and a trend for late resorption; however, these high dose levels did not result in prenatal or postnatal developmental effects. Rabbit studies were also conducted to evaluate the potential effects of anti-rHuPH20 antibody exposure on reproduction and development. These studies showed no adverse effects on general toxicity endpoints, on male or female fertility, or on embryo-fetal development. Genotoxicity and carcinogenicity studies have not been conducted.

See the rHuPH20 IB for detailed descriptions of the nonclinical pharmacology, PK, and toxicity studies of rHuPH20 and results.

3.2.4.2 Clinical Pharmacology of Recombinant Human Hyaluronidase PH20

rHuPH20 may enable co-administered therapeutics to overcome administration, time, and volume barriers to SC drug delivery. Overall, data from a number of studies suggest that rHuPH20 can increase the utility of SC drug administration by improving ease of administration and the PK profile of concurrently administered large proteins. The half-life of rHuPH20 in skin is < 30 minutes,[12] and the local permeability barrier in these tissues is restored to pre-injection levels within 24 hours to 48 hours after injection of hyaluronidase.[13] A study of the PK of rHuPH20 (Halozyme Study HALO-104-104) demonstrated a plasma $t_{1/2}$ for IV doses of 10,000 or 30,000 units of rHuPH20 in the range of less than 10 minutes. Knowledge of the mechanisms involved in the disappearance of injected hyaluronidase is limited.

As of Nov-2017, rHuPH20 has been administered to 2321 participants in 28 clinical studies conducted under the US Investigational New Drug (IND) application for rHuPH20. In these clinical studies, the maximum duration of exposure was 12 weeks, and individual doses ranged from 15 U to 96,000 U rHuPH20. One study evaluated rHuPH20 injected intradermally as a single agent. A total of 26 studies evaluated rHuPH20 injected SC immediately prior to another agent or co-administered SC with another agent, including 11 studies evaluating rHuPH20 coformulated with recombinant human insulin (insulin-PH20) or rapid-acting insulin analogs (aspart-PH20 and lispro-PH20). One IV dosing study was conducted using 10,000 U or 30,000 U rHuPH20 in healthy volunteers. All but 2 studies were conducted in adult populations; pediatric exposure (< 18 years of age) in 2 clinical studies included 139 participants with mild-to-moderate dehydration who received SC infusions of isotonic fluids. In partnered trials, the maximum duration of participant exposure to rHuPH20 was up to 3.5 years (187.69 patient-years).[14]

Across all studies, SC injections of rHuPH20 were generally well-tolerated in healthy participants, dehydrated pediatric participants, hospice and palliative care participants, participants with type 1 and 2 diabetes, and participants with rheumatoid arthritis. Subcutaneous injections of rHuPH20 either alone or in combination with lactated Ringer's, normal saline, co-injected drugs (morphine, ceftriaxone, insulin and insulin analogues) or biologic products (immunoglobulin G [IgG] and adalimumab) have been well-tolerated in all clinical trials. Most AEs were mild, transient injection-site reactions, including erythema, pain, bruising, pruritus, burning, tenderness, edema, induration, irritation, paresthesia, numbness and rash. Moderate injection-site reactions, which have occurred less frequently, include burning, erythema, pain and numbness. Mild-to-moderate headache was also commonly reported. Adverse events in these trials have otherwise generally reflected the adverse reaction profiles of the co-administered drug or have been associated with the rapid introduction of a relatively large volume of fluid into the SC space.

Antibodies to rHuPH20 have been evaluated in several nonclinical and clinical studies. To date, no clinical signs or symptoms have been associated with positive rHuPH20 antibody titers in clinical trials with rHuPH20 and no rHuPH20-neutralizing antibody activity has been detected.

In addition to these studies, a large clinical safety database exists for rHuPH20 as a tissue permeability enhancer in combination with several approved products in the US and/or EU including:

- HYQVIA® (Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (PH20) (sequential SC administration));
- Herceptin® SC (trastuzumab coformulated with rHuPH20);
- MabThera® SC/RITUXAN HYCELA® (rituximab coformulated with rHuPH20);
- HYLENEX® (rHuPH20 alone; US only);
- DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj); and,
- PHESGO™ (pertuzumab, trastuzumab, and hyaluronidase-zzxf; US only).

3.2.5 Nonclinical Toxicity of Subcutaneous Nivolumab

A nonclinical study was conducted in cynomolgus monkeys to evaluate local tolerance and systemic exposures to nivolumab when administered twice (3 weeks apart) as a SC formulation with and without rHuPH20.[15] Nivolumab was supplied as 154.57 mg/mL (BMS-986298) and was administered by SC injection at doses of 0 mg/kg (vehicle), 50 mg/kg (no rHuPH20), or 50 mg/kg (with rHuPH20, 2000 U/mL), twice (Days 1 and 22/20 [males/females]), to groups of 3 monkeys per sex. All doses were administered at 0.5 mL/kg in a vehicle/carrier consisting of 20 mM histidine, 250 mM sucrose, 0.05% polysorbate-80, and 50 µM pentetic acid (histidine buffer). Samples for toxicokinetic analysis were collected following dosing on Day 1 and scheduled necropsies were conducted at 72 hours following dosing on Day 22/20 (males/females).

[redacted]

[redacted]

Table 3.2.5-1: Toxicokinetic Summary - [redacted]

	SC Nivolumab (BMS-986298)	
	[redacted] mg/kg (no [redacted])[a]	[redacted] mg/kg (with [redacted])[a]
[redacted]		
Cmax (µg/mL)		
Tmax (h)		

[a] Value was calculated with all/exclusion of monkeys with detectable treatment-emergent anti-nivolumab antibodies.

[redacted]

3.3 Benefit/Risk Assessment

Extensive details of the IV nivolumab safety profile is available in the nivolumab (BMS-936558) IB and will not be repeated herein. Overall, the safety profile of IV nivolumab monotherapy is manageable and generally consistent across completed and ongoing clinical trials, with no maximum tolerated dose reached at any dose tested up to 10 mg/kg.[16,17,18,19] 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 IV nivolumab dose level. A pattern of immune-related adverse events (IMAEs) has been defined, for which management algorithms have been developed (Appendix 6). Most high-grade IMAEs were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

[redacted] Based on the E-R analyses conducted thus far, this change in pharmacokinetic profile is not expected to alter the efficacy or safety profile of nivolumab.

As outlined in the protocol, until the SC nivolumab (BMS-986298) dose was confirmed to ensure non-inferior Cavgd28 exposures to nivolumab IV 3mg/kg dosing, participants were transitioned

to IV nivolumab (BMS-936558) 480mg Q4W in Cycle 2+. In addition, since SC administration of nivolumab may be associated with a risk of local injection-site reactions not observed with IV administration, these risks were monitored, assessed, and managed in this study. The potential effect of immunogenicity on the safety and PK of SC nivolumab (BMS-986298) will also be assessed. However, these potential risks to participants seem reasonably compensated by the potential benefits of decreased administration times and decreased need for visits to specialized IV infusion centers.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the SC nivolumab (BMS-986298) IB and IV nivolumab (BMS-936558) IB.

[redacted] BMS is collecting immunogenicity data for rHuPH20 throughout this study.

Revised Protocol 03

Interim analyses from Parts A & B include safety experience of SC Nivolumab 720 mg and 960 mg (with rHuPH20). There were thirty-two participants dosed with SC nivolumab (720 mg or 960 mg with rHuPH20) on Cycle 1 Day 1 (C1D1) followed by IV nivolumab. Specifically, twenty-two participants in Group 1 (720 mg SC nivolumab + rHuPH20) and ten participants in Group 3 (960 mg SC nivolumab + rHuPH20) were included for safety considerations with the co-administered formulation. Demographics and baseline characteristics of study population included participants with broad representation of ages, weights & tumors (advanced/metastatic setting in line with current previously studied patient populations). [redacted] Revised Protocol 03 introduces this dose for Parts C & D to assess primary objective of characterizing PK of SC nivolumab. Objectives include assessment of safety of SC nivolumab in these settings (from initiation of therapy and in the context of switching from IV nivolumab). The predicted exposures are expected to fall within nivolumab 10 mg/kg Q2W IV dosing previously explored in early nivolumab studies. Since these early trials have shown that a similar clinical profile can be anticipated relative to 3 mg/kg Q2W, this dose is expected to provide a similar benefit risk profile to previous studies.

Protocol Amendment 04

Safety results from 28 participants in Part C (data cutoff date: 30-Sept-2020; Part A/B participants who were treated with nivolumab [BMS-986298] 720 mg or 960 mg [with or without rHuPH20], followed by nivolumab IV 480 mg Q4W, and later transitioned to nivolumab SC 1200 mg Q4W with rHuPH20) [redacted]

Safety results from 36 participants in Part D [redacted] showed that [redacted].

Across treatment groups, ADAs were reported with nivolumab (BMS-986298) with and without rHuPH20. [redacted]

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints:

Objectives	Endpoints
Primary Parts A- D: To describe the pharmacokinetics of nivolumab administered subcutaneously, with or without rHuPH20 Part E: To evaluate the pharmacokinetics of SC nivolumab 600 mg Q2W coformulated with rHuPH20	• Serum nivolumab Parts A, B, D, and E: – Cmax – Tmax – AUC(TAU) – Ctau • Serum nivolumab Part C: – Ctrough
Secondary To assess the safety profile of SC nivolumab.	• Incidences of AEs, TRAEs, SAEs, TRSAEs, AEs/TRAEs leading to discontinuation, deaths, and laboratory abnormalities.
To evaluate incidence of AEs in the broad standardized MedDRA query (SMQ) of Anaphylactic Reaction and the select AE hypersensitivity/infusion reaction category.	• Incidence of AEs in the broad SMQ of Anaphylactic Reaction occurring within 2 days after study drug administration • Incidence of events within the hypersensitivity/infusion reaction select AE category occurring within 2 days after study drug administration.
To assess the immunogenicity of nivolumab	• Incidence of anti-nivolumab antibodies and neutralizing antibodies, if applicable
Exploratory To evaluate preliminary efficacy in all participants	• ORR, PFS, and OS
To characterize biomarker measures [redacted]	• Including, but not limited to: summary measures of change (or % change) from baseline in various biomarkers and molecular characteristics of the tumor (Parts A-D, and based on tissue availability for Part E)/blood
To assess the immunogenicity of rHuPH20	• Incidence of anti-rHuPH20 antibodies and neutralizing antibodies, if applicable
To assess the preliminary participant experience and preference for SC or IV administration of nivolumab.	• Patient experience and preference questionnaire • Qualitative Patient Interviews

Abbreviations: AE = adverse event; AUC(TAU) = area under the concentration-time curve over the dosing interval; Cmax = maximum observed serum nivolumab concentration; Ctau = observed serum nivolumab concentration at the end of the dosing interval; Ctrough = trough observed serum nivolumab concentration; IV = intravenous; MedDRA = Medical Dictionary for Regulatory Activities; ORR= objective response rate; OS = overall survival; PFS = progression-free survival; Q2W = every 2 weeks; rHuPH20 = recombinant human hyaluronidase PH20; SAE = serious adverse event; SC = subcutaneous; SMQ = standardized MedDRA queries; TRAE = treatment-related adverse event; TRSAE = treatment-related serious adverse event.

5 STUDY DESIGN

5.1 Overall Design

Study CA2098KX is a multicenter, randomized, open-label, Phase 1/2 study that will evaluate the PK, safety, and tolerability of SC nivolumab (BMS-986298) administered with and without rHuPH20 subcutaneously in participants with 1 of the following tumor types: NSCLC; RCC; unresectable or metastatic melanoma; HCC; or CRC (MSI-H or dMMR). Additional tumors were permitted in Part B where PK was well characterized and discussed with the Sponsor. In addition to the above tumors, Part E will also include participants with mUC.

The study is divided into the following periods: a Screening period; a Treatment period consisting of Part A, Part B, Part C, Part D, and Part E; and a Safety Follow-up period.

Parts A-E: Approximately 139 total participants will receive study treatment as follows (also see study design schematic in Figure 5.1-1):

- **Part A/B:**
  - **Part A** :
    - Group 1: Single dose of nivolumab (BMS-986298) 720 mg administered SC with rHuPH20 manually by syringe (n=22)
  - **Part B** : After participants were dosed in Part A, 45 participants were dosed in Part B. The first 10 participants were assigned to Group 3. The next 35 participants were randomized 1:1 into Group 2 (n=18) and Group 4 (n=17).
    - Group 2: Single dose of nivolumab (BMS-986298) 720 mg administered SC without rHuPH20 by syringe pump
    - Group 3: Single dose of nivolumab (BMS-986298) 960 mg administered SC with rHuPH20 manually by syringe
    - Group 4: Single dose of nivolumab (BMS-986298) 960 mg administered SC without rHuPH20 by syringe pump
  - Four (4) weeks after the single SC nivolumab (BMS-986298) dose, all participants in Part A and Part B received IV nivolumab (BMS-936558) 480 mg Q4W dosing until Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 progression, unacceptable toxicity, withdrawal of consent, completion of 104 weeks of treatment, cross over to SC nivolumab dosing in Part C, or study termination by the Sponsor, whichever occurs first.
- **Part C:** Participants in Part A and Part B crossed over from nivolumab (BMS-936558) IV dosing (four [4] weeks after last IV dose) to nivolumab (BMS-986298) 1200 mg administered SC with rHuPH20 manually by syringe every 4 weeks.
- **Part D:** (Approximately 36; of which approximately 10 with baseline BW < 65kg): On Day 1 of each treatment cycle, nivolumab (BMS-986298) 1200 mg administered SC with rHuPH20 manually by syringe every 4 weeks.
- **Part E:** (Approximately 36; of which approximately 10 with mUC): nivolumab (BMS-986298) 600 mg coformulated with rHuPH20 administered SC manually by syringe every 2 weeks.

For Parts A-D, SC nivolumab and rHuPH20 were mixed at the site pharmacy (coadministration) prior to study drug administration. As of Protocol Amendment 04, coformulated drug product (SC nivolumab and rHuPH20 solutions pre-mixed in 1 vial with the same dose ratio) will be introduced for Part E. In addition, all ongoing participants in Parts C & D may switch to the coformulated drug product.

Parts A, B and D: Each treatment group in Part A, Part B, and Part D [redacted] by immunohistochemistry (IHC) or with MSI-H/dMMR (for CRC).

Part E: Tissue PD-L1 assessment is optional.

Doses for Part B (Group 3 & 4) were adjusted based on PK and safety information from Part A to be 960 mg Q4W and confirmed by an administrative letter to the investigators.

Parts A & B: Four weeks after the SC dose of study treatment (ie, Study Day 29), participants received 480 mg IV nivolumab (BMS-936558) Q4W until Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 progression, unacceptable toxicity, withdrawal of consent, completion of 104 weeks of treatment, cross over to SC nivolumab dosing in Part C, or study termination by the Sponsor, whichever occurs first. For each participant who was unable to complete the planned Cycle 1 (SC study treatment) and Cycle 2 (IV nivolumab) treatments and PK sampling, an additional participant was assigned.

Parts C & D: An outline of the considerations for Part C and Part D dose selection is presented in Section 10.3.8 (Interim Analyses).

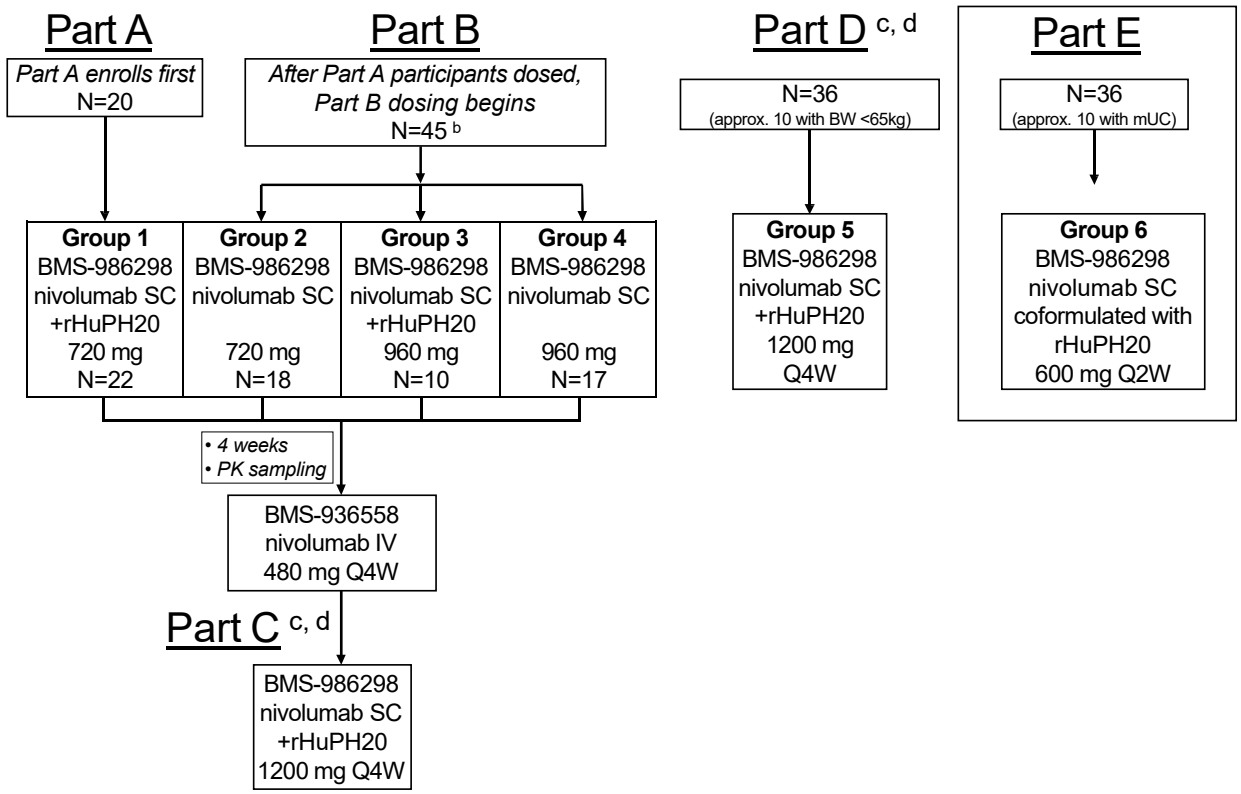
Part E: The dose in Part E is 600 mg SC nivolumab coformulated with rHuPH20 Q2W. [redacted] For each participant who is unable to complete the planned study treatments and PK sampling following the first dose, an additional participant may be assigned via interactive response technology (IRT).

Dosing in the study will continue until RECIST v.1.1 progression, unacceptable toxicity, withdrawal of consent, completion of 104 weeks of total nivolumab treatment (IV and SC combined), or study termination by the Sponsor, whichever occurs first.

[redacted]

Approximately 750 mL of blood (for PK, biomarker and safety assessments) in total will be drawn from each participant during the entire study (two-year period).

Figure 5.1-1: CA2098KX Study Design Schematic[a]



Abbreviations: BW = body weight; IV = intravenous; PK = pharmacokinetic; Q4W = every 4 weeks; mUC = metastatic urothelial carcinoma; rHuPH20 = recombinant human hyaluronidase PH20; Q2W = every 2 weeks; Q4W = every 4 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SC = subcutaneous.

[a] Schema represent the actual numbers of participants enrolled for Parts A, B, and D.

[b] Actual enrollment: The first 10 participants were assigned to Group 3. The next 35 participants were randomized 1:1 into Group 2 (n=18) and Group 4 (n=17).

[c] Crossover into Part C and dosing in Part D (Group 5) begin after the SC nivolumab (BMS-986298) dosing regimen is identified from analysis of PK data from Parts A & B. At the time of Protocol Amendment 04, enrollment for Part D has completed and actual enrollment was 36 participants.

Note: Group 2 and Group 4 will receive SC nivolumab (BMS-986298) by syringe pump without rHuPH20.

[d] Any ongoing participants on SC nivolumab + rHuPH20 treatment may switch over to nivolumab coformulated with rHuPH20 drug product.

Safety monitoring will consist of physical examinations, vital sign measurements, and clinical laboratory evaluations at selected times throughout the dosing interval. Participants will be closely monitored for adverse events (AEs) throughout the study. Collection of AEs and severity per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.5 criteria will also include local injection-site reactions after SC administration and IV-related infusion reactions.

5.1.1 Screening Period

Participants will provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations not considered to be part of the participants' standard care. After signing the informed consent form (ICF), participants will be evaluated for entry criteria during the Screening period within 28 days before administration of study drug. Rescreening after screen failure will be allowed. The participant is enrolled using IRT.

Parts A-D: Sufficient, recent tumor tissue obtained within 12 months prior to enrollment from a metastatic tumor lesion or from an unresectable primary tumor lesion that has not been previously irradiated (formalin-fixed paraffin-embedded block (FFPE) [redacted], obtained from core needle biopsy, excisional, or incisional biopsy) will be submitted. 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. Pre-treatment tissue must be collected and locally confirmed for adequate tissue quantity and quality during the screening period prior to first dose of study treatment and then sent to the central laboratory for testing. Please refer to lab manual for detailed biopsy collection instructions. Up to 5 participants (part A & B) who did not meet tissue requirements were allowed treatment after discussion with the Medical Monitor.

Approximately 15 participants (Part D) who do not meet tissue requirements will be allowed treatment after discussion with the Medical Monitor. Participants should not have received any systemic anticancer therapy after the date that the submitted tumor tissue was obtained. Tumor-cell [redacted] must be assessed by IHC, but participants may receive treatment before results are available. Participants with CRC must have documentation of prior local testing for MSI-H/dMMR status. Each treatment group in Part A, Part B, and Part D [redacted] by IHC or with MSI-H/dMMR (for CRC). Additional participants may be enrolled to meet this minimum accrual at the Sponsor's discretion.

[redacted]

Part E: Tumor tissue collection is highly recommended, but optional. For all participants in Part E, including mUC participants, submission of an archival FFPE tissue block (preferred) or unstained slides of tumor tissue from core biopsy, excisional biopsy, or surgical specimen obtained within 12 months of enrollment is highly recommended.

[redacted]

See Section 9.8.1 for more details.

Participants will be evaluated based on the assessments as outlined in Table 2-1 for Parts A-D and Table 2-2 for Part E and inclusion and exclusion criteria (Section 6). IRT contact must occur for participant number assignment at the time informed consent is obtained.

5.1.2 Treatment Period

Each treatment cycle (28 days) is associated with evaluations and procedures specific to each tumor type. For each participant, on-study tumor assessments will first occur at Week 12 (± 7 days) from first dose date, then every 8 weeks (± 7 days) before the subsequent dose, namely within 7 days of dosing on Day 22 in Cycles 5, 7, 9, etc., up to Week 104 of total treatment until investigator-assessed disease progression or treatment is discontinued, whichever occurs later (see Section 9.1.1). Results of the assessments must be reviewed and documented before administering the first dose of the next cycle. Every effort should be made to schedule visits within the protocol-specified windows. Assessments and frequency are described in Section 2.

Dosing in Parts A through E of the study will continue until RECIST v.1.1 progression, unacceptable toxicity, withdrawal of consent, completion of 104 weeks of total nivolumab treatment (IV and SC), death, or study termination by the Sponsor, whichever occurs first. In certain circumstances, participants with progressive disease per RECIST v1.1 but with otherwise stable or improved performance and clinical status may continue to be treated in the event of a perceived benefit per Investigator; see Section 8.1.2 for treatment beyond progression criteria.

5.1.3 Safety Follow-up Period

The Safety Follow-up Period (Table 2-4) begins when the decision to discontinue a participant from study therapy is made (ie, no further treatment with study therapy). All participants who discontinue study treatment will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All AEs will be documented at visits scheduled on Day 30 and Day 100 from the last study drug dose to monitor for AEs. After completion of the first two follow-up visits, participants will be followed every 3 months for survival for up to 5 years.

Beyond 100 days from the last dose of study therapy, participants will be followed for drug-related AEs until AE resolves, returns to baseline, or is deemed irreversible, or until the participant is lost to follow-up or withdraws study consent.

All AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, the condition stabilizes, or is deemed irreversible, or until the participant is lost to follow-up (as defined in Section 8.3). For suspected cases, participants should be followed until SARS-CoV-2 infection is ruled out as per institutional policy on SARS-CoV-2.

Response/Survival follow-up: Participants who discontinue treatment for reasons other than tumor progression should continue to have tumor assessments if clinically feasible (contrast-enhanced computed tomography [CT] of the chest, CT/magnetic resonance imaging [MRI] of the abdomen, pelvis, and all other known and/or suspected sites of disease) every 12 weeks (± 7 days) until

investigator-assessed disease progression or withdrawal of consent, whichever occurs first. Radiographic assessments for these participants should not be delayed until the planned follow-up visits.

BMS may request that survival data be collected on all treated/randomized participants outside of the protocol-defined window as detailed in Section 2. At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact.

5.1.4 Data Monitoring Committee and Other External Committees

A data monitoring committee and other external committees will not be used in this study.

5.2 Number of Participants

Approximately 139 total participants with any of the included advanced or metastatic tumor types will receive study treatment as follows:

- In Part A, 22 participants received 720 mg SC nivolumab (BMS-986298) manually by syringe with rHuPH20.
- In Part B, 45 participants were dosed. The first 10 participants were assigned to Group 3. The next 35 participants were randomized 1:1 into Group 2 (n=18) and Group 4 (n=17).
- In Part D, approximately 36 participants (approximately 10 with baseline BW < 65 kg) will receive nivolumab (BMS-986298) 1200 mg with rHuPH20 administered SC manually by syringe every 4 weeks.
- In Part E, approximately 36 participants, including approximately 10 participants with mUC, will receive nivolumab (BMS-986298) 600 mg coformulated with rHuPH20 administered SC manually by syringe every 2 weeks.

Additional participants may have been assigned/randomized to study treatment for each participant who was unable to complete one of the following:

- Planned Cycle 1 (SC study treatment) and/or Cycle 2 (IV nivolumab) treatments and PK sampling in Part A
- Planned Cycle 1 (SC study treatment) and/or Cycle 2 (IV nivolumab) treatments and PK sampling in Part B
- Planned Cycle 1 and/or Cycle 2 treatments and PK sampling in Part D

For Part E, additional participants may be assigned to study treatment for each participant who is unable to complete the first dose and up to [redacted] of PK sampling.

Each treatment group in Part A, Part B, and Part D [redacted] by IHC or with MSI-H/dMMR (for CRC). For Part E, tissue PD-L1 assessment is optional.

Randomization- where applicable - will not be stratified by tumor type or by any demographic or disease characteristic.

5.3 End of Study Definition

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

5.4 Scientific Rationale for Study Design

BMS is evaluating ways to improve the conditions for use of nivolumab to meet the needs of patients and HCPs. Currently, nivolumab treatment as monotherapy is administered via IV infusion. As an alternative to IV infusion, BMS is developing a SC formulation of nivolumab with rHuPH20, a recombinant human hyaluronidase PH20 enzyme that enhances permeation of subcutaneously administered fluids, to significantly decrease administration times of nivolumab and improve accessibility to treatment. SC dosing incorporating a flat dose of a biologic drug product provides several potential advantages to HCPs that include reducing dosing errors, decreasing the time needed for dose preparation and administration, and alleviation of IV infusion center occupancy.

In the current study, multiple dose regimens of nivolumab are assessed to gather information on the pharmacokinetic and safety profile of SC nivolumab (BMS-986298). PK results from Parts A and B of this study were used to establish the recommended SC dose of nivolumab with rHuPH20 in Parts C, D, and E as well as for future studies utilizing the SC nivolumab formulation.

5.4.1 Rationale for Subcutaneous Administration

Because systemic exposures of IV nivolumab at or above those historically achieved in clinical studies correlate with response, BMS proposes to dose SC nivolumab to meet average systemic exposures based on the scientific rationale that systemic nivolumab exposure, irrespective of the route of administration, is associated with safety and efficacy. Nivolumab (BMS-936558) exposures with 240 mg Q2W and 480 mg Q4W flat-dose IV regimens across tumor types are maintained at levels comparable to 3 mg/kg Q2W dosing and well below the corresponding exposures observed with the well-tolerated 10 mg/kg IV nivolumab Q2W dose regimen.

Intravenous flat doses of 240 mg Q2W nivolumab, 360 mg Q3W nivolumab, and 480 mg Q4W nivolumab have been incorporated in monotherapy and combination oncology studies, and the 240 mg Q2W and 480 mg Q4W nivolumab dose regimens are approved in multiple indications. Q4W dosing regimens can reduce the burden to patients of frequent, lengthy IV treatments and provide more flexibility in combining with the dosing schedules of other agents.

5.4.2 Rationale for Selection of Tumor Types

The PK properties of nivolumab after IV administration have been characterized across multiple tumors including NSCLC, RCC, melanoma, CRC, urothelial carcinoma, squamous cell carcinoma of the head and neck, and classic Hodgkin lymphoma (cHL). The patient population for this study include participants with 1 of the following tumor types currently approved for treatment with IV nivolumab (BMS-936558): NSCLC, RCC, advanced/metastatic melanoma, HCC, MSI-H/dMMR CRC, and mUC.

Selection of tumor types in Parts A-E of this study is based on their similar IV PK properties (specifically clearance). Analysis of the effect of covariate tumor type on clearance showed that these tumor types do not have statistically significant effects on the clearance of nivolumab, while the effects of other tumors with statistically significant effects on clearance (eg, cHL) were not considered to be clinically meaningful.[22] The enrollment of participants with mUC in Part E will enable characterization of the PK profile after SC nivolumab in this tumor type. Enrolling multiple tumor types with similar nivolumab systemic PK properties, and minimizing the variability in systemic PK, will allow for adequate characterization of the absorption PK properties of nivolumab following SC administration.

In Part B, in addition to the tumor types listed above, other solid tumor types were considered for enrollment at the discretion of the Sponsor.

5.4.3 Rationale for PK and Immunogenicity Sampling Plan

The PK sampling plan is devised to collect data that would also be informative in a PPK model. The PK sampling for nivolumab will be relatively intense after SC dosing to characterize absorption after SC administration to enable non-compartmental analysis as well as PPK analysis. Because the PK of IV nivolumab (BMS-936558) is well characterized, BMS does not plan to conduct intense PK sampling following IV nivolumab.

BMS plans to collect nivolumab immunogenicity samples. See Section 2 (Schedule of Activities) and Section 9.5.1 (PK and Anti-drug Antibody Sample Collection and Processing).

For this PK study of SC nivolumab, BMS does not plan to collect PK data for rHuPH20. The pharmacological effects of rHuPH20 are exclusively local at the site of injection. The plasma t1/2 of IV administered rHuPH20 is < 10 minutes, and blood levels are barely above detectable levels > 45 minutes after administration of IV doses of 10,000 U.[14] Systemic exposure to SC doses of rHuPH20 has been undetectable in studies involving SC doses up to 30,000 U.[23]

BMS plans to collect immunogenicity data for rHuPH20. However, no clinical signs or symptoms have been associated with positive rHuPH20 antibody titers in clinical trials with rHuPH20, and no confirmed rHuPH20-neutralizing antibody activity has been detected.[20]

5.4.4 Rationale for Two Year Duration of Treatment

The optimal duration of immunotherapy is an important question and continues to be investigated. Clinical trials across different tumors types in the nivolumab and ipilimumab development program indicate that most of the responses occur early, with a median time to response of 2-4 months, and emerging data suggests that benefit can be maintained in the absence of continued treatment. A retrospective pooled analysis of two melanoma studies suggest the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment.[24] Furthermore, a limited duration of ipilimumab, including only 4 induction doses, resulted in long term survival in patients with metastatic melanoma, with a sustained plateau in survival starting around 2 years after the start of treatment.[25]

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long term benefit. CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with previously treated advanced solid tumors (including 129 patients with NSCLC), specified a maximum treatment duration of 2 years. Among 16 patients with non-small cell lung cancer (NSCLC) who discontinued nivolumab after completing 2 years of treatment, 12 patients were alive >5 years and remained progression-free without any subsequent therapy. In the CA209003 NSCLC cohort, the overall survival (OS) curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years.[26] These survival outcomes are similar to Phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2 year OS rates of 23% and 29%, and 3 year OS rates of 16%-18% for squamous and non-squamous NSCLC respectively).[27]

Taken together, these data suggest that treatment beyond 2 years is unlikely to confer additional clinically meaningful benefit and that the risk of progression after discontinuing treatment at 2 years is low.

In contrast, a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated patients with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153, patients with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 patients still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in PFS compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached vs 10.3 months, respectively; hazard ratio = 0.42 (95% confidence interval [CI], 0.25 to 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for patients on continued treatment to live longer (OS hazard ratio = 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (ie, 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years. [28]

Collectively, these data suggest that there is minimal if any benefit derived from continuing IO treatment beyond two years in advanced tumors. Even though immunotherapy is well tolerated, patients will be at risk for additional toxicity with longer term treatment. Therefore, in this study, treatment will be given for a maximum of 2 years from the start of study treatment.

5.5 Justification for Dose

5.5.1 Justification for 480 mg Q4W IV Dose

The IV flat dose of nivolumab 480 mg in Parts A and B was selected based on comprehensive PPK analyses and E-R data using Cavgd28 as the primary driver of efficacy across multiple tumor types. The IV nivolumab 480 mg Q4W regimen presents a comparable benefit-risk profile as the IV nivolumab 3 mg/kg Q2W dosing regimen across multiple tumor types.

In exposure-efficacy analyses using Cavgd28 as the driver of efficacy, probabilities of achieving a response and survival probabilities at 1 year and 2 years for IV nivolumab 480 mg Q4W were similar to those of IV 3 mg/kg Q2W.

Exposure-safety analysis showed that the exposure margins for safety were maintained following IV nivolumab 480 mg Q4W, and the predicted risks of AEs leading to discontinuation/death, Grade ≥ 3 AEs, and Grade ≥ 2 IMAEs were shown to be similar following IV nivolumab 480 mg Q4W relative to IV nivolumab 3 mg/kg Q2W across tumor types. Safety analyses using available data following IV nivolumab 3 mg/kg Q2W and 10 mg/kg Q2W administration indicated there were no differences in AE profiles across body weight groups. Finally, initial evidence shows that, following administration of 480 mg Q4W, nivolumab has been shown to be well tolerated.

5.5.2 Justification of Subcutaneous Doses of Nivolumab

Studies have consistently shown that the mean population estimate for bioavailability of monoclonal antibodies following SC administration approximates 75% of that with IV administration, with a lower Cmax and a delayed Tmax.[29] The PK data from the nonclinical toxicokinetic study of SC nivolumab (BMS-986298) in cynomolgus monkeys support this prediction; higher weight-based (mg/kg) doses of SC nivolumab than those planned in CA2098KX were well tolerated (see Section 3.2.5).

The typical range for bioavailability for monoclonal antibodies is approximately 60 to 80%. [redacted]

[redacted]

Based on the outcomes of Part A, a single SC dose of 960 mg was tested in Group 3 and Group 4 to acquire additional SC nivolumab PK data. The Cmax with SC nivolumab (BMS-986298) 960 mg is within the safety margin established with nivolumab IV 10 mg/kg Q2W. The Cycle 1 doses for Group 3 and Group 4 was confirmed by administrative letter to the investigators.

5.5.3 Revised Protocol 03: Selection of SC Nivolumab Dose in Part C and D (1200 mg Q4W)

PK data from participants enrolled in Parts A and B where nivolumab (720 mg and 960 mg) was administered SC with rHuPH20 and historical IV data across several tumor types was used to characterize the absorption profile of nivolumab when given subcutaneously.

[redacted] All the other PK parameters and effects of covariates on these parameters were consistent with that estimated previously with IV PPK model.

[redacted]

5.5.4 *Protocol Amendment 04: Rationale for SC Nivolumab Dose Coformulated with rHuPH20 in Part E (600 mg Q2W)*

In interim PPK analysis 03, PK data from participants who received 720 mg, 960 mg, and 1200 mg of SC nivolumab with or without rHuPH20, and historical IV nivolumab data across several tumor types (data from ~ 3,000 patients) were used to update the characterization of the absorption profile of nivolumab when given SC. The typical value (90% CI) bioavailability and first-order rate of absorption were estimated to be 70% (66% to 74%) and 0.250 (0.225 to 0.274) day-1, respectively.[21] [redacted]

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) **Signed Written Informed Consent**
   a) Participants must have signed and dated an Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved written informed consent form (ICF) in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care. **Part E participants, refer to Appendix 2 for details.**
   b) Participants must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, patient preference questionnaires and other requirements of the study.
2) **Type of Participant and Target Disease Characteristics**
   a) Participants must have histologic or cytologic confirmation of advanced (metastatic and/or unresectable) solid tumors of one of the following tumor types:
      i) **Parts A -E:** Metastatic squamous or non-squamous NSCLC
         (1) Participants must have experienced disease recurrence or progression during or after one prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease.
         (2) Participants with epidermal growth factor receptor or anaplastic lymphoma kinase genomic tumor aberrations should have disease progression on approved therapy for these aberrations prior to receiving nivolumab treatment.
      ii) **Parts A -E:** Renal cell carcinoma, advanced or metastatic:
         (1) Participants who had experienced disease progression during or after 1 or 2 prior anti-angiogenic therapy regimens (including, but not limited to sunitinib, sorafenib, pazopanib, axitinib, tivozanib, and bevacizumab) in the advanced or metastatic setting.

iii) **Parts A-E:** Melanoma

(1) Unresectable or metastatic melanoma, previously untreated except for prior anti-BRAF/MEK targeted therapy in the adjuvant setting

iv) **Parts A-E**: Hepatocellular carcinoma not amenable for management with curative intent by surgery or local therapeutic measures

(1) Must have received sorafenib or lenvatinib treatment and be either intolerant or have had documented radiographic or symptomatic progression during or after sorafenib or lenvatinib therapy

(2) Child-Pugh A (ie, Child-Pugh score ≤ 6) (Appendix 9)

(3) AST and ALT ≤ 5x times the upper limit of normal (ULN)

(4) **Not applicable per Protocol Amendment 04. See (a) immediately below for all Parts A-E.** Total bilirubin < 3 mg/dL.

(a) Total bilirubin ≤ 3 mg/dL

(5) Prothrombin International normalized ratio (INR) ≤ 2.3 or prothrombin time (PT) ≤ 6 seconds above control

(6) Albumin ≥ 2.8 g/dL

(7) Participants with chronic hepatitis B virus (HBV) infection must be on antiviral therapy and must have HBV DNA < 500 IU/mL.

(8) Platelets ≥ $60x10^3/\mu L$

v) **Parts A-E**: Colorectal cancer, metastatic (MSI-H or dMMR):

(1) MSI-H or dMMR CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

vi) **Part B only:** other solid tumor types were permitted where PK was well characterized and discussed with the Sponsor.

vii) **Part E only:** Metastatic urothelial carcinoma:

(1) Participants with metastatic or locally advanced (cT4b, or any N+ [N1-N3], or any M1) urothelial carcinoma (including mixed histology with elements of other subtypes) of the renal pelvis, ureter, bladder, or urethra.

(2) Participants must have progression

(a) After treatment with at least 1 platinum-based chemotherapy regimen for metastatic or locally advanced disease

OR

(b) Within 12 months of neoadjuvant or adjuvant platinum-based chemotherapy.

b) Measurable disease as per RECIST version 1.1 criteria (see Appendix 5 for criteria)

c) Participants must have an ECOG performance status of 0 or 1 (see Appendix 7 for ECOG Performance Status scales).

d) All participants must have the ability to comply with treatment, patient-reported outcomes, PK, pharmacodynamic sample collection, and study follow-up requirements.

e) Prior radiotherapy must have been completed at least 2 weeks prior to study treatment administration.

f) Screening laboratory values must meet the following criteria (using CTCAE v.5). The laboratory values for platelets, AST/ALT, and total bilirubin are adjusted for participants with HCC and are defined under Inclusion Criteria 2, Letter a, iv.

i) White blood cell (WBC) count ≥ 2000/μL

ii) Neutrophils ≥ 1500/μL

iii) Platelets ≥ $100x10^3$/μL

iv) Hemoglobin ≥ 9.0 g/dL

v) Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or calculated creatinine clearance (CrCL) > 40 mL/min (using the Cockcroft Gault formula):

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

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

vi) AST ≤ 3.0 x ULN

vii) ALT ≤ 3.0 x ULN

viii) Total bilirubin ≤ 1.5 x ULN (except participants with Gilbert Syndrome who must have a total bilirubin level of < 3.0x ULN)

g) Participants may be re-enrolled if the participant has discontinued the study as a pre-treatment failure (ie, participant has not been treated/randomized). If re-enrolled, the participant must re-consent.

h) **Parts A-D:** Participants must provide either a FFPE tissue block or unstained tumor tissue sections, obtained within 12 months prior to enrollment with an associated pathology report, for submission to the core laboratory for inclusion. Pre-treatment tissue must be collected and locally confirmed for adequate tissue quantity and quality during the screening period prior to first dose of study treatment and then sent to the central laboratory for testing. Up to 5 participants (part A & B) who did not meet tissue requirements were allowed treatment after discussion with the Medical Monitor. Part D: Approximately 15 participants who do not meet tissue requirements may be allowed treatment after discussion with the Medical Monitor. Biopsy should be excisional, incisional, or core needle. Fine needle aspiration, drainage of pleural effusions with cytospins, or punch biopsies are unacceptable for submission. 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. Participants should not have received any systemic anticancer therapy after the date that the submitted tumor tissue was obtained.

i) **Part E:** Tumor tissue collection/submission is optional for participants in Part E. Refer to Section 9.8.1 for further details, including for mUC participants.

i) Participants must have abdominal skin free of any skin disease, condition (including but not limited to scarring, tattoos, or stretch marks), or skin pigmentation that could interfere with an assessment of an SC injection site.

j) Participants must be assessed for tumor PD-L1 expression by IHC. Results of PD-L1 testing from Part A are required prior to opening study Part B, Part C, and Part D. Participants are able to receive therapy prior to availability of results of PD-L1 assessment. Tumor PD-L1 assessment is not required for participants with CRC with prior documented MSI-H/dMMR status. **Not applicable for Part E.**

i) **Part E:** Tumor PD-L1 expression by IHC is an optional assessment.

3) **Age and Reproductive Status**

a) Male and female participants must be ≥ 18 years old or age of majority at the time of informed 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. **Not applicable for Part E.**

i) **Part E:** WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study treatment. An extension up to 72 hours prior to the start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window.

ii) **All Parts (Parts A-E):** Additional requirements for pregnancy testing during and after study intervention are located in Section 2, Schedule of Activities.

c) **Not applicable per Protocol Amendment 04. See i) immediately below for all Parts A-E.** Women must not be breastfeeding.

i) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

(1) Is not a WOCBP

OR

(2) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, as described in Appendix 4 during the intervention period and for at least 5 months and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period.

d) **Not applicable per Protocol Amendment 04. See i) and ii) immediately below for all Parts A-E.** WOCBP must agree to follow instructions for method(s) of contraception (see Appendix 4: Women of Childbearing Potential Definitions and Methods of Contraception) for the duration of treatment with study treatment plus 5 months after the last dose of study treatment.

i) WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below and included in the ICF.

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

e) **Not applicable per Protocol Amendment 04. See h) below for all Parts A-E.** Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with study treatment plus 7 months after the last dose of study treatment. In addition, male participants must be willing to refrain from sperm donation during this time.

f) **Not applicable per Protocol Amendment 04. See h) below for all Parts A-E.** Males who are azoospermic 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.

g) **Part E:** Female Participants:

i) Women who are not of childbearing potential are exempt from contraceptive requirements.

ii) Women participants must have documented proof that they are not of childbearing potential.

iii) 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.

h) Male Participants. No additional contraceptive measures are required to be used.

For all Parts A-E per Protocol Amendment 04: Investigators shall counsel WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy, and the potential of fetal toxicity occurring due to transmission of study drug to a developing fetus.

6.2 Exclusion Criteria

1) **Medical Conditions**

a) Participants must not have active brain metastases or leptomeningeal metastases. Participants with brain metastases are eligible if these have been treated and there is no MRI evidence of progression for at least 4 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration. **Not applicable for Part E.**

i) **Part E:** Untreated, symptomatic CNS metastases. Participants are eligible if CNS metastases are asymptomatic and do not require immediate treatment, or have been treated and participants have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment). In addition, participants must have been either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to treatment assignment. Imaging performed within 28 days prior to treatment assignment must document radiographic

stability of CNS lesions and be performed after completion of any CNS-directed therapy

ii) **Part E:** Leptomeningeal metastases

b) Participants must not have ocular melanoma

c) Participants with HCC must not have the following:

i) Any history of hepatic encephalopathy

ii) Any prior (within 1 year) or current clinically significant ascites as measured by physical examination and that requires active paracentesis for control

iii) Active coinfection with both hepatitis B and C

iv) Hepatitis D infection in participants with hepatitis B

d) Participants must not have active, known, or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

e) Participants must not have a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of treatment assignment/randomization. Inhaled or topical steroids and adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease. **Not applicable for Part E.**

i) **Part E:** Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) within 14 days or other immunosuppressive medications within 30 days of treatment assignment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

f) Participants must not have a prior malignancy active within the previous 2 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix or breast. **Not applicable for Part E.**

i) **Part E:** Concurrent malignancy (present during screening) requiring treatment or history of prior malignancy active within 2 years prior to treatment assignment (ie, participants with a history of prior malignancy are eligible if treatment was completed at least 2 years before treatment assignment and the patient has no evidence of disease). Participants with history of prior early stage basal/squamous cell skin cancer or non-invasive or in situ cancers that have undergone definitive treatment at any time are also eligible.

g) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways

h) Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally (see Appendix 8). **Not applicable for Part E.**

i) **Part E:** Known human immunodeficiency virus (HIV) positive with an AIDS defining opportunistic infection within the last year, or a current CD4 count < 350 cells/μL. Participants with HIV are eligible if

(1) They have received antiretroviral therapy (ART) for at least 4 weeks prior to treatment assignment as clinically indicated while enrolled on study.

(2) They continue on ART as clinically indicated while enrolled on study.

(3) CD4 counts and viral load are monitored per standard of care by a local health care provider.

NOTE: Testing for HIV must be performed at sites where mandated locally. HIV positive participants must be excluded where mandated locally (see Appendix 8).

i) Positive pregnancy test at enrollment or prior to administration of study medication.

j) **Not applicable for per Protocol Amendment 04. See Section 6.1, 3) c).** Women who are breastfeeding.

k) Participants must not have any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study treatment administration, impair the ability of the participant to receive protocol therapy, or interfere with the interpretation of study results. **Not applicable for Part E.**

i) **Part E:** Participants must not have any serious or uncontrolled medical disorder or severe infection within 4 weeks prior to screening.

(1) Note: In the case of prior SARS-CoV-2 infection, acute symptoms must have resolved based on investigator clinical judgment and, in consultation with the Medical Monitor, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment to be eligible.

l) Participants must not have received any vaccines containing live/attenuated virus within 30 days prior to start of study treatment.

i) Treatment with any live attenuated vaccine (including any live attenuated COVID-19 vaccine) within 30 days of first study treatment. Details regarding COVID-19 vaccination are available in Section 7.7.1.

m) Participants must not have treatment with botanical preparations (eg, herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to treatment assignment/randomization. Refer to Section 7.7.1 for prohibited therapies. **Not applicable for Part E.**

i) **Part E:** Treatment with complementary medications (eg, herbal supplements or traditional Chinese medicines) to treat the disease under study within 2 weeks prior to first study treatment. Such medications are permitted if they are used as supportive care. Refer to Section 7.7.1 for prohibited therapies.

n) Participants must not have 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.

o) Left ventricular ejection fraction (LVEF) assessment with documented LVEF < 50% by either transthoracic echocardiogram (TTE) or multigated acquisition (MUGA) scan (TTE preferred test) within 6 months prior to start of study treatment. **Only applicable to first-in-human Parts A, B, C, and D. Not applicable for Part E.**

p) Positive urine screen for drugs of abuse. **Not applicable per Protocol Revision 02.**

q) Participants must not have any positive test result for HBV or hepatitis C virus (HCV) indicating presence of virus, eg, hepatitis B surface antigen (HBsAg, Australia antigen) positive, or hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative). For HCC, participants with chronic HBV infection are permitted and must be on antiviral therapy and must have HBV DNA < 500 IU/mL. **Not applicable for Part E.**

   i) **Part E:** Any positive test result for hepatitis B virus (HBV) indicating presence of virus, eg Hepatitis B surface antigen (HBsAg, Australia antigen) positive.

   ii) **Part E:** Any positive test result for hepatitis C virus (HCV) indicating presence of active viral replication (detectable HCV-RNA). Note: Participants with positive HCV antibody and an undetectable HCV RNA are eligible to enroll.

r) Participants currently in other interventional trials for COVID-19, including investigational COVID-19 vaccination trials that are not authorized or approved by relevant Health Authorities, should not participate in BMS clinical trials until the protocol-specific washout period is achieved. If a study participant has received an investigational COVID-19 vaccine prior to screening, enrollment should be delayed until the full dosing schedule of the vaccine has been completed and the impact of the vaccine is stabilized, UNLESS a delay would compromise the patient's health or suitability for enrollment, as determined by the investigator, and in discussion with the BMS Medical Monitor.

s) Prior radiation therapy within 2 weeks prior to first study treatment. Participants must have recovered (ie, Grade ≤ 1 or at baseline) from radiation-related toxicities prior to first study treatment.

2) **Allergies and Adverse Drug Reaction**

a) Participants must not have a history of allergy to immunotherapies (eg, anti-PD-1/PD-L1 or anti-CTLA-4 treatment or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways) or related compounds.

b) Participants must not have a history of any significant drug allergy (such as anaphylaxis or hepatotoxicity).

c) Participants must not have a history of allergy or hypersensitivity to study drug components.

3) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under specific circumstances a person who has been imprisoned may be included as a participant. Strict conditions apply and Bristol-Myers Squibb 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

Not applicable. No restrictions are required

6.4 Screen Failures

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

6.4.1 Retesting During Screening or Lead-In Period

This study permits the re-enrollment of a participant that has discontinued the study as a pre-treatment failure. Retesting of laboratory parameters and/or other assessments during the Screening will be permitted per the inclusion criteria (this does not include parameters that require a confirmatory result).

Testing for asymptomatic COVID-19, for example by reverse transcriptase polymerase chain reaction (RT-PCR) or viral antigen, is not required. However, some participants may develop suspected or confirmed symptomatic COVID-19, or be discovered to have asymptomatic COVID-19 during the screening period. In such cases, participants may be considered eligible for the study after meeting all inclusion/exclusion criteria (including those related to active COVID-19 infection), and after meeting *all* of the following criteria:

- At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or test result (eg, positive RT-PCR or viral antigen), and
- At least 24 hours have passed since last fever without the use of fever-reducing medications, and
- Acute symptoms (eg, cough, shortness of breath) have resolved, and
- In the opinion of the investigator, there are no COVID-19-related sequelae that may place the participant at a higher risk of receiving investigational treatment, and
- Negative follow-up COVID-19 test (for example by RT-PCR or viral antigen) based on institutional, local, or regional guidelines.

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

7 TREATMENT

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

An investigational product (IP, also known as investigational medicinal product [IMP] in some regions) is defined 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.

IPs used in this trial are provided in Table 7-1. There are no non-investigational products in this trial.

Table 7-1: Study Treatments for CA2098KX

Product Description/Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Nivolumab (BMS-986298) Solution for SC Injection	960 mg (120 mg/mL)	IP	Open-label	Vial or various packaging configurations	Refer to the label on container and/or pharmacy manual
Nivolumab and rHuPH20 (BMS-986298) Solution for SC Injection	600 mg and [redacted] units [redacted] mg and 2000 units/mL)	IP	Open-label	Vial and various packaging configurations	Refer to the label on container and/or pharmacy manual
Nivolumab (BMS-936558-01) Solution for IV Injection	100 mg (10 mg/mL) and 40 mg (10 mg/mL)	IP	Open-label	Vial and various packaging configurations	Refer to the label on container and/or pharmacy manual
[redacted] (rHuPH20)[a]	[redacted] Units/mL ([redacted] mg/mL)	IP[b]	Open-label	Vial and various packaging configurations	Refer to the label on container and/or pharmacy manual

Abbreviations: EU = European Union; IMP = investigational medicinal product; IP = investigational product; rHuPH20 = recombinant human hyaluronidase PH20; SC = subcutaneous; US = United States.

[a] [redacted] is a formulation containing the enzyme rHuPH20 and is referred as rHuPH20 in the protocol.

[b] rHuPH20 is classified as an IP per local guidelines (as an active ingredient in the US, and as an excipient in the EU).

7.1 Treatments Administered

Table 7.1-1 presents the selection and timing of dose for each participant.

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit dose strength(s)/ Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
Study Part A			
Group 1 SC Nivolumab (BMS-986298) + [redacted] (rHuPH20)	Nivolumab 720 mg + rHuPH20 2000 Units/mL	Solution for SC injection/ Cycle 1 Day 1	SC injection manually by syringe
All Treatment Groups: Nivolumab (BMS-936558-01) Solution for IV Injection	Nivolumab 480 mg	**All Treatment Groups:** Solution for IV injection/ Q4W Cycle ≥2 Day1	IV
Study Part B			
Group 2 SC Nivolumab (BMS-986298)	Nivolumab 720 mg	Solution for SC injection/ Cycle 1 Day 1	SC injection by syringe pump
Group 3 SC Nivolumab (BMS-986298) + [redacted] (rHuPH20)	Nivolumab 960 mg[a]+ rHuPH20 2000 Units/mL	Solution for SC injection/ Cycle 1 Day 1	SC injection manually by syringe
Group 4 SC Nivolumab (BMS-986298)	Nivolumab 960 mg[b]	Solution for SC injection/ Cycle 1 Day 1	SC injection by syringe pump
All Treatment Groups: Nivolumab (BMS-936558-01) Solution for IV Injection	Nivolumab 480 mg	**All Treatment Groups:** Solution for IV injection/ Q4W Cycle ≥2 Day 1	IV
Study Part C[a]			
SC Nivolumab (BMS-986298) + [redacted] (rHuPH20)	Nivolumab 1200 mg+ rHuPH20 2000 Units/mL	Solution for SC injection	SC injection manually by syringe
Study Part D[a]			
Group 5 SC Nivolumab (BMS-986298) + [redacted] (rHuPH20)	Nivolumab 1200 mg + rHuPH20 2000 Units/mL	Solution for SC injection Cycle ≥1 Day 1	SC injection manually by syringe
Study Part E			
Group 6 Nivolumab Coformulated with rHuPH20 (BMS-986298) Solution for SC Injection	Nivolumab [redacted] mg/mL coformulated with rHuPH20 2000 Units/mL	Solution for SC injection Cycle ≥1 [redacted]	SC injection manually by syringe

Note: A treatment cycle is defined as 28 days/4 weeks.

Abbreviations: [redacted] IV = intravenous; Q4W = every 4 weeks; rHuPH20 = recombinant human hyaluronidase PH20; SC = subcutaneous.

[a] Any ongoing participant on SC nivolumab + [redacted] treatment may switch over to nivolumab coformulated with rHuPH20 drug product. Nivolumab and rHuPH20 solutions are pre-mixed in 1 vial when they are coformulated.

[b] Cycle 1 dose was confirmed by administrative letter to the investigator.

7.1.1 Intravenous Administration of Nivolumab Injection

In Part A and Part B only, participants received IV nivolumab (BMS-936558) at a dose of 480 mg nivolumab as a 30-minute (± 5 minutes) infusion on Day 1 of treatment Cycle 2 and beyond until progression, unacceptable toxicity, withdrawal of consent, completion of a total of 104 weeks of treatment, cross over to SC nivolumab dosing in Part C, or the study ends, whichever occurs first. Participants in Part B began study treatment within 3 calendar days of assignment/randomization.

There will be no dose escalations or reductions of nivolumab allowed. After Cycle 2, participants may be dosed within a ± 3-day window. Premedications are not recommended for the first dose of nivolumab.

Participants were monitored for approximately 60 minutes post infusion on Cycle 2 Day 1. 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.

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.

Instructions for preparation of the IV nivolumab (BMS-936558) dose are provided in the Pharmacy Manual. Guidelines for administration of IV nivolumab (BMS-936558) doses are described in the IV nivolumab (BMS-936558) IB.

Participants in Part A and Part B will receive SC nivolumab (BMS-986298) dosing in Part C (characterization of PK and safety outlined in Section 10.3.8).

7.1.2 Subcutaneous Administration of Nivolumab

Detailed instructions for the preparation of the SC study treatments are provided in the CA2098KX Pharmacy Manual.

In Part A and Part B, SC nivolumab (BMS-986298) was administered in the abdomen only. Appendix 10 provides instructions for choice of SC injection site and preparation for administration of SC injection for both manual injection by syringe and injection by external syringe pump. The site of SC injection must be recorded in the electronic case report form (eCRF).

7.1.3 Subcutaneous Administration of Nivolumab with rHuPH20

Revised Protocol 03

In Part C and Part D, 1200 mg SC nivolumab (BMS-986298) + rHuPH20 (rHuPH20 concentration of 2,000 U/mL), should be administered via manual injection in one of the quadrants of the abdomen or, alternatively, in the thigh as steadily as possible (ie, no start or stop, and at a steady rate) over a period of approximately 3-5 minutes. Participants will be monitored for approximately 60 minutes following first manual injection of 1200 mg SC nivolumab + rHuPH20. Participants receiving subsequent SC injections may be monitored for approximately 15-30 minutes post injection at the discretion of the investigator. The site of SC injection, duration and needle type must be recorded in the electronic case report form (eCRF). Instructions for preparation of the SC nivolumab (BMS-986298) dose are provided in the Pharmacy Manual.

Protocol Amendment 04

In Part E, 600 mg SC nivolumab (BMS-986298) coformulated with rHuPH20 10,000 units (2000 Units/mL) should be administered on [redacted] of each treatment cycle, via manual injection in one of the quadrants of the abdomen or, alternatively, in the thigh as steadily as possible (ie, no start or stop, and at a steady rate) over a period of approximately 2-5 minutes. Participants will be evaluated for approximately 30 minutes post [redacted] SC injections. In addition, all participants will be contacted approximately 24 hours after the [redacted] SC injection and [redacted] SC injection for reporting of any injection-site reactions. The site of SC injection, duration, and needle type must be recorded in the electronic case report form (eCRF).

For Parts A-D, SC nivolumab and rHuPH20 were mixed at the site pharmacy (coadministration) prior to study drug administration. As of Protocol Amendment 04, coformulated drug product (SC nivolumab and rHuPH20 solutions pre-mixed in 1 vial with the same dose ratio) will be introduced for Part E. In addition, all ongoing participants in Parts C & D may switch to the coformulated drug product.

Instructions for preparation of the SC nivolumab (BMS-986298) coformulation dose are provided in the Pharmacy Manual.

7.1.3.1 Subcutaneous Administration of Nivolumab without rHuPH20

The appropriate volume of SC nivolumab injection (BMS-986298) is pulled into a syringe. For example, for a 720 mg SC dose, the total dose volume to be administered is approximately 6.0 mL, and using a syringe pump (external infusion pump), the dose is administered subcutaneously over approximately 30 minutes.

7.2 Method of Treatment Assignment

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

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

In Part B, approximately 45 participants were dosed. The first 10 participants were assigned to Group 3. The next set participants were randomized 1:1 into Group 2 and Group 4. Participants will be assigned or randomized in Part B to receive different dose levels of nivolumab with rHuPH20 or to nivolumab alone according to a computer-generated randomization scheme prepared by a Randomization Coordinator within the Drug Supply Management Department of BMS Research and Development. Randomization assignments will be released to the bioanalytical laboratory, as needed, in order to minimize unnecessary analysis of samples.

During the screening visit, the investigative site will call into the enrollment option of the 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], (eg, [redacted]). The patient identification number (PID) will ultimately be comprised of the site number and participant number. For example, the first participant screened (ie, enrolled) at site number 1, will have a PID of

[redacted]. Once it is determined that the participant meets the eligibility criteria following the screening visit, the investigative site will call the IRT to assign/randomize the participant into the open Part B dose group.

7.3 Blinding

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

7.4 Dosage Modification

7.4.1 Dose Modifications

Dose delay criteria apply for all drug-related adverse events (regardless of whether the event is attributed to nivolumab). Delay administration of nivolumab if any of the delay criteria in Table 7.4.1-1 are met. Delay nivolumab dosing for any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

For participants who require delay of nivolumab, re-evaluate weekly, or more frequently, if clinically indicated and resume dosing when criteria to resume treatment are met (see Section 7.4.3). Continue tumor assessments per protocol even if dosing is delayed.

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Subcutaneous Nivolumab with or without rHuPH20

Drug-related AE per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Gastrointestinal			
Colitis or Diarrhea	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 3	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 4	Permanently discontinue	
Renal			
Serum Creatinine Increased	Grade 2 or 3	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value
	Grade 4	Permanently discontinue	
Pulmonary			
Pneumonitis	Grade 2	Delay dose	Dosing may resume after pneumonitis has resolved to ≤ Grade 1
	Grade 3 or 4	Permanently discontinue	

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Subcutaneous Nivolumab with or without rHuPH20

Drug-related AE per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Hepatic			
AST, ALT, or T.bili increased (For non-HCC participants; For HCC participants, see Section 7.4.2 and Section 7.4.3)	AST or ALT > 3× and ≤ 5× upper limit of normal (ULN) or T.Bili >1.5× and ≤ 3× ULN, regardless of baseline value	Delay dose	Dosing may resume when laboratory values return to baseline.
	AST or ALT > 5× ULN or T. bili > 3× ULN, regardless of baseline value	Delay dose or permanently discontinue	In most cases of AST or ALT > 5× ULN, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the Medical Monitor/ designee must occur and approval from Medical Monitor prior to resuming therapy.
	Concurrent AST or ALT > 3× ULN and T.bili > 2× ULN, regardless of baseline value	Permanently discontinue	
Endocrinopathy			
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Delay dose	Dosing may resume after adequately controlled with hormone replacement
	Grade 3 or 4 adrenal insufficiency or adrenal crisis	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If adrenal insufficiency resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Subcutaneous Nivolumab with or without rHuPH20

Drug-related AE per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Hyperglycemia	Hyperglycemia requiring initiation or change in daily management (Grade 2 or 3)	Delay dose	Dosing may resume if hyperglycemia resolves to Grade ≤ 1 or baseline value, or is adequately controlled with glucose-controlling agents
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If hyperglycemia resolves, or is adequately controlled with glucose-controlling agents, participant may not require discontinuation of study drug
Hypophysitis/Hypopituitarism	Symptomatic Grade 1-3 that is also associated with corresponding abnormal lab and/or pituitary scan	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Subcutaneous Nivolumab with or without rHuPH20

Drug-related AE per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Hyperthyroidism or Hypothyroidism	Grade 2 or 3	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement or other medical management
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement or other medical management, participant may not require discontinuation of study drug
Skin			
Rash	Grade 2 rash covering >30% body surface area or Grade 3 rash	Delay dose	Dosing may resume when rash reduces to ≤ 10% body surface area
	Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS)	Delay dose	Dosing may resume if SJS, TEN, or DRESS is ruled out and rash reduces to is ≤ 10% body surface area
	Grade 4 rash or confirmed SJS, TEN, or DRESS	Permanently discontinue	
Neurological			
Guillain-Barre Syndrome (GBS)	Any Grade	Permanently discontinue	
Myasthenia Gravis (MG)	Any Grade	Permanently discontinue	
Encephalitis	Any Grade encephalitis	Delay dose	After workup for differential diagnosis (ie, infection, tumor-related), if encephalitis is not drug-related, then dosing may resume when AE resolves

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Subcutaneous Nivolumab with or without rHuPH20

Drug-related AE per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Encephalitis (continued)	Any Grade drug-related encephalitis	Permanently discontinue	
Myelitis	Any Grade myelitis	Delay dose	After workup for differential diagnosis (ie, infection, tumor-related), if myelitis is not drug-related, then dosing may resume when AE resolves
	Any Grade drug-related myelitis	Permanently discontinue	
Neurological (other than GBS, MG, encephalitis, or myelitis)	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 3 or 4	Permanently discontinue	
Cardiovascular			
Myocarditis	Symptoms induced from mild to moderate activity or exertion	Delay dose	Dosing may resume after myocarditis has resolved
	Severe or life threatening, with symptoms at rest or with minimal activity or exertion, and/or where intervention indicated	Permanently discontinue	
Other Clinical AEs			
Pancreatitis: Amylase or Lipase Increased	Grade 3 with symptoms	Delay dose	Note: Grade 3 increased amylase or lipase without signs or symptoms of pancreatitis does not require dose delay Dosing may resume when participant becomes asymptomatic
	Grade 4	Permanently discontinue	
Uveitis	Grade 2 uveitis	Delay dose	Dosing may resume if uveitis responds to topical therapy (eye drops) and after uveitis resolves to Grade ≤ 1 or baseline. If participant requires oral

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Subcutaneous Nivolumab with or without rHuPH20

Drug-related AE per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
			steroids for uveitis, then permanently discontinue study drug
	Grade 3 or 4 uveitis	Permanently discontinue	
Other Drug-related AE (**not listed above**)	Grade 2 non-skin AE, except fatigue	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value
	Grade 3 AE - First occurrence lasting ≤ 7 days	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value
	Grade 3 AE- First occurrence lasting > 7 days	Permanently discontinue	
	Recurrence of Grade 3 AE of any duration	Permanently discontinue	
	Grade 4 or Life-threatening adverse reaction	Permanently discontinue	
Other Laboratory Abnormalities			
Other Drug-related Laboratory Abnormality (**not listed above**)	Grade 3	Delay dose	Exceptions: No delay required for: Grade 3 lymphopenia Permanent Discontinuation for: Grade 3 thrombocytopenia > 7 days or associated with bleeding
	Grade 4	Permanently discontinue	Exceptions: The following events do not require discontinuation of study drug: • Grade 4 neutropenia ≤ 7 days • Grade 4 lymphopenia or leukopenia • Grade 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Subcutaneous Nivolumab with or without rHuPH20

Drug-related AE per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
			responding to supplementation/appropriate management within 72 hours of their onset
Infusion Reactions (manifested by fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions)			
Hypersensitivity reaction or infusion reaction	Grade 3 or 4	Permanently discontinue	See Section 7.7.4 (Management of Treatment-related Infusion Reactions)
SARS-CoV-2 infection either confirmed or suspected		Delay dose	Participants with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment after 1) at least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (eg, RT-PCR or viral antigen), 2) resolution of acute symptoms (including at least 24 hours has passed since last fever without fever-reducing medications), 3) evaluation by the Investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment, and 4) consultation with the BMS Medical Monitor. For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled-out as per institutional policy for testing of SARS-CoV-2 and other criteria to resume treatment are met

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; DRESS = drug reaction with eosinophilia and systemic symptoms; GBS = Guillain-Barre Syndrome; HCC = hepatocellular carcinoma; MG = Myasthenia Gravis; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SJS = Stevens-Johnson syndrome; T.bili = total bilirubin; TEN = toxic epidermal necrolysis; ULN = upper limit of normal.

7.4.2 Dose Delay Criteria

Delay administration of nivolumab if any of the delay criteria in Table 7.4.1-1 and Section 7.4.1 are met. Nivolumab administration should also be delayed for the following:

- For participants with HCC:
  - Any Grade 3 drug-related laboratory abnormality with the following exceptions:
    - Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay.
  - Dose delay for changes in AST or ALT as follows:
    - If a participant has a baseline AST or ALT that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity (2 grade shift)
    - If a participant has baseline AST or ALT within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity (2 grade shift)
    - If a participant has baseline AST or ALT > within the Grade 2 toxicity range, delay dosing for a 2-fold drug-related increase in AST or ALT or for AST or ALT values 8× ULN (whichever is lower)
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Participants who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met. For participants with HCC, it is recommended to monitor elevations in AST or ALT approximately every 3 days till levels peak or begin to decline.

If dosing is resumed after a delay, study treatment may be resumed as soon as possible after the criteria to resume treatment are met (see Section 7.4.3).

7.4.3 Criteria to Resume Treatment

Participants may resume treatment with study drug if they have completed AE management (ie corticosteroid taper) or are on ≤ 10 mg prednisone or equivalent, and meet the requirements per Table 7.4.1-1.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks, the Medical Monitor (or designee) must be consulted. Continue tumor assessments per protocol even if dosing is delayed. Continue periodic study visits to assess safety and laboratory studies every 6 weeks in Parts A-D or every 2 weeks in Part E or more frequently if clinically indicated during such dosing delays.

- Participants with HCC
  - Participants with baseline Grade 1 AST, ALT, or total bilirubin who require dose delays for reasons other than a drug-related hepatic event may resume treatment in the presence of Grade 2 AST, ALT, or total bilirubin.
  - Participants who require dose delays for drug-related elevations in AST, ALT, or total bilirubin may resume treatment when these values have returned to their baseline CTCAE Grade or normal, provided the criteria for permanent discontinuation are not met (Section 8.1.1).

Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by BMS medical monitor or designee.

Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS medical monitor or designee.

For all AEs, corticosteroid therapy must be tapered to prednisone 10 mg/day or equivalent prior to resuming study therapy unless being used as adrenal replacement steroid therapy.

If the criteria to resume treatment are met, the participant should restart treatment at the next scheduled timepoint per protocol. If treatment is delayed > 6 weeks from the last dose, the participant must be permanently discontinued from study therapy, except as specified in Section 8.1.1 and Section 8.1.2. Please see also Appendix 6 (Management Algorithms) for guidance on appropriate management and follow-up of adverse events. For hepatic AE management, see Section 7.4.4.2.

7.4.4 Management Algorithms for Immuno-Oncology Agents

7.4.4.1 Program Safety Management Algorithms

Immuno-oncology (IO) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered as an IO agent and the

management algorithms in Appendix 6 provide guidance on assessing and managing the following groups of AEs:

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

Appendix 6 provides the management algorithms for AEs in the above categories. Note that the program management algorithm for Hepatic AEs in participants with HCC has been modified for this protocol (see the following Section 7.4.4.2).

7.4.4.2 Recommendations for Management of Hepatic Events in Nivolumab Participants with HCC

The nivolumab program has developed a standardized approach for the management of hepatic events based on cumulative data across the program in participants with normal hepatic function.

Across most nivolumab studies, the eligibility criteria for inclusion are based on a maximum AST or ALT < 3× ULN; therefore, only participants with normal to Grade 1 liver function tests have been enrolled. Participants with advanced HCC generally have underlying cirrhosis with decreased hepatic function. They may also have a concomitant chronic viral infection. For CA2098KX, the upper limits for inclusion were therefore adjusted to account for baseline liver dysfunction. Participants with AST or ALT elevations within the CTCAE Grade 2 range are eligible for inclusion. In contrast, the majority of participants included in prior nivolumab studies have had no higher than a CTCAE Grade 1 AST or ALT elevation. Criteria for dose delay, resumption, & discontinuation are in Section 7.4.2, Section 7.4.3, and Section 8.1.1. The tumor-specific approach for the management of hepatic events is as follows:

- If AST or ALT levels do not improve with a dose delay of 3-5 days or if the levels worsen, initiate steroid therapy at 0.5-2 mg/kg/day methylprednisolone or oral equivalent.
- For ALT or AST levels > 8× ULN, initiate steroid therapy promptly at 1-2 mg/kg/day methylprednisolone or oral equivalent.
- For all participants initiating steroids, consult the BMS Medical Monitor within 24 hours after initiation of steroids. Gastroenterology consult is recommended.

- If AST or ALT levels do not improve within 3-5 days or the levels worsen after the start of steroid therapy, discuss with the BMS Medical Monitor the possibility of adding mycophenolate mofetil at 1 g BID.
  - If no response to mycophenolate mofetil, consider treatment with tacrolimus or other immunosuppressants per local guidelines and in discussion with the BMS Medical Monitor. Avoid infliximab due to potential risk of liver failure.
- Tapering of steroids can start once AST or ALT levels have declined by 1 CTCAE grade. Taper steroids slowly over no less than 1 month.

As outlined in Section 7.4.3, nivolumab therapy may resume when AST or ALT have returned to near baseline unless the criteria for permanent discontinuation are reached (Section 8.1.1).

7.5 Preparation/Handling/Storage/Accountability

For nivolumab, refer to the current version of the IV nivolumab (BMS-936558) IB, SC nivolumab (BMS-986298) IB, and/or Pharmacy Manual for complete storage, handling, dispensing, and infusion information. For rHuPH20, refer to the current version of the rHuPH20 IB for complete storage, handling, dispensing, and infusion information.

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 BMS should be contacted immediately.

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

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

Instructions for the preparation of SC study treatments are described in detail in the Pharmacy Manual. Further guidance and information for final disposition of unused study treatment are provided in Pharmacy Manual.

7.5.1 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability, medical record, and eCRF. Drug 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

Concomitant medications are recorded at baseline and throughout the treatment phase of the study in the appropriate section of the eCRF. All medications (prescriptions or over-the-counter medications) continued at the start of the study or started during the study and different from the study treatment must be documented in the concomitant therapy section of the eCRF.

7.7.1 Prohibited and/or Restricted Treatments

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

The following medications are prohibited during the study (unless utilized to treat a drug-related AE):

- Immunosuppressive agents.
- Immunosuppressive doses of systemic corticosteroids. Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents for treatment of malignancy).
- Any non-palliative radiation therapy. Radiation therapy administered with palliative intent (ie, for pain, bleeding, spinal cord compression, brain metastasis, new or impending pathologic fracture, superior vena-cava syndrome, or obstruction) is permitted.
- Any complementary preparation (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study. Such medications are permitted if they are used as supportive care.
- Any live/attenuated vaccine (eg, live COVID-19 vaccines, varicella, zoster, yellow fever, rotavirus, oral polio, and measles, mumps, rubella [MMR]) within 30 days prior to randomization/treatment assignment, during treatment, and until 100 days post last dose.
- COVID-19 vaccines that are NOT live * are permitted prior to study, during the study, and after the last dose of nivolumab.
- The effect of taking COVID-19 vaccines in patients taking nivolumab is unknown. Therefore, the decision to vaccinate should be made by the principal investigator after careful risk/benefit analysis.
- To avoid potential overlap between side effects with COVID-19 vaccine and nivolumab treatment, consider not giving the vaccination on the same week as nivolumab administration.

NOTES:

*The following categories are NOT considered live vaccines: inactivated vaccines including heat-killed and formalin-killed, subunit vaccines, toxoid vaccines, nucleic acid vaccines that do

not encode potentially infectious virus, and replication incompetent recombinant vector vaccines. Please contact the Medical Monitor or designee with any questions related to COVID-19 vaccines or other vaccines for participants on study.

If a study participant has received a live COVID-19 vaccine prior to screening, enrollment should be delayed until the impact of the vaccine is stabilized, UNLESS a delay would compromise patient health, as determined by the investigator in consultation with Medical Monitor. For COVID-19 vaccines requiring more than 1 dose, the full series (eg, both doses of a 2-dose series) should be completed prior to enrollment when feasible, and when a delay in enrollment would not put the study participant at risk. Ideally, enrollment would occur after any acute reactions (eg, reactions occurring within 24 hours of vaccine administration) resolve.

7.7.2 Other Restrictions and Precautions

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

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 they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, participants with severe renal insufficiency (ie, estimated GFR < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this participant population. In addition, participants may be excluded from MRI if they have tattoos, metallic implants, pacemakers, etc.

Gentle hydration before and after IV contrast should follow local standard of care.

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

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

7.7.4 Treatment of Infusion-related Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were

to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. Report all Grade 3 or 4 infusion reactions within 24 hours as an SAE if it meets the criteria.

Treatment recommendations are provided below and based on CTCAE v5 grading definitions and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms: (mild reaction; infusion interruption not indicated; intervention not indicated):

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

For Grade 2 symptoms: (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs):

- Stop the study treatment infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 mg to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further study treatment will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 mg to 1000 mg should be administered at least 30 minutes before infusion. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or 4 symptoms: (severe reaction, Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated):

- Immediately discontinue infusion of study treatment. Begin an IV infusion of normal saline and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for 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. Monitor participant until the Investigator judges that the symptoms will not recur. Study drug will be permanently discontinued. Follow institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.

In 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).

7.8 Treatment After the End of the Study

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS-supplied study treatment for the maximum treatment duration specified in protocol Section 5.1.2. Study treatment will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee, or through another mechanism at the discretion of BMS.

Should the study be terminated before the end of the treatment period specified in Section 7.1, participants who continue to demonstrate clinical benefit will be eligible to receive BMS-supplied study treatment for the protocol-specified maximum treatment duration at the discretion of BMS.

BMS reserves the right to terminate access to BMS-supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of SC nivolumab is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; or c) the participant can obtain medication from a government-sponsored or private health program. In all cases BMS will follow local regulations.

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
- Pregnancy
- Termination of the study by 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 specific circumstances, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- Additional protocol-specified reasons for discontinuation (Table 7.4.1-1)
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation of study drug, with the following exceptions:

- Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed
- Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Medical Monitor (or designee)

Refer to the Schedule of Activities (Section 2) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

In the case of pregnancy, the investigator must immediately 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 Nivolumab Dose Discontinuation

Nivolumab treatment must be permanently discontinued per criteria in Table 7.4.1-1 in Section 7.4.1. Discontinue nivolumab for any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued nivolumab dosing.

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

- Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
- Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Medical Monitor (or designee).

In participants with HCC, nivolumab treatment should be permanently discontinued for the following:

- Hepatotoxicity as evidenced by the following:
  - AST or ALT > 10 x ULN for > 2 weeks,
  - AST or ALT > 15 x ULN irrespective of duration,
  - Total bilirubin > 5 x ULN for those with normal total bilirubin at entry or > 8 x ULN for participants with elevated bilirubin at study entry, irrespective of duration.

8.1.2 Nivolumab Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease (PD).[30]

Participants treated with nivolumab will be permitted to continue nivolumab treatment beyond initial RECIST v1.1 defined PD, as assessed by the investigator, up to a maximum of 24 months from the date of the first dose as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Tolerance of study treatment
- Stable performance status
- Participant provides written informed consent prior to receiving additional nivolumab treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply

Continue radiographic assessment/scan(s) in accordance with the Section 2 Schedule of Activities for the duration of the treatment beyond progression. Balance the assessment of clinical benefit with clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

For the participants who continue nivolumab 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. Upon documentation of further progression, permanently discontinue nivolumab treatment unless the clinical judgement of the investigator is that continuing treatment is in the patient's best interest.

New lesions are considered measurable 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-measurable at the time of initial progression may become measurable 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.

8.1.3 Criteria to Resume Treatment

See Section 7.4.3 for criteria to resume treatment.

8.1.4 Post Study Drug Follow-up

In this study, OS is an exploratory 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 the collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

BMS may request that survival data be collected on all treated/randomized participants outside of the protocol defined window (see Schedule of Activities, Section 2). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contacts or is lost to follow-up.

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 one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain 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.

9 STUDY ASSESSMENTS AND PROCEDURES

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

Perform additional measures, including non-study required laboratory tests, as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on-site/local labs until all study drug-related toxicities resolve, return to baseline, or are deemed irreversible.

Evaluate participant immediately to rule out cardiac or pulmonary toxicity if participant shows cardiac or pulmonary-related signs (hypoxia, abnormal heart rate or changes from baseline) or symptoms (eg, dyspnea, cough, chest pain, fatigue, palpitations).

Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

9.1 Efficacy Assessments

9.1.1 Imaging Assessment for the Study

Images will be submitted to an imaging core laboratory and may undergo blinded independent central review (BICR) at any time during the study. Prior to scanning the first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA2098KX Imaging Manual provided by the imaging core lab.

Screening and on study images should be acquired as outlined in Section 2 (Schedule of Activities).

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 scans should be submitted to the 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.

9.1.1.1 Methods of Measurement

Contrast-enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease should be performed for tumor assessments.

Images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging timepoints. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Change in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the Investigator using the RECIST v1.1 criteria.

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 MR 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.

Guidelines for use of CT component of a PET-CT scanner are as follows. Combined modality scanning such as with 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 PET-CT are of limited use in anatomically based efficacy assessments; therefore, it is 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 PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET-CT can be used for RECIST v1.1 measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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

scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

Bone scans may be collected per local standards, as clinically indicated.

MRI of the brain should be acquired as outlined in Section 2 (Schedule of Activities). CT of the brain (without and with contrast) can be performed if MRI is contraindicated.

9.1.1.2 Imaging and Clinical Assessment

Tumor assessments should continue even if dosing is delayed or discontinued. Changes in tumor measurements and tumor responses will be assessed by the same investigator using RECIST v1.1 criteria. Investigators will report the number and size of new lesions that appear while on study. The timepoint of tumor assessments will be reported on the eCRF based on the investigator's assessment using RECIST v1.1 criteria (See Appendix 5 for specifics of RECIST v1.1 criteria to be utilized in this study). A best overall response (BOR) of stable disease (SD) requires a minimum of 78 days on study date of first dose to the date of the first imaging assessment.

9.2 Adverse Events

The definitions of an AE or serious adverse event (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 caused the participant to discontinue before completing the study.

Use CTCAE v5 definitions and grading for safety reporting of all AE and SAEs on the case report form.

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

Contacts for SAE reporting are specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

Appendix 1 in the nivolumab (BMS-936558) IB and SC nivolumab (BMS-986298) IB 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 100 days of discontinuation of dosing. The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure (eg, a follow-up skin biopsy). For

participants assigned/randomized to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assignment/randomization.

Collect all nonserious AEs (not only those deemed to be treatment-related) continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment.

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF 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 this being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

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

COVID-19 or positive SARS-CoV-2 test results should be reported to BMS within 24 hours regardless of the seriousness criteria.

All SAEs and AEs/SAEs related to SARS-CoV-2 must be collected from the date of the participant's written consent until 100 days following discontinuation of dosing. For participants who are enrolled but not randomized, all SAEs and AEs/SAEs related to SARS-CoV-2 must be collected for 30 days from the date of signing consent. For participants randomized but never treated with study drug, collect for an additional 30 days from date of randomization. Collect all nonserious AEs continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment.

All AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, the condition stabilizes, or is deemed irreversible, or until the participant is lost to follow-up (as defined in Section 8.3). For suspected cases, participants should be followed until SARS-CoV-2 infection is ruled out as per institutional policy on SARS-CoV-2.

9.2.2 Method of Detecting AEs and SAEs

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

All nonserious AEs (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment.

Every AE must be assessed by the investigator with regard to whether it is considered immune-mediated. For events that are potentially immune-mediated, additional information will be collected on the participant's case report form.

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).

All AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, the condition stabilizes, or is deemed irreversible, or until the participant is lost to follow-up (as defined in Section 8.3). For suspected cases, participants should be followed until SARS-CoV-2 infection is ruled out as per institutional policy on SARS-CoV-2.

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

9.2.4 Regulatory Reporting Requirements for SAEs

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

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

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least for 5 months after study product administration then 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.

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.

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 versus low hemoglobin value).

9.2.7 Potential Drug-induced Liver Injury (DILI)

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 in participants without HCC is defined as:

1) AT (ALT or AST) elevation > 3 x ULN

AND

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

AND

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

The following definition takes into account anticipated baseline compromise of liver function in participants with HCC. Potential drug induced liver injury for participants with HCC is defined as:

1) Concurrent ALT ≥ 10 x ULN

AND

2) Total bilirubin ≥ 2 times ULN or baseline value (if elevated bilirubin at study entry)

AND

3) No other immediately apparent possible causes of ALT elevation and hyperbilirubinemia, including, but not limited to, tumor progression, acute viral hepatitis, cholestasis, pre-existing hepatic disease or the administration of other drug(s), herbal medications and substances known to be hepatotoxic.

9.2.8 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, 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).

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities (Section 2).

9.4.1 Physical Examinations

Refer to Schedule of Activities (Section 2).

9.4.2 Vital signs

Refer to Schedule of Activities (Section 2).

9.4.3 Electrocardiograms

Refer to Schedule of Activities (Section 2).

9.4.4 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

All clinical safety laboratory assessments will be performed locally per the Schedule of Activities (Section 2).

A central/local laboratory will perform the analyses and will provide reference ranges for these tests. Results of clinical laboratory tests performed on Day -1 must be available prior to dosing.

Table 9.8-1 and Table 9.8-2 list other various serologic tumor markers, gene mutation status, and genomic analyses.

Table 9.4.4-1: Laboratory Assessment Panels

Hematology - Complete Blood Count (CBC)	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Chemistry	
Aspartate aminotransferase (AST)	Albumin - screening only
Alanine aminotransferase (ALT)	Sodium
Total bilirubin	Potassium
Alkaline phosphatase (ALP)	Chloride
Lactate dehydrogenase (LDH)	Calcium
Creatinine	Phosphorus
Blood urea nitrogen (BUN) or serum urea	TSH, free T3, and free T4 - **screening**
Fasting glucose	TSH, with reflexive fT3 and fT4 if TSH is abnormal - **on treatment**
Serum alpha-fetoprotein (HCC only)	
Serology (at screening)	
Hepatitis B/C (HBV sAG, HCV antibody, or HCV RNA)	
Testing for HIV-1 and HIV-2 must be performed at sites where mandated by local requirements (see Appendix 8).	
Coagulation Panel (HCC only)	
PT/INR	
aPTT	
Fibrinogen	
Other Analyses	
Pregnancy test (WOCBP only: minimum sensitivity 25 IU/L or equivalent units of HCG).	
Follicle stimulating hormone (FSH) screening (only required to confirm menopause in women aged < 55 years)	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; aPTT = activated partial thromboplastin time; BUN = blood urea nitrogen; CBC = complete blood count; FSH = follicle stimulating hormone; fT3 = free triiodothyronine; fT4 = free thyroxine; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV-1/2 = human immunodeficiency virus 1/2; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; RNA = ribonucleic acid; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; WOCBP = women of childbearing potential.

9.4.5 Suicidal Risk Monitoring

Not applicable.

9.4.6 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.

9.4.7 Assessment of Subcutaneous Injection Site

The Investigator or designated study staff will assess the proposed injection site for signs of local irritation and inflammation. The proposed injection site will be evaluated prior to all SC doses and approximately 60 minutes after the Cycle 1 Day 1 injection (Parts A, B and D) and following the first SC injection after transitioning to 1200 mg dose in Part C. Part E participants will be monitored for approximately 30 minutes following the [redacted] and [redacted] SC manual injections. Participants receiving subsequent SC injections may be monitored post injection as clinically warranted and at the discretion of the investigator. There will be five pre-specified injection site reactions of interest: injection site erythema; injection site pain, injection site pruritus, injection site hematoma, and injection site swelling. Injection site reactions will be recorded as AEs on the appropriate page of the CRF. In addition, all participants will be contacted approximately 24 hours after the first 2 SC injections for reporting of injection site reactions. The injection site will also be evaluated predose at the next dosing visit.

9.5 Pharmacokinetics

Full details on the clinical pharmacology aspects of nivolumab can be found in the nivolumab IB.

The PK of nivolumab (BMS-936558 and BMS-986298) will be derived from serum concentration versus time measurements. The PK parameters to be assessed include:

- Cmax: Maximum observed serum nivolumab concentration
- Tmax: Time to maximal concentration
- AUC(TAU): Area under the concentration-time curve over the dosing interval
- Ctau: Observed serum nivolumab concentration at the end of the dosing interval
- Ctrough: Trough observed serum nivolumab concentration

Individual participant PK parameter values will be derived by non-compartmental and, if appropriate, population PK methods by a validated pharmacokinetic analysis program. Actual times of collection will be used in all PK analyses.

9.5.1 Pharmacokinetics and Anti-drug Antibody Sample Collection and Processing

[redacted]

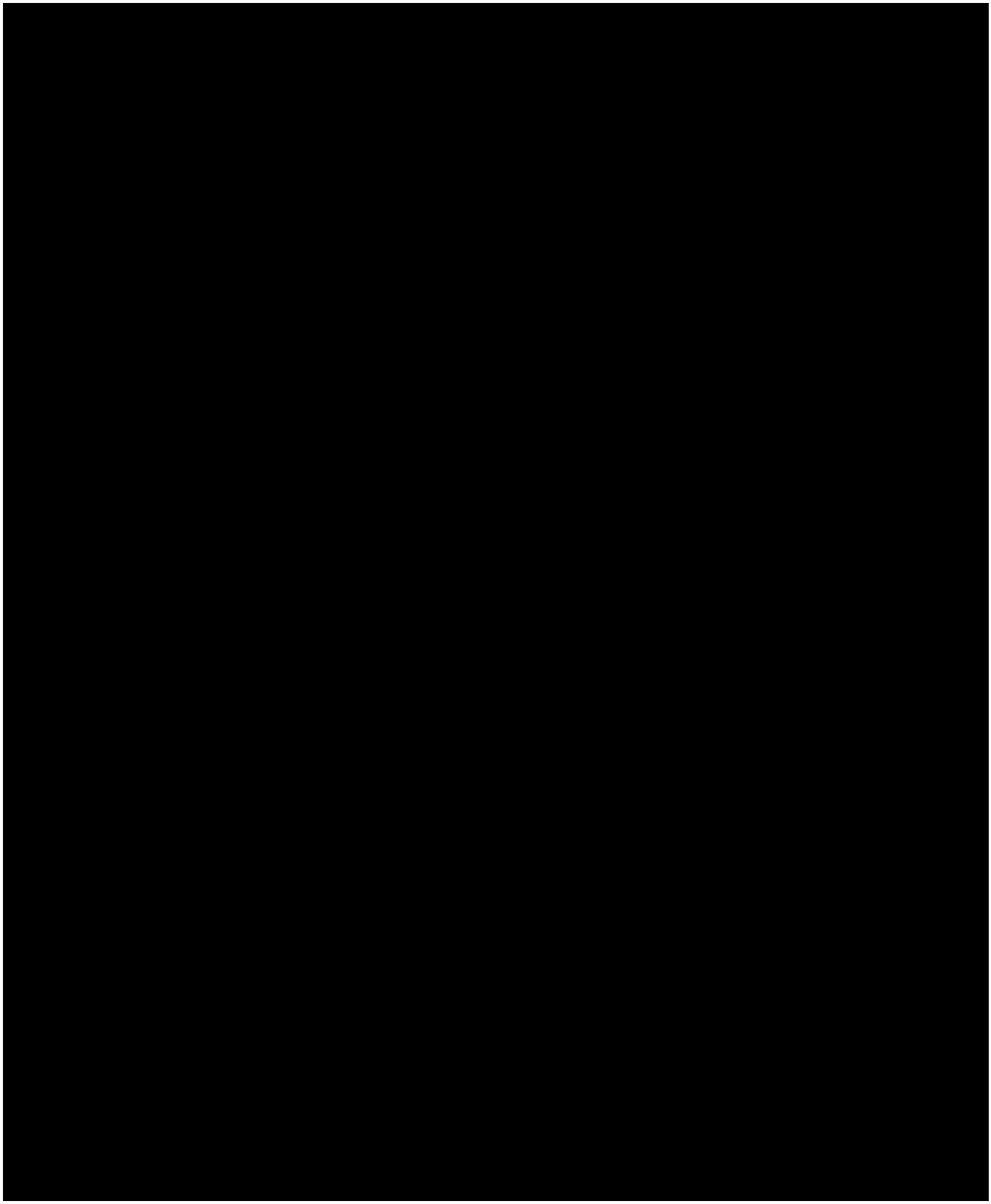
time points are relative to the start of study drug administration. Predose samples should be collected within 30 minutes before the start of dose administration. End-of-infusion (EOI) samples should be taken just prior to the end of the IV infusion (preferably within 2 minutes from

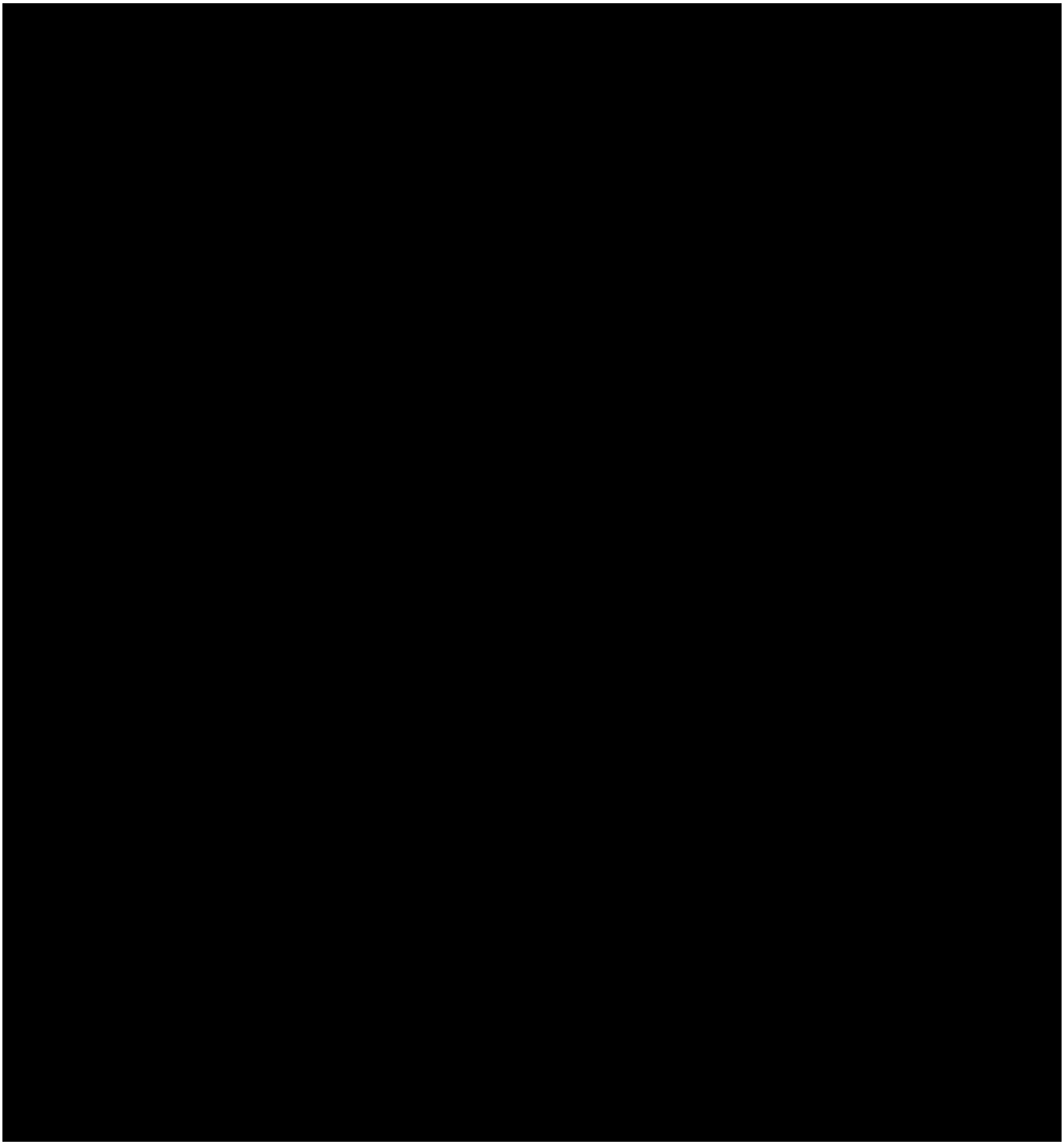
completing the saline flush). Details of sample collection, processing, and shipment will be provided in the laboratory procedures manual.

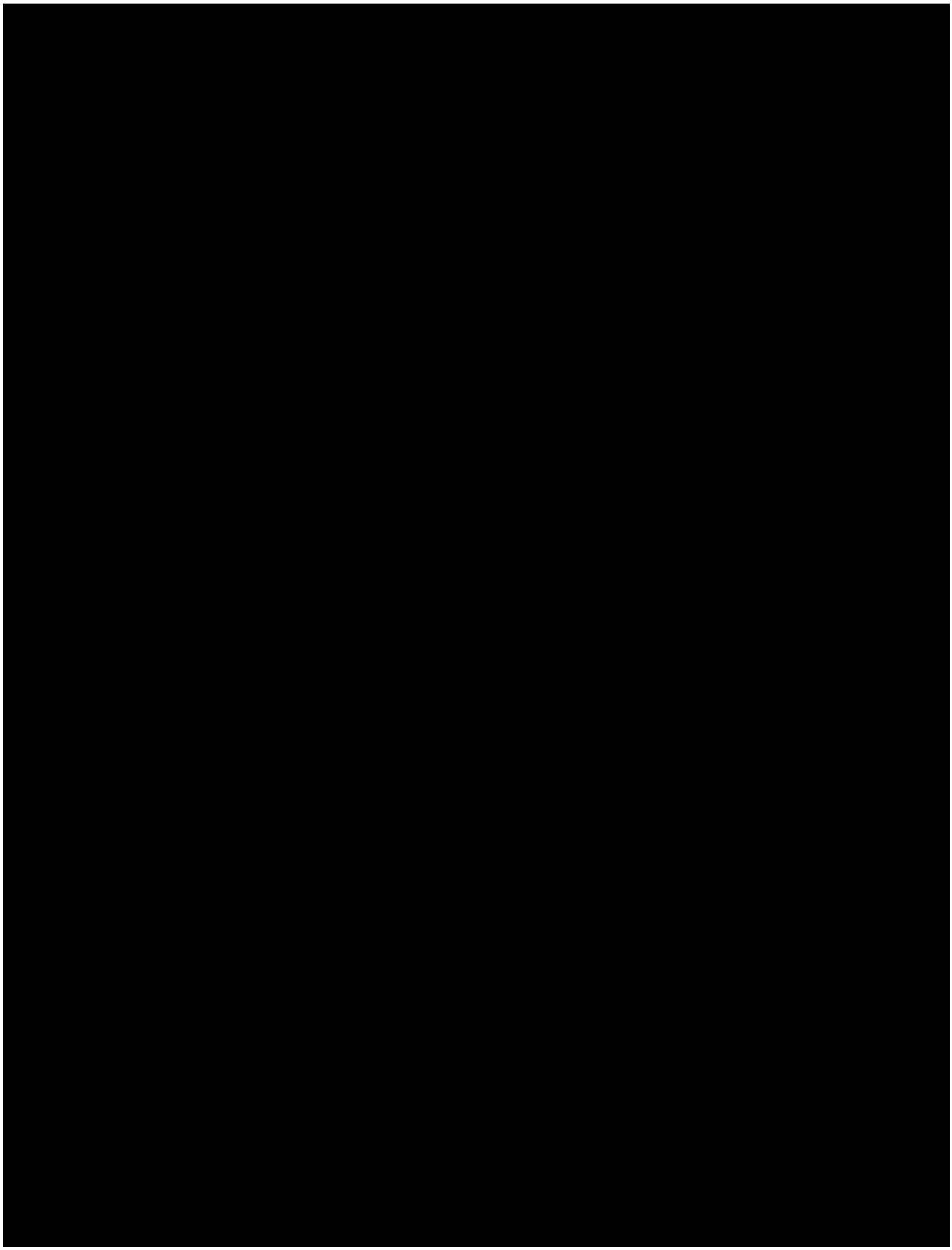
Draw blood samples from a site other than the infusion site (ie, contralateral arm) on days of infusion for all predose and end of infusion-PK (EOI-PK) samples.

On-treatment PK samples are intended to be drawn relative to actual dosing days. If a dose occurs on a different day within the cycle due to delays or minor schedule adjustments, PK samples should be adjusted accordingly.

Immunogenicity of nivolumab will assessed per the standard nivolumab immunogenicity analysis plan. PK data for rHuPH20 will not be collected in this study; however, immunogenicity data for rHuPH20 will be collected and may be analyzed and reported separately.







9.5.2 Pharmacokinetics and Immunogenicity Sample Analyses

The samples will be analyzed for nivolumab and ADA (anti-nivolumab and anti-rHuPH20 antibodies) by validated immunoassays. Samples with a positive ADA response may also be analyzed for neutralizing ADA response to nivolumab and/or rHuPH20. Neutralizing ADA testing is conditional upon assay availability.

In addition, selected serum samples may be analyzed by an exploratory method that measures nivolumab or detect ADAs for technology exploration purposes; exploratory results will not be reported. The corresponding serum samples designated for either PK, immunogenicity or biomarker assessments may also be used for any of those analyses, if required (eg, insufficient sample volume to complete testing or to follow up on a suspected immunogenicity-related AE).

9.6 Pharmacodynamics

Pharmacodynamic parameters evaluated in this study are described in the Biomarkers section (Section 9.8).

9.7 Pharmacogenomics

Refer to Section 9.8 (Biomarkers).

9.8 Biomarkers

Features within the periphery and in the tumor microenvironment (TME) have been established as pharmacodynamic (PD) biomarkers of nivolumab biological activity. In the periphery, these include increased soluble factors including, but not limited to, CXCL9, CXCL10, and soluble PD-1. In the TME, these include increases in intratumoral inflammation, as measured by increases in tumor-infiltrating lymphocytes (TILs) and increases in PD-L1 protein expression. Pre- and on-treatment peripheral blood and tumor biopsies will be collected and will be used to characterize the PD activity of subcutaneous nivolumab. Optional peripheral blood and tumor biopsies will also be collected at disease progression (Table 9.8-1, Table 9.8-2). In addition to characterizing the PD activity of subcutaneous nivolumab, [redacted]. All samples collected may also be used for exploratory analyses to assess biomarkers associated with a specific indication and/or with immunotherapy treatment. Complete instructions on the collection, processing, handling, and shipment of all samples described herein will be provided in a separate procedure manual.

Table 9.8-1: Biomarker Sampling Schedule - Part A, Part B, and Part D - Study CA2098KX

Study Day 1 Cycle = 4 Weeks	Time (Event) Hour[a]	Tumor Biopsy	Serum	[redacted]
Screening		X		
Cycle 1 Day 1	Predose		X	
Cycle 1 Day 2	--		X	
Cycle 1 Day 4 (±1 days)	--		X	
Cycle 1 Day 8 (±2 days)	--		X	
Cycle 1 Day 15	--	X[c]	X[d]	
Cycle 1 Day 21 (±5 days)	--		X	
Cycle 2 Day 1	Predose		X	
[redacted]				

Abbreviations: [redacted] N/A = not applicable; [redacted]
SAE = serious adverse event.

[a] Predose samples should be collected just before the administration of the nivolumab (preferably within 30 minutes).

[redacted]

[c] For Part A the tumor biopsy is highly recommended, but optional. For Part B and Part D, participants will be required to undergo on-treatment biopsy at acceptable clinical risk as judged by the investigator. Biopsy should be collected on Cycle 1 Day 15, preferably from the same lesion as the pre-treatment biopsy.

[d] [redacted] serum sample collection should occur within ± 5 days of Cycle 1 Day 15.

[redacted]

Table 9.8-2: Biomarker Sampling Schedule - Part E - Study CA2098KX

Study Day (1 Cycle = 4 weeks)	Time (Event) Hour[a]	Tumor Biopsy	Serum	[redacted]
Screening (Optional)		X[b]		
Cycle 1 Day 1	Predose		X	
Cycle 1 Day 2	--		X	
Cycle 1 Day 8 (+/- 2 days)	--		X	
Cycle 1 Day 15	Predose	X[b]	X	
Cycle 2 Day 1	Predose		X	
[redacted]				

Abbreviations: [redacted] DNA = deoxyribonucleic acid; SAE = serious adverse event; [redacted]

[a] Predose samples should be collected just before the administration of the nivolumab (preferably within 30 minutes).

[b] For Part E, screening and Cycle 1 Day 15 tumor biopsies are highly recommended, but optional.

[redacted]

9.8.1 Tumor Tissue Specimens

For Part A, the Cycle 1 Day 15 tumor biopsy is highly recommended but optional. For Part B and Part D, participants will be required to undergo on-treatment biopsy unless judged as posing unacceptable risk by the investigator. Sufficient, recent tumor tissue FFPE block from a metastatic tumor lesion or from an unresectable primary tumor lesion, which has not been previously irradiated, must be submitted. If a participant had a biopsy in the preceding 12 months, participants can be enrolled without needing a repeat biopsy after discussion with the Medical Monitor and availability of FFPE blocks [redacted] as delineated below. For Part E, screening and on-treatment tumor biopsies are highly recommended, but optional.

[redacted]

1) **Parts A-D only:** Pre-treatment tissue must be collected and locally confirmed for adequate tissue quantity and quality during the screening period prior to first dose of study treatment and then sent to the central laboratory for testing. Please refer to lab manual for detailed biopsy collection instructions. Up to 5 participants from each part of the trial (Part A and B) who do not meet tissue requirements may be allowed treatment after discussion with the Medical Monitor. Other exceptions may be provided at the discretion of the Medical Monitor.
   a) Approximately 15 participants in Part D, who do not meet tissue requirements may be allowed treatment after discussion with the Medical Monitor.
   b) Participants should not have received any systemic anticancer therapy after the date that the submitted tumor tissue was obtained. Exceptions may be made with Medical Monitor approval in cases where fresh tumor tissue or recent tumor tissue are inaccessible.
2) **Part E:** Tumor tissue collection is highly recommended, but optional. For all participants in Part E, including mUC participants, submission of an archival FFPE tissue block (preferred) or unstained slides of tumor tissue from core biopsy, excisional biopsy, or surgical specimen obtained within 12 months of enrollment is highly recommended.

   [redacted]

3) The tumor tissue specimen must be a core biopsy, excisional biopsy, or surgical specimen. 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.

9.8.2 Biomarker assessments in tumor

Pre- and on-treatment PD-L1 expression will be assessed using the Dako PharmDx 28-8 assay. PD-L1 stained tissue sections will be assessed by a pathologist and membranous PD-L1 expression

[redacted]

In addition to PD-L1 assessment, the pre-treatment and on-treatment tumor sample may be used to assess other putative predictive and PD biomarkers of SC nivolumab to better characterize the TME. [redacted]

9.8.3 Biomarker assessments in peripheral blood

A variety of biomarkers that may inform on [redacted] PD activity of nivolumab will be investigated in peripheral blood specimens taken from all participants prior to and during treatment. Several analyses will be completed and are described briefly below. Additional biomarker assessments may also be performed if samples are available.

[redacted]

9.8.3.2 Exploratory Serum [redacted] Biomarkers

Blood samples for exploratory serum [redacted] biomarker analyses will be drawn at the specified time points indicated in the biomarker tables (Table 9.8-1 and Table 9.8-2). [redacted] Separate blood samples will be collected and processed for serum [redacted] and then put in frozen storage. Serum [redacted] samples may be assessed by ELISA [redacted]

[redacted]

9.8.4 Additional Research Collection

[redacted]

For All US sites:

Additional research is required for all study participants except where prohibited by IRBs/ethics committees, or academic/institutional requirements. Where one 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 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.

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

[redacted]

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

Table 9.8.4-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Timepoints for which Residual Samples Will Be Retained
PK	All
[redacted]	[redacted]

Abbreviations: [redacted] PK = pharmacokinetic; [redacted]

9.8.5 Immunogenicity Assessments

Samples for testing potential nivolumab and rHuPH20 immunogenicity will be collected per the PK and immunogenicity sampling schedule [redacted].

9.9 Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters will not be evaluated in this study.

9.10 Patient-reported Outcomes

9.10.1 Patient Experience and Preference Questionnaire

In order to better understand experiences with and preferences for mode of nivolumab administration, participants will complete a Patient Experience and Preference Questionnaire at various time points during the study. The core questionnaire contains items assessing patient perceptions regarding the convenience and acceptability of the mode of administration, treatment-related symptoms, and satisfaction with treatment.

The questionnaire will be administered immediately following completion of the injection or infusion on Day 1 of treatment Cycle 1 and Cycle 2 in Part A and Part B, and on Day 1 Cycle 1 of Part C, Part D, and Part E.

9.10.2 Qualitative Patient Interviews

Qualitative interviews will be performed with participants to gather insights not covered by the Patient Experience and Preference Questionnaire. The interviews will be conducted via telephone by a trained interviewer using a semi-structured interview guide. They will be conducted in the participant's native language and will be audio recorded and transcribed for analysis using qualitative data analysis techniques. Interviews conducted in languages other than English will be translated to English prior to analysis. Interviews will be conducted within 14 days of completing Cycle 1 Day 1 and Cycle 2 Day 1 in Part A, Part B, and Part C. For Part D and Part E, interviews will be conducted within 14 days of completing Cycle 1 Day 1 or any other cycle thereafter, if not captured at Cycle 1 Day 1. Participation in the interviews is optional and will be subject to the availability of interview materials and the fluency of trained interviewers. Failure to complete either interview will not constitute a protocol deviation.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

Calculation of precision estimates is based on AUC(TAU).

In Part A and Part B, administration of SC nivolumab (BMS-986298) to 20 participants will provide [redacted] % confidence that the range between [redacted] % and [redacted] % of the point estimate of geometric mean AUC(TAU) will encompass the true value. Administration of SC nivolumab (BMS-986298) to 10 participants will provide [redacted]% confidence that the range between [redacted] % and [redacted] % of the point estimate of geometric mean AUC(TAU) will encompass the true value. These calculations assume that AUC is log-normally distributed with standard deviation of [redacted] for log(AUC[TAU]), based on coefficient of variation estimates for IV nivolumab 480 mg of [redacted]% for AUC.

In Part D, administration of 1200 mg SC nivolumab Q4W to 36 PK evaluable participants will provide [redacted] % confidence that the range between [redacted] % and [redacted] % of the point estimate of geometric mean AUC(TAU) will encompass the true value. Administration of 1200 mg SC nivolumab Q4W to 10 PK evaluable participants will provide [redacted]% confidence that the range between [redacted]% and [redacted]% of the point estimate of geometric mean AUC(TAU) will encompass the true value. This calculation assumes that AUC is log-normally distributed with standard deviation of [redacted] for

log(AUC[TAU]), based on an estimated coefficient of variation for nivolumab SC of [redacted] % (for AUC[TAU]). Variability has been estimated via modelling and simulation.

In Part E, administration of 600 mg SC nivolumab Q2W to [redacted] PK evaluable participants will provide [redacted] % confidence that the range between [redacted] % and [redacted] % of the point estimate of geometric mean AUC(TAU) will encompass the true value. Administration of 600 mg SC nivolumab Q2W to [redacted] PK evaluable participants will provide [redacted]% confidence that the range between [redacted]% and [redacted]% of the point estimate of geometric mean AUC(TAU) will encompass the true value. This calculation assumes that AUC is log-normally distributed with standard deviation of [redacted] for log(AUC[TAU]), based on an estimated coefficient of variation for nivolumab SC o[redacted]% (for AUC[TAU]). Coefficient of variation of [redacted]% for AUC(TAU) has been observed in interim analysis 4 for the 1200 mg SC nivolumab Q4W dosing regimen.

Precision of measurements were calculated by nQuery Advisor 7.0.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

- **All Enrolled Participants**: all participants who sign an ICF and are registered into the IRT. This is the dataset for disposition.
- **All Randomized Participants**: all participants who are assigned/randomized to any treatment arm in the study. This dataset will be used for efficacy analyses.
- **All Treated Participants**: all participants who receive at least 1 dose of nivolumab. This is the dataset for safety analyses.
- **PK Participants**: All treated participants with available PK data.
- **Evaluable PK Participants:** The Evaluable PK Participants population is a subset of the PK Participants Population who have adequate dosing and adequate nivolumab serum concentration time data for estimation of PK endpoints. All available derived PK parameter values will be included in the PK data set and reported, but only participants in the Evaluable PK Participants population will be included in the summary statistics and statistical analysis.
- **Immunogenicity Evaluable Participants**: All treated participants who have a baseline and at least 1 post-baseline immunogenicity assessment.

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses and the 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 reported statistical output, including subgroups of age, gender, race, and tumor type. Frequency distributions of gender and race will be tabulated by treatment. Summary statistics for age, body weight, height, and body surface area (BSA) will be tabulated by treatment.

10.3.1 Efficacy Analyses

All efficacy analyses are exploratory and will be described in the statistical analysis plan finalized before database lock.

10.3.2 Safety Analyses

Safety analyses will be performed on the All Treated Participants population. Descriptive statistics of safety will be presented using NCI CTCAE v.5 by treatment group.

Endpoint	Statistical Analysis Methods
Incidences of AEs, TRAEs, SAEs, TRSAEs, AEs/TRAEs leading to discontinuation, and deaths	All on-study AEs, TRAEs, SAEs, TRSAEs, and AEs/ TRAEs leading to discontinuation will be tabulated using worst grade per NCI CTCAE v.5 criteria by system organ class and preferred term. Frequency distribution of treated participants with AE using the worst CTC grade. Participants will only be counted: (1) once at the PT level, (2) once at the SOC level, and (3) once in the "total participant" row at their worst CTC grade, regardless of SOC or PT. Deaths will be summarized by treatment group.
Incidence of clinical laboratory test abnormalities	On study laboratory parameters including hematology, chemistry, liver function, and renal function will be summarized using worst grade NCI CTCAE v.5 criteria.
Incidence of AEs in the MedDRA Anaphylactic Reaction broad scope SMQ occurring within 2 days after study drug administration	Descriptive statistics will be presented using NCI CTCAE v.5 criteria by treatment group.
Incidence of events within the hypersensitivity/infusion reaction select AE category occurring within 2 days after any study drug administration	Descriptive statistics will be presented using NCI CTCAE v.5 criteria by treatment group.

Abbreviations: AE = adverse event; CTC = Common Terminology Criteria; MedDRA = Medical Dictionary for Regulatory Activities; NCI CTCAE v5 = National Cancer Institute Common Terminology Criteria for Adverse Events version 5; PT = preferred term; SAE = serious adverse event; SMQ = standardized MedDRA query; SOC = system organ class; TRAE = treatment-related adverse event; TRSAE = treatment-related serious adverse event.

10.3.3 Pharmacokinetic Analyses

Pharmacokinetic analyses will be conducted using non-compartmental analysis and, if appropriate, PPK analysis. These analyses will be used to characterize the PK of SC nivolumab in Part A, Part B, Part D, and Part E, as well as to inform future clinical trials using SC nivolumab. Analyses from Part A and Part B were used to inform dose selection for Part C, Part D, and additional treatment groups in Part B.

Primary Pharmacokinetic Analysis: PK parameters will be summarized by cycle (dose and route of administration). Evaluable PK parameters will be summarized as follows:

For Parts A, B, D, and E: Geometric means and coefficients of variation will be presented for Cmax, Ctau, and AUC(TAU). Means and standard deviations will also be provided. Medians and ranges will be presented for Tmax. Other exposure measures may be summarized as appropriate.

For Part C: Geometric means and coefficients of variation will be presented for Ctrough.

To assess the dependency on dose after subcutaneous administration of the SC nivolumab (BMS-986298) formulation, scatter plots of Cmax and AUC versus dose will be provided.

Population PK analysis will be conducted as appropriate to determine a subcutaneous dose for future nivolumab trials as outline in Section 10.3.7.1.

10.3.4 Immunogenicity Analyses

All immunogenicity analyses will be performed on the immunogenicity-evaluable population.

Endpoint	Statistical Analysis Methods
Incidence of anti-nivolumab antibodies and neutralizing antibodies, if applicable.	Frequency distribution of baseline ADA-positive participants and ADA-positive participants after initiation of the treatment, as well as neutralizing antibody-positive participants will be presented. Baseline ADA-positive participant is defined as a participant who has an ADA-positive detected sample at baseline. ADA-positive participant is a participant with at least 1 ADA-positive sample relative to baseline after initiation of the treatment.
Incidence of anti-rHuPH20 antibodies and neutralizing antibodies, if applicable	Frequency distribution of baseline ADA-positive participants and ADA-positive participants after initiation of the treatment, as well as neutralizing antibody-positive participants will be presented. Baseline ADA-positive participant is defined as a participant who has an ADA-positive detected sample at baseline. ADA-positive participant is a participant with at least 1 ADA-positive sample relative to baseline after initiation of the treatment.

Abbreviations: ADA = anti-drug antibody; rHuPH20 = recombinant human hyaluronidase PH20.

10.3.5 Outcomes Research

All outcomes research and patient preferences analyses are exploratory and will be described in the statistical analysis plan finalized before database lock.

10.3.6 Biomarker Analyses

Descriptive summary statistics of biomarker assessments will be presented at baseline and at each on-study time point described in Section 9.8, Table 9.8-1, and Table 9.8-2, unless otherwise specified.

10.3.7 Other Analyses

Further exploratory analyses not specified here will be described in the Statistical Analysis Plan, which will be finalized before database lock and may be presented separately from the main clinical study report.

10.3.7.1 Population Pharmacokinetic Analysis of SC Nivolumab

The nivolumab serum concentration versus time data obtained in this study will be combined with data from other studies in the nivolumab clinical development program to develop PPK models. These studies will inform the systemic PK parameters of nivolumab disposition. The SC nivolumab PK data gathered from the Study CA2098KX will inform the absorption kinetics of nivolumab from the SC space to the systemic circulation. Thus, PPK models will inform the effect

of route of administration on nivolumab pharmacokinetics. These models may be further used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab to determine measures of individual exposure (eg, steady-state peak, trough, and time-averaged concentration). Model-determined exposures may be used for E-R analyses of selected efficacy and safety endpoints. If these analyses are conducted, the results of PPK and E-R analyses will be reported separately.

10.3.8 Interim Analyses

PK and safety analyses will be performed in the study on an ongoing basis. Interim analyses will be conducted in this study to select the SC nivolumab (BMS-986298) dose for Part C and for long-term dosing in Part D, and to inform additional dosing regimens to be assessed in Part B. Interim analysis are planned also for Parts C, D, and E as specified below. Details regarding interim analyses can be found in the Statistical Analysis Plan.

The following will be considered as part of determination of the SC dose:

- Interim analysis 1 included the first [redacted] participants in Part A after single dose of subcutaneous nivolumab. Participants in Part A - Group 1 were analyzed.
- Interim analysis 2 occurred when all participants in Part B Group 3 had completed the single dose of subcutaneous nivolumab. Participants in Part A - Group 1 and Part B - Group 3 were analyzed.

Data from at least [redacted] participants from Part A and from additional participants from Part B, were used to identify the SC nivolumab (BMS-986298) dose regimen in Part C and Part D of this study.

Based on preliminary PK results from Part A and Part B, SC dose of 1200 mg Q4W nivolumab is selected for Part C and Part D participants.

Interim analysis 3 will occur when the first 10 participants in Part D have completed the single dose of subcutaneous nivolumab. All participants enrolled in all Parts of the study up to the lock will be analyzed.

Interim analysis 4 will occur when all participants in Part D have completed the single dose of subcutaneous nivolumab. All participants enrolled in all Parts of the study up to the lock will be analyzed.

Interim analysis 5 will occur when all participants in Part E have completed a minimum of 6 months of follow-up from first dose date. All participants enrolled in all Parts of the study up to the lock will be analyzed.

Additional analysis for internal decision making or external publication purposes may be performed. No formal comparisons or inferences requiring any adjustment to statistical significance level will be performed.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ADA	anti-drug antibody
AE	adverse event
AFP	alpha fetoprotein
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve over the dosing interval
β-HCG	beta-human chorionic gonadotrophin
BMS	Bristol-Myers Squibb
BOR	best overall response
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
BW	body weight
C1D1	Cycle 1 Day 1
[redacted]	
Cavg	average concentration
Cavgd28	time-averaged concentration over 28 days
CBC	complete blood count
ccRCC	clear cell renal cell carcinoma
CD	cluster of differentiation
CI	confidence interval
CL	clearance
CLL	chronic lymphocytic leukemia
CLss	steady state clearance
cm	centimeter
Cmax	maximum observed serum nivolumab concentration

Term	Definition
[redacted]	
CMV	cytomegalovirus
CNS	central nervous system
COVID-19	coronavirus disease 2019
CRC	colorectal cancer
CrCL	creatinine clearance
CRF	case report form, paper or electronic
CRR	complete response rate
CT	computed tomography
CTAg	clinical trial agreement
Ctau	observed serum nivolumab concentration at the end of the dosing interval
CTC	Common Terminology Criteria
[redacted]	
CTLA	cytotoxic T lymphocyte antigen
Ctrough	trough observed serum nivolumab concentration
CV	coefficient of variation
dL	deciliter
DLBCL	diffuse large B cell lymphoma
dMMR	mismatch repair deficient
DS	drug substance
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4^{th} Edition)
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EFS	event-free survival
eg	exempli gratia (for example)
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EOI	end-of-infusion
EU	European Union
FDA	Food and Drug Administration

Term	Definition
FFPE	formalin-fixed paraffin-embedded
FSH	follicle-stimulating hormone
fT3	free triiodothyronine
fT4	free thyroxine
g	gram
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
h	hour
HBsAG	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IHC	immunohistochemistry
IL	interleukin
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
INR	international normalized ratio
IO	immuno-oncology
IRB	Institutional Review Board
IRT	interactive response technology
IU	International Unit
IUS	intrauterine hormone-releasing system
IV	intravenous
KA	first order absorption rate constant

Term	Definition
kg	kilogram
L	liter
LAM	lactation amenorrhea method
LDH	lactate dehydrogenase
MDSC	myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	
MICA	MHC class I chain-related A
MLR	mixed lymphocyte reaction
MRI	magnetic resonance imaging
MSI-H	high microsatellite instability
MTD	maximum tolerated dose
mUC	metastatic urothelial carcinoma
N	number of subjects or observations
N/A	not applicable
Nab	neutralizing antibody
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
[redacted]	
NOAEL	no-observed-adverse-effect level
NSCLC	non-small cell lung cancer
ODAC	Oncologic Drugs Advisory Committee
ORR	objective response rate
OS	overall survival
[redacted]	
PD	pharmacodynamic
PD-1	programmed death receptor 1
PD-L1/2	programmed death ligand 1/2
PFS	progression-free survival
PK	pharmacokinetics
PT	prothrombin time
PT	preferred term
PTT	partial thromboplastin time
QnW	every n weeks

Term	Definition
Q2W	every 2 weeks
RBC	red blood cell
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
rHuPH20	recombinant human hyaluronidase PH20
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
sAG	surface antigen
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SD	standard deviation
SMQ	standardized MedDRA queries
SNP	single nucleotide polymorphism
SOC	system organ class
$t_{1/2}$	half life
T3	triiodothyronine
T4	thyroxine
TB/T.bili	total bilirubin
TIL	tumor-infiltrating lymphocyte
Tmax	time of maximum observed concentration
[redacted]	
TME	tumor microenvironment
TRAE	treatment-related adverse event
TRSAE	treatment-related serious adverse event
TSH	thyroid stimulating hormone
TTE	transthoracic echocardiogram
US	United States
Vss/F (or Vss)	apparent volume of distribution at steady state
WBC	white blood cell
[redacted]	
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The term 'Participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'Subject' used in the eCRF 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 Sponsor or designee immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

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. 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 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.

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 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 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 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, 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, 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 must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' 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 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 treatment with rHuPH20 [redacted] (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, 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 commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable 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 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

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

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	It is the investigator's or designee's responsibility to dispose of all containers

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

It is the investigator's or designee's responsibility to arrange for disposal, 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.

CLINICAL STUDY REPORT AND PUBLICATIONS

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

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

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.

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

ADVERSE EVENTS

Adverse Event Definition:

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

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

Events Meeting the AE Definition

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

Events NOT Meeting the AE Definition

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

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

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.)

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 9.2.5 for reporting pregnancies).

EVALUATING AES AND SAES

Assessment of Causality

The causal relationship to study treatment is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study treatment administration and the AE.

Not related: There is not a reasonable causal relationship between study treatment administration and the AE.

- The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

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; pregnancies on a Pregnancy
- Surveillance Form (electronic or paper forms).
- The preferred method for SAE data reporting collection is through the eCRF.
- The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning.
- For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.
- **The process for Paper SAE Reporting and Contact Details will be made available locally.**

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Appendix 4 provides general information and definitions related to Woman of Childbearing Potential and methods of contraception that can be applied to most clinical trials. For information specific to this study regarding acceptable contraception requirements for female and male participants, refer to Section 6.1 of the protocol. Only the contraception methods as described in Section 6.1 are acceptable for this study.

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

Note: Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. Suggested guidelines for the duration of the washout periods for HRT types are presented below. 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 products

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

End of Relevant Systemic Exposure

End of relevant systemic exposure is the timepoint where the Investigational Medicinal Product (IMP) or any active major metabolites have 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 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 <u>User Dependent</u> *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 (rings) – 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 • Progestogen-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. (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. • 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, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study.

NOTES:

[a] Typical use failure rates may differ from failure rates when contraceptive methods are used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. For information specific to this study regarding permissibility of hormonal contraception, refer to Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol.

[c] IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. For information specific to this study regarding permissibility of hormonal contraception, refer to Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol.

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.
- LAM.

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 Appendix 3.

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]
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

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
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.

Grade of Diarrhea/ Colitis (NCI CTCAE v5)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or Grade 3-4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated < 24 hrs; Limiting instrumental ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to Grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recurs: • 0.5-1 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as Grade 3-4
Grade 3-4 Diarrhea (G3): ≥ 7 stools per day over baseline; IV fluids ≥24 hrs; limiting self care ADL Colitis (G3): severe abdominal pain, peritoneal signs G4: life-threatening, perforation	• Discontinue or delay I-O therapy per protocol* • 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication) or other immunosuppressants. • Consider testing CMV for steroid refractory colitis Note: Infliximab should not be used in cases of perforation or sepsis

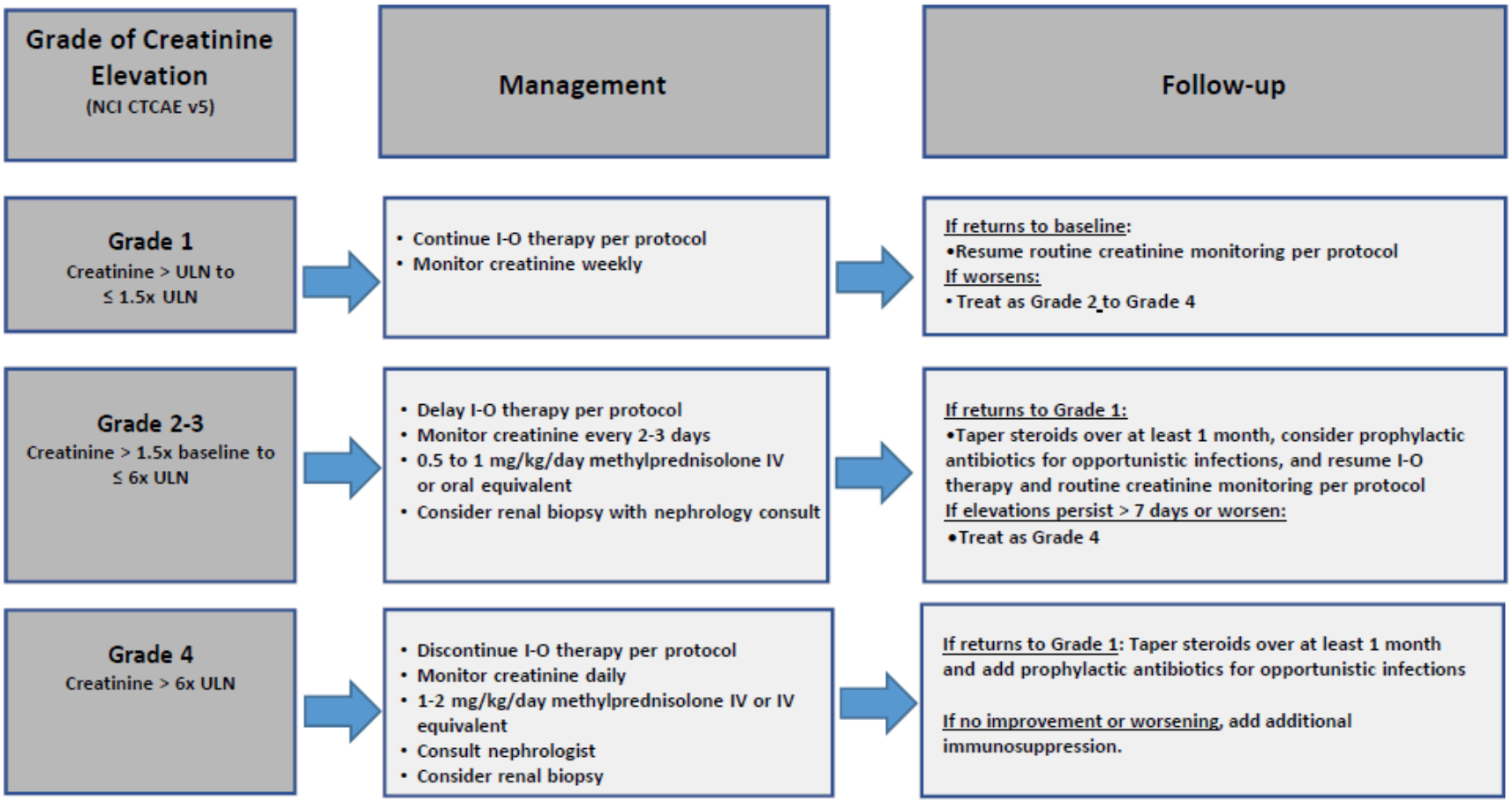
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

* Discontinue for Grade 4 diarrhea or colitis. For Grade 3 diarrhea or colitis, 1) Nivolumab monotherapy: Nivolumab can be delayed. 2) Nivolumab+ Ipilimumab combination: Ipilimumab should be discontinued while nivolumab can be delayed. Nivolumab monotherapy can be resumed when symptoms improve to Grade 1. Please refer to protocol for dose delay and discontinue criteria for other combinations.

28-Sep-2020

Renal Adverse Event Management Algorithm

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

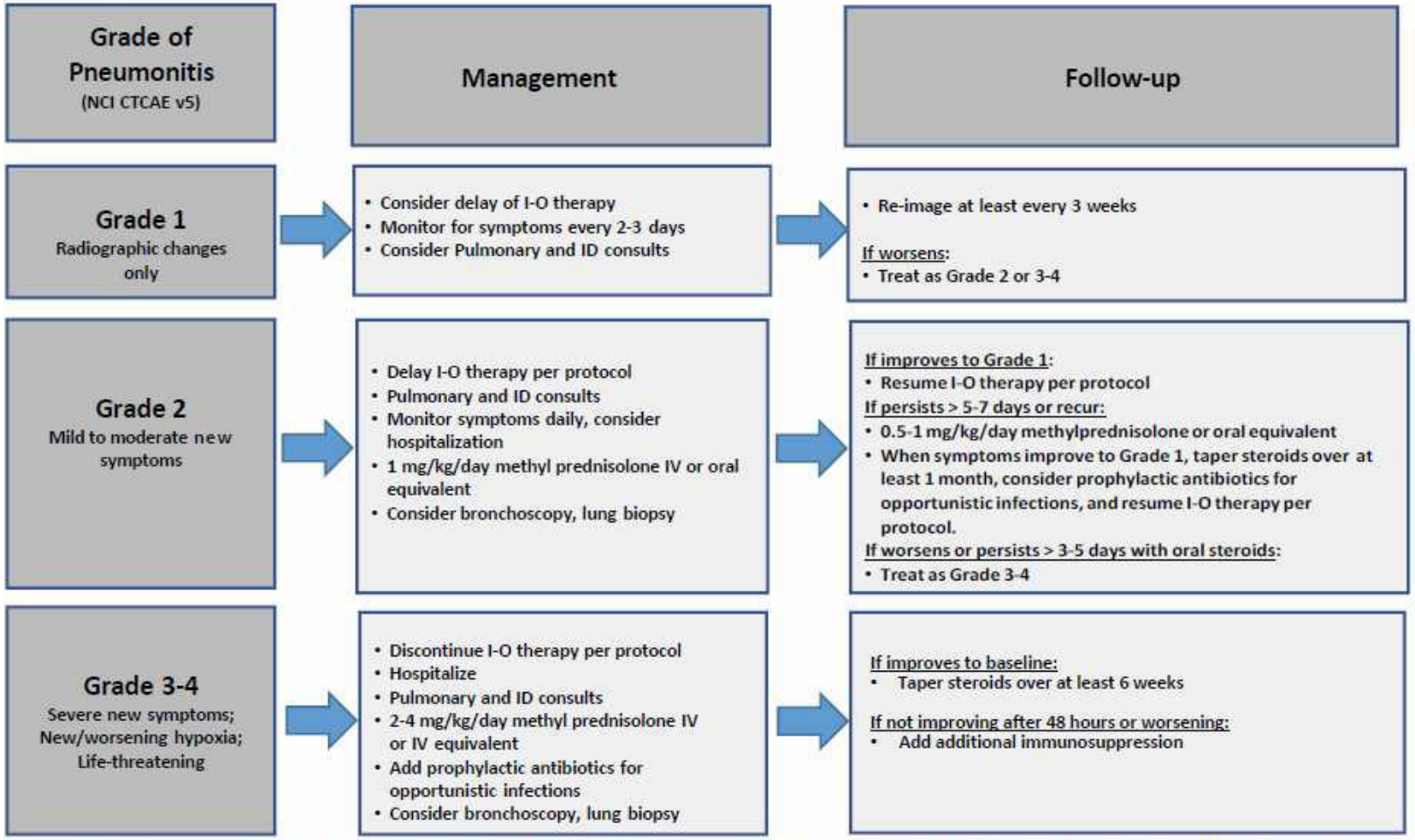


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

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.

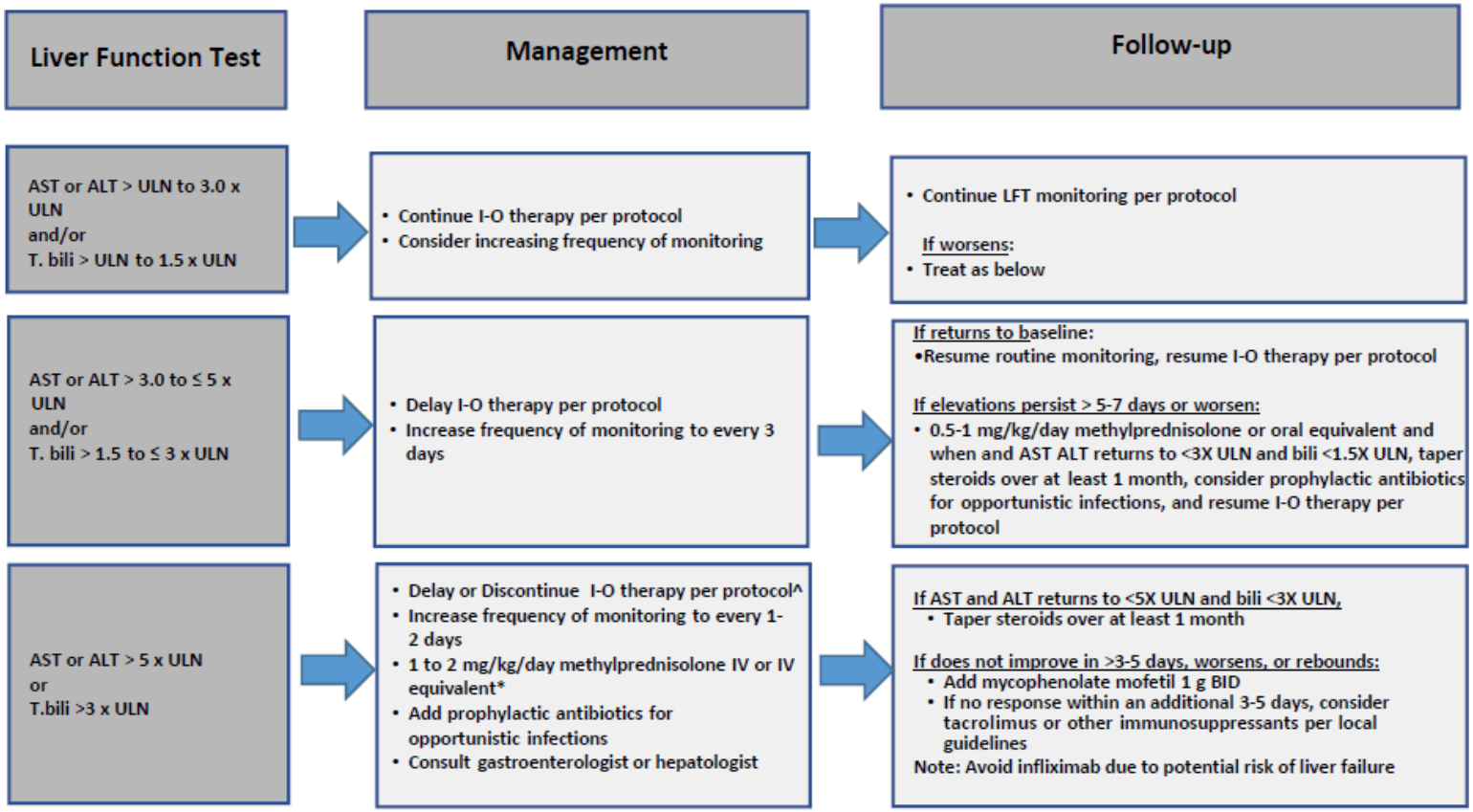


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

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, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

^ Please refer to protocol dose delay and discontinue criteria for specific details.

*The recommended starting dose for AST or ALT > 20 x ULN or bilirubin >10 x ULN is 2 mg/kg/day methylprednisolone IV.

28-Sep-2020

Note: Management of Hepatic Adverse Events is modified for HCC participants (see below modifications)

HEPATIC ADVERSE EVENT MANAGEMENT ALGORITHM

(MODIFIED FOR HCC PARTICIPANTS)

The nivolumab program has developed a standardized approach for the management of hepatic events based on cumulative data across the program in participants with normal hepatic function.

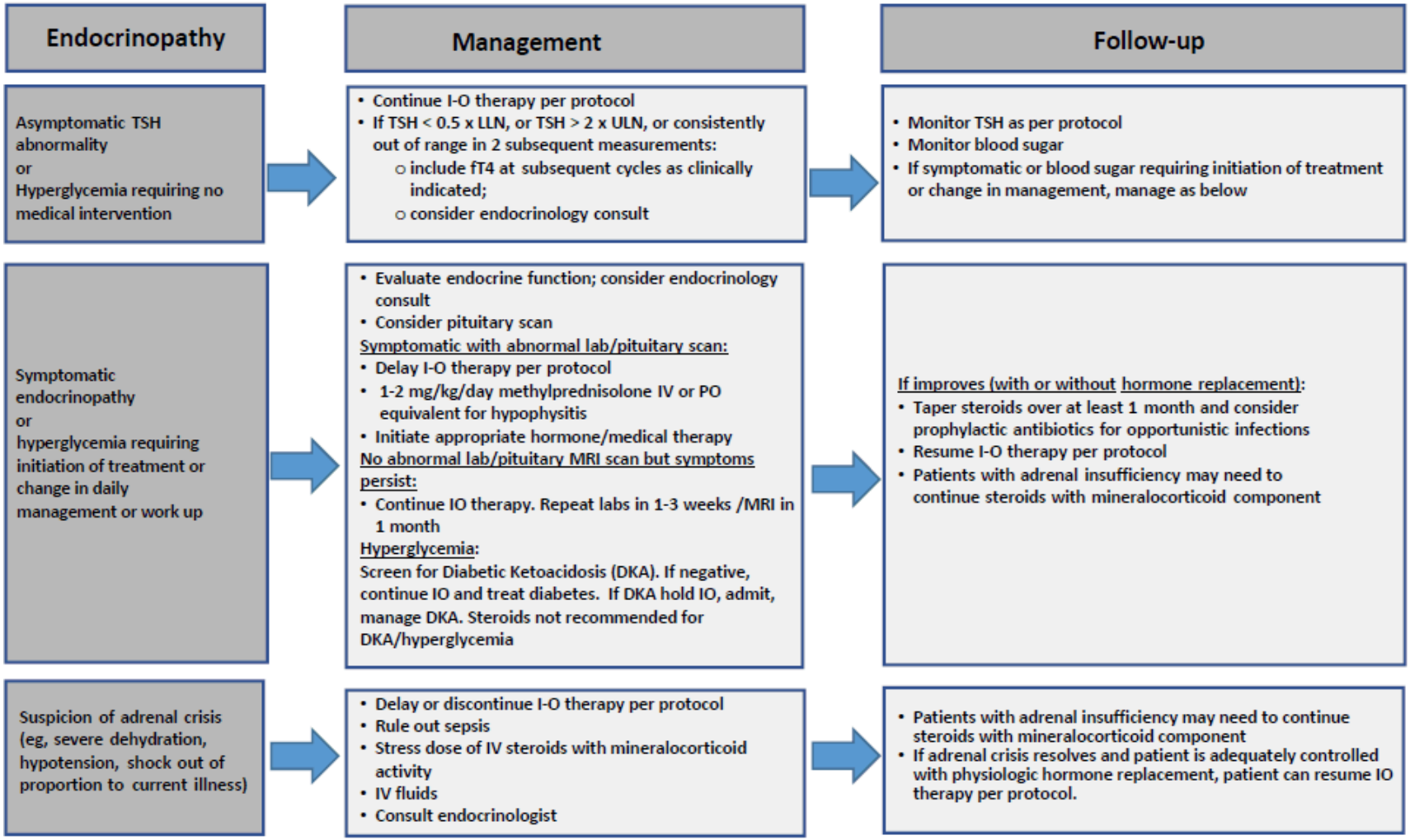
Across most nivolumab studies, the eligibility criteria for inclusion are based on a maximum AST or ALT < 3× ULN; therefore, only participants with normal to Grade 1 liver function tests have been enrolled. Participants with advanced HCC generally have underlying cirrhosis with decreased hepatic function. They may also have a concomitant chronic viral infection. For CA2098KX, the upper limits for inclusion were therefore adjusted to account for baseline liver dysfunction. Participants with AST or ALT elevations within the CTCAE Grade 2 range are eligible for inclusion. In contrast, the majority of participants included in prior nivolumab studies have had no higher than a CTCAE Grade 1 AST or ALT elevation. Criteria for dose delay, resumption, & discontinuation are in Section 7.4.2, Section 7.4.3, and Section 8.1.1. The tumor-specific approach for the management of hepatic events is as follows:

- If AST or ALT levels do not improve with a dose delay of 3-5 days or if the levels worsen, initiate steroid therapy at 0.5-2 mg/kg/day methylprednisolone or oral equivalent.
- For ALT or AST levels > 8× ULN, initiate steroid therapy promptly at 1-2 mg/kg/day methylprednisolone or oral equivalent.
- For all participants initiating steroids, consult the BMS Medical Monitor within 24 hours after initiation of steroids. Gastroenterology consult is recommended.
- If AST or ALT levels do not improve within 3-5 days or the levels worsen after the start of steroid therapy, discuss with the BMS Medical Monitor the possibility of adding mycophenolate mofetil at 1 g BID.
  - If no response to mycophenolate mofetil, consider treatment with tacrolimus or other immuno-suppressants per local guidelines and in discussion with the BMS Medical Monitor. Avoid infliximab due to potential risk of liver failure.
- Tapering of steroids can start once AST or ALT levels have declined by 1 CTCAE grade. Taper steroids slowly over no less than 1 month.

As outlined in Section 7.4.3, nivolumab therapy may resume when AST or ALT have returned to near baseline unless the criteria for permanent discontinuation are reached (Section 8.1.1).

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.

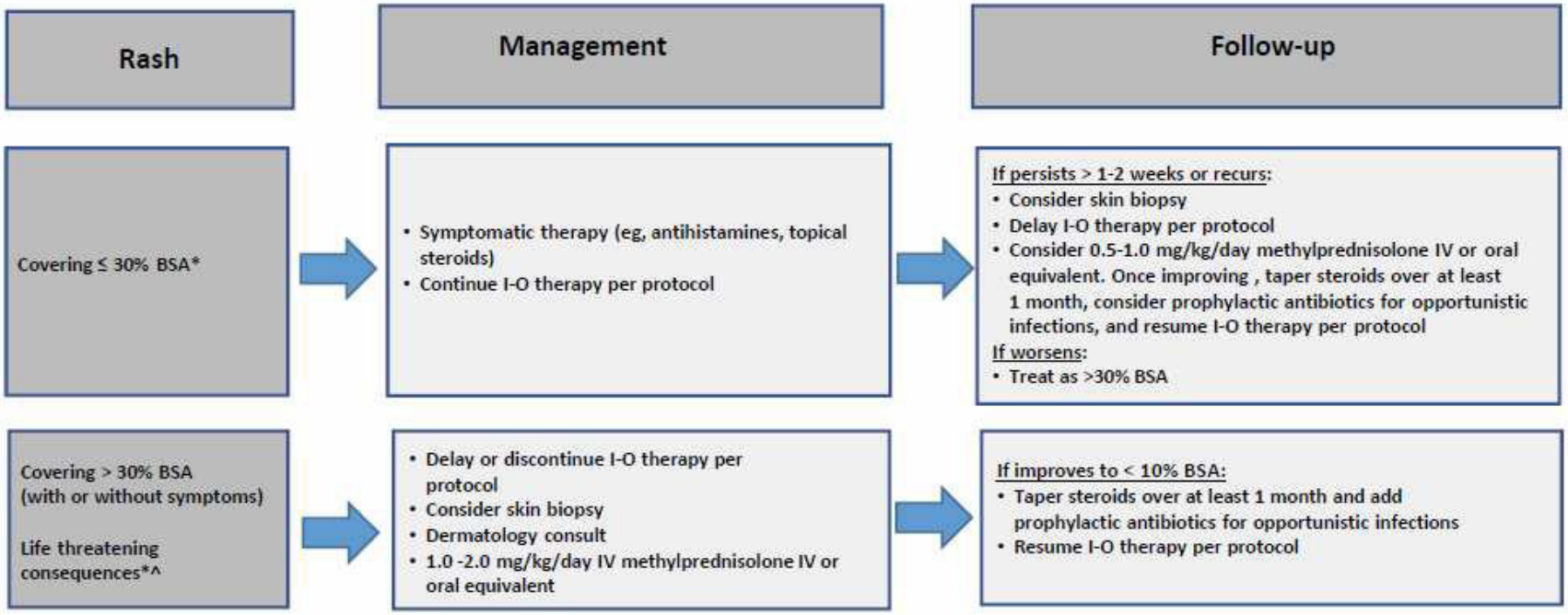


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

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, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

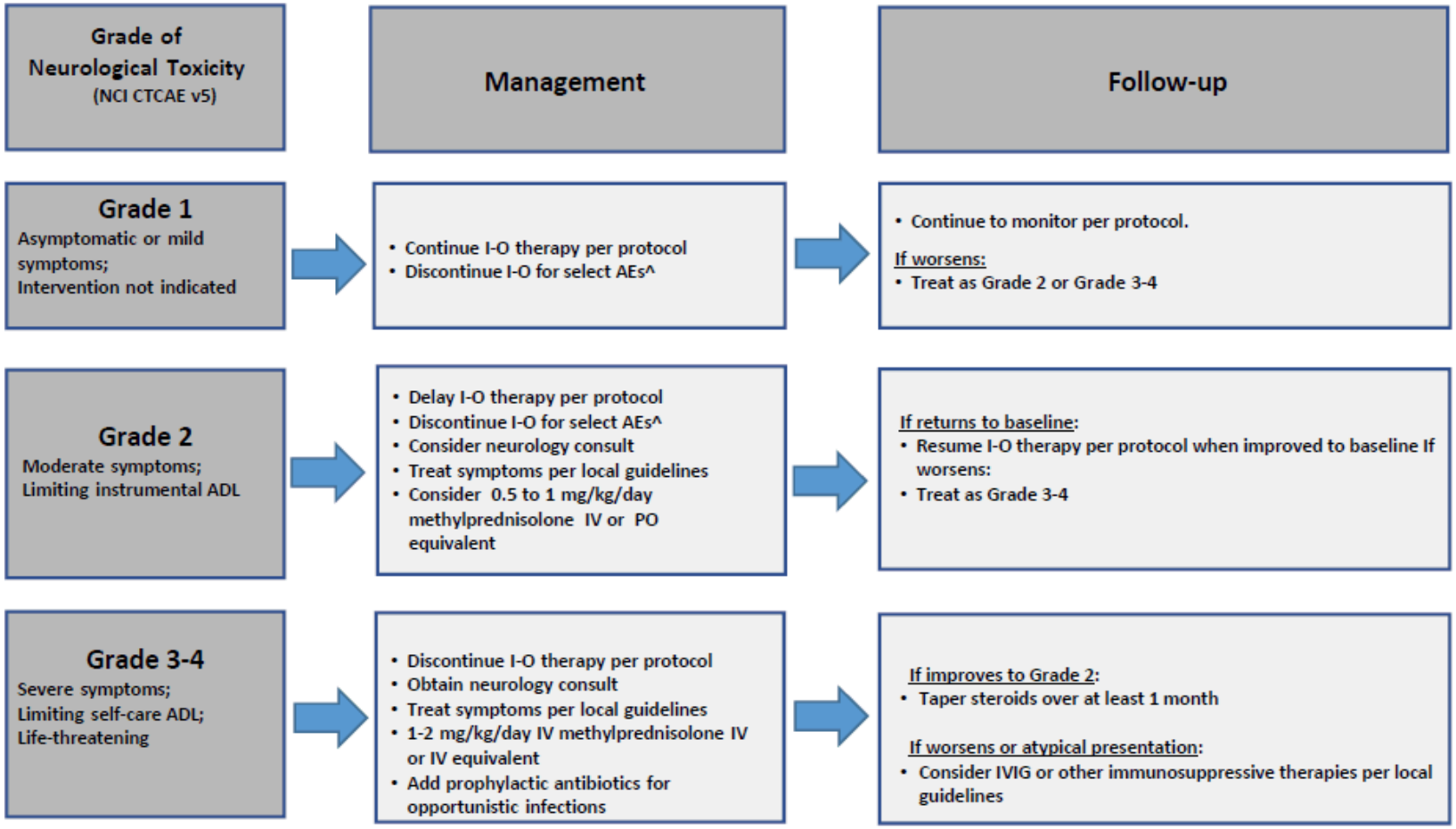
*Refer to NCI CTCAE v5 for term-specific grading criteria.

^If Steven-Johnson Syndrome (SJS),toxic epidermal necrosis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS, TEN, or DRESS is diagnosed, permanently discontinue I-O therapy.

28-Sep-2020

Neurological Adverse Event Management Algorithm

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



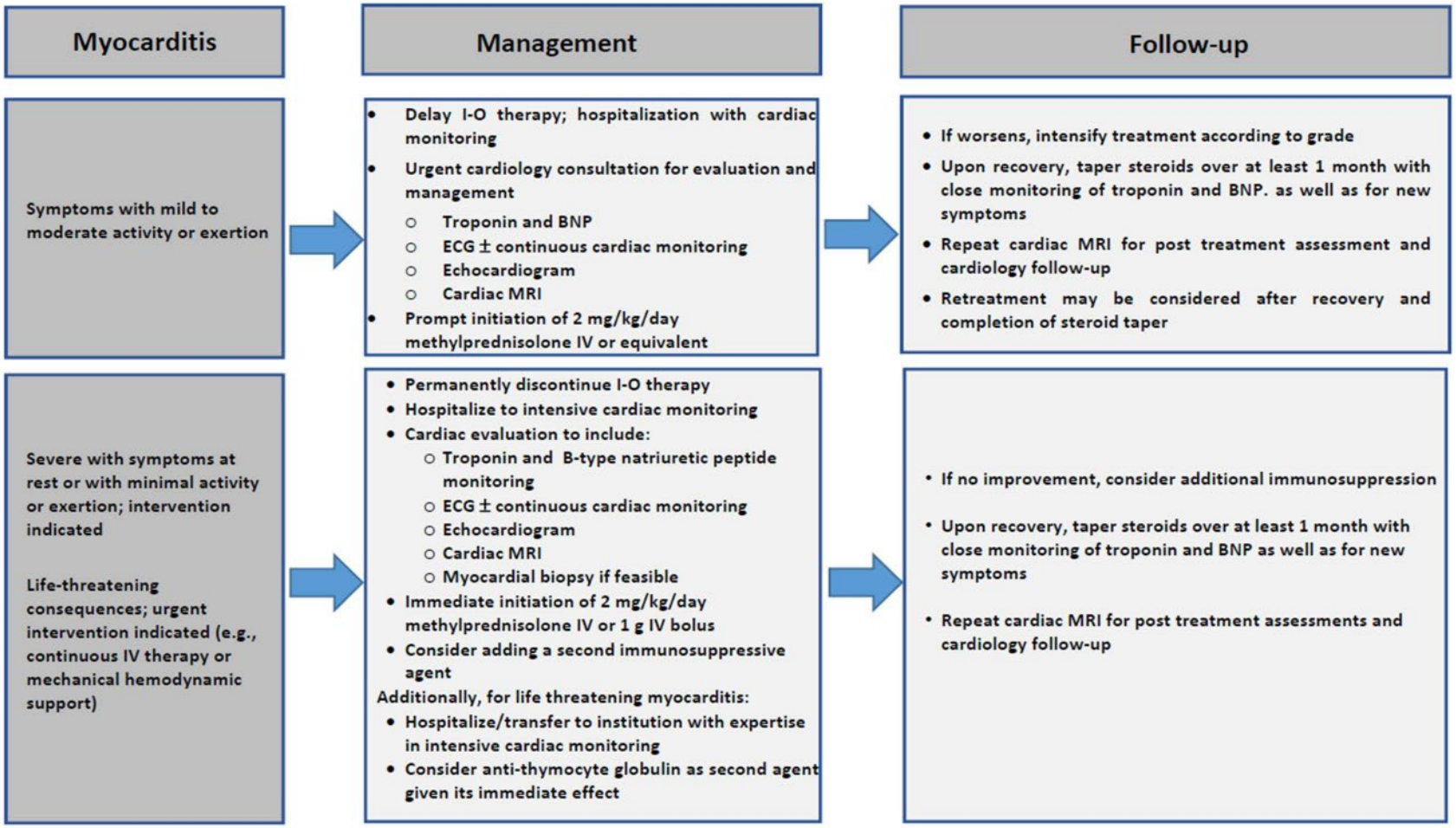
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

^Discontinue for any grade myasthenia gravis, Guillain-Barre syndrome, treatment-related myelitis, or encephalitis.

28-Sep-2020

Myocarditis 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 (eg, prednisone) at start of tapering or earlier, after 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.

28-Sep-2020

APPENDIX 7 PERFORMANCE STATUS SCALES

STATUS	SCALES		STATUS
	KARNOFSKY	ZUBROD-ECOG-WHO	
Normal, no complaints	100	0	Normal activity
Able to carry on normal activities Minor signs or symptoms of disease	90	0	Symptoms, but fully ambulatory
Normal activity with effort	80	1	
Cares for self. Unable to carry on normal activity or to do active work	70	1	Symptomatic, but in bed < 50% of the day.
Requires occasional assistance, but able to care for most of his needs	60	2	
Requires considerable assistance and frequent medical care	50	2	Needs to be in bed > 50% of the day, but not bedridden
Disabled. Requires special care and assistance	40	3	
Severely disabled. Hospitalization indicated though death non imminent	30	3	Unable to get out of bed
Very sick. Hospitalization necessary. Active supportive treatment necessary	20	4	
Moribund	10	4	
Dead	0	5	Dead

APPENDIX 8 COUNTRY SPECIFIC AMENDMENTS

Criteria for exclusion of HIV-positive subjects in Argentina, and any other countries where exclusion of HIV-positive participants is locally mandated

Protocol Section	Revised Protocol Text
Table 2-1 Screening Procedural Outline (CA2098KX)	Add "HIV testing" to list of laboratory tests.
Section 6.2 Exclusion Criteria, 1) Medical Conditions g)	Replace "Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). Testing for HIV must be performed at sites mandated by local requirements" with "Positive test for HIV"
Section 9.4.4 Clinical Safety Laboratory Assessments	Replace "Testing for HIV-1 and HIV-2 must be performed at sites where mandated by local requirements" with "Testing for HIV-1 and HIV-2 must be performed."

APPENDIX 9 CHILD-PUGH SCORE

Score	Points
Child-Pugh A	5 - 6
Child-Pugh B	7 - 9
Child-Pugh C	> 9

Scoring

	Score		
Measure	1 Point	2 Points	3 Points
Ascites	Absent	Slight	Moderate
Serum bilirubin (mg/dl)	< 2.0	2.0 - 3.0	> 3.0
Serum albumin (g/dl)	> 3.5	2.8 - 3.5	< 2.8
PT prolongation or INR	< 4 sec < 1.7	4 - 6 sec 1.7 - 2.3	> 6 sec > 2.3
Encephalopathy grade	None	1 - 2	3 - 4

Encephalopathy Grading

Encephalopathy Grade	Clinical Definition
Grade 0	Normal consciousness, personality, and neurological examination
Grade 1	Restless, sleep disturbed, irritable/agitated, tremor, and impaired handwriting
Grade 2	Lethargic, time-disoriented, inappropriate, asterixis, and ataxia
Grade 3	Somnolent, stuporous, place-disoriented, hyperactive reflexes, and rigidity
Grade 4	Unrousable coma, no personality/behavior, decerebrate

APPENDIX 10 INJECTION SITE SELECTION AND PREPARATION AND ADMINISTRATION OF STUDY DRUG

Subcutaneous Injection Site Selection and Preparation:

Subcutaneous injections of nivolumab (BMS-986298) alone and nivolumab with rHuPH20 will be administered in the abdominal area. An abdominal site that is approximately at the level of the navel (as allowed by skin condition) and approximately 15 cm (minimum 10 cm) away from the margin of the navel should be selected. The lateral portion of the abdomen is preferred over the midline area. The selected site should include fatty tissue.

Subcutaneous injections of nivolumab (BMS-986298) alone by syringe pump and nivolumab (BMS-986298) with rHuPH20 manually by syringe will be administered in the abdominal area. An abdominal site that is approximately at the level of the navel (as allowed by skin condition) and approximately 15 cm (minimum 10 cm) away from the margin of the navel should be selected. The lateral portion of the abdomen is preferred over the midline area. The selected site as determined by the Investigator should include fatty tissue and be free of any skin disease, condition (including, but not limited to, scarring, tattoos, or stretch marks), or skin pigmentation that could interfere with an assessment of the injection site.

Administration of Subcutaneous Injection:

The subject should be in a semi-reclined position during the injection (ie, semi-Fowler's position: 30-45°) and in a supine position immediately following injection for the evaluation of the injection site (ie, laying flat on back).

After the injection site for subcutaneous administration has been chosen, the total dose of nivolumab (BMS-986298) with rHuPH20 will be administered as a single subcutaneous injection, while nivolumab (BMS-986298) alone will be administered as 1 to 4 injections as described briefly below.

- Wipe skin with alcohol to cleanse. Allow to dry.
- Gently pinch and lift the skin of the abdomen (ie, "tenting').
- Insert the needle with bevel up close and parallel to the skin or at an angle that is < 20°. Once the needle is inserted, gently release the pinched and lifted skin ("untent the skin"). When the skin in in its normal state, the needle should have a slight upward angle of 20°-30°. If the subject is obese, a steeper angle for needle insertion can be used but it is recommended keeping the angle < 45°. In practical terms, the needle placement should resemble the angle of an IV needle placement in the arm. The purpose of pinching and lifting the skin is to make sure the needle is properly inserted in the SC space and is not intradermal.
- Release the subcutaneous tissue.

Care should be taken to avoid inadvertent IV or IM injection.

APPENDIX 11 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for the Protocol Amendment 04, 02-Apr-2021

Changes were made to the protocol to add a new cohort (Part E) with a 600 mg every 2 weeks (Q2W) regimen of subcutaneous (SC) nivolumab coformulated with recombinant human hyaluronidase PH20 (rHuPH20), administered manually by syringe. Approximately 36 participants with advanced/metastatic tumors, including approximately 10 participants with metastatic urothelial carcinoma (mUC), will be enrolled in Part E.

[redacted]

For Parts A-D, SC nivolumab and rHuPH20 were mixed at the site pharmacy (coadministration) prior to study drug administration. As of Protocol Amendment 04, coformulated drug product (SC nivolumab and rHuPH20 solutions pre-mixed in 1 vial with the same dose ratio) will be introduced for Part E. In addition, all ongoing participants in Parts C & D may switch to the coformulated drug product.

Additionally, the screening and on-treatment tumor tissue collection is optional in Part E, as these samples will be used for exploratory research of translational biomarkers. Biomarker and PK assessments have been streamlined for Part E.

Information was added to address administration and safety monitoring of SC nivolumab in the context of the coronavirus disease 2019 (COVID-19) pandemic, including guidance on COVID-19 vaccination. [redacted]

Other edits, including those pertaining to safety information and contraceptive requirements for nivolumab, were added in harmonization with the updated nivolumab Investigator's Brochure (IB). Nivolumab dose modification criteria were updated to align with the latest Common Terminology Criteria for Adverse Events (CTCAE) guidelines version 5 (v5).

Revisions apply to future participants enrolled in the study and, where applicable, to all participants currently enrolled. Other edits were made throughout the protocol and the synopsis to fix minor errors, to add clarity and for consistency.

Summary of key changes for Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Added contact information for Clinical Scientist.	Updated key study personnel.

Summary of key changes for Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2: Schedule of Activities, Section 3: Introduction, Section 5.1.3: Safety Follow-up Period, Section 6.2: Exclusion Criteria, Section 6.4.1: Retesting During Screening or Lead-In Period, Section 7.4.1: Dose Modifications, Section 7.7.1: Prohibited and/or Restricted Treatments, Section 9.2.1: Time Period and Frequency for Collecting AE and SAE Information, Section 9.2.3: Follow-up of AEs and SAEs, [redacted]	Added information on safety reporting related to SARS-CoV-2 and COVID-19 eligibility and vaccine guidance. [redacted]	Added to optimize adverse event (AE) and serious adverse event (SAE) collection, safety, participant eligibility, and vaccination in the context of the COVID-19 pandemic. [redacted]

Summary of key changes for Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2: Schedule of Activities, Section 3.1: Study Rationale, Section 3.1.1: Research Hypothesis, Section 4: Objectives and Endpoints, Section 5.1: Overall Design, Section 5.1.1: Screening Period, Section 5.1.2: Treatment Period, Section 5.2: Number of Participants, Section 5.4: Scientific Rationale for Study Design, Section 5.4.2: Rationale for Selection of Tumor Types, Section 5.5.4: Protocol Amendment 04: Rationale for SC Nivolumab Dose Coformulated with rHuPH20 in Part E (600 mg Q2W), Section 6.1: Inclusion Criteria, Section 6.2: Exclusion Criteria, Section 7: Treatment, Section 7.1: Treatments Administered, Section 7.1.3: Subcutaneous Administration of Nivolumab with rHuPH20, Section 7.4.3: Criteria to Resume Treatment, Section 9.4.7: Assessment of Subcutaneous Injection Site, Section 9.5.1: Pharmacokinetics and Anti-drug Antibody Sample Collection and Processing, Section 9.8: Biomarkers, Section 9.8.1: Tumor Tissue Specimens, Section 9.10.1: Patient Experience and Preference Questionnaire, Section 9.10.2: Qualitative Patient Interviews, Section 10.3.3: Pharmacokinetic Analyses	Added Table 2-2 to provide a screening procedural outline specific for Part E and updated Table 2-3 and Table 2-4 to add on-treatment and follow-up procedures for Part E. Added relevant information specific to Part E (eg, research hypothesis, objectives and endpoints, study design, inclusion of mUC participants, inclusion/exclusion criteria, PK sampling, biomarker sampling, [redacted] and patient-reported outcomes). Described the new coformulated drug product (SC nivolumab and rHuPH20 pre-mixed in 1 vial with the same dose ratio) to be introduced to Part E participants. Any ongoing participants in Parts C or D may also be switched to the coformulated drug product.	Updated to provide information for Part E cohort including study design, objectives, study population, dosing, and introduction of coformulated drug product.

Summary of key changes for Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.2.1: Nivolumab Mechanism of Action, Section 3.2.2: Nivolumab Clinical Activity, Section 3.2.3: Clinical Pharmacology of Nivolumab, Section 5.4.4: Rationale for Two Year Duration of Treatment	Updated background information on mechanism of action for nivolumab, nivolumab clinical activity in several tumor types, nivolumab PK information, and rationale for two year duration of treatment.	Updated to align with the current nivolumab IB and to provide current background information relevant to this amendment.
Section 3.2.4.2: Clinical Pharmacology of Recombinant Human Hyaluronidase PH20	Added DARZALEX FASPRO™ and PHESGO™ to list of approved products in the United States (US) and/or European Union (EU) that are in combination with rHuPH20.	Updated to align with information in updated rHuPH20 IB.
Section 3.3: Benefit/Risk Assessment	Added updated safety and immunogenicity results from Part C and Part D.	Updated for completeness since last protocol revision.
Section 4: Objectives and Endpoints, Section 10.3.2: Safety Analyses	Updated secondary endpoints to include treatment-related adverse events (TRAEs), treatment-related serious adverse events (TRSAEs), and TRAEs leading to discontinuation.	Clarified that safety analyses include collection of TRAEs and TRSAEs.
Section 6.1: Inclusion Criteria	Updated inclusion criteria related to tumor types, tumor tissue collection, tumor programmed death ligand 1 (PD-L1) expression, and reproductive status/contraceptive requirements for females.	Updated for clarity and to provide inclusion criteria for Part E.

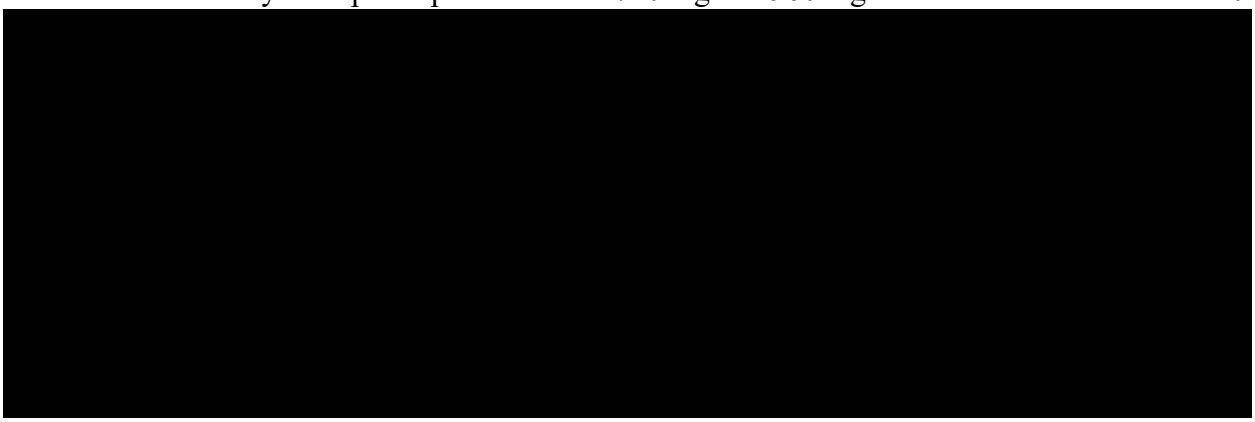
Summary of key changes for Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.1: Inclusion Criteria, Section 9.2.5: Pregnancy, Appendix 4: Women of Childbearing Potential Definitions and Methods of Contraception	Removed contraception requirements for all males. Updated duration of pregnancy surveillance from at least 5 half-lives to at least 5 months after study product administration.	Updated to align with modified nivolumab contraception and pregnancy requirements. Updated male contraception requirements due to no genotoxicity and no transmission of biologically relevant amount to women of childbearing potential (WOCBP) partner.
Section 6.2: Exclusion Criteria	Updated exclusion criteria related to brain metastases, leptomeningeal metastases, treatment with corticosteroids/immunosuppressive medications, prior malignancy, HIV/AIDs, women who are not breastfeeding, serious or uncontrolled medical disorders, complementary medicines, hepatitis B virus (HBV)/hepatitis C virus (HCV) and prior radiation therapy.	Updated for clarity and to provide exclusion criteria for Part E.
Section 7.4.1: Dose Modifications, Section 7.4.2: Dose Delay Criteria, Section 7.4.3: Criteria to Resume Treatment, Section 7.7.4: Treatment of Infusion-related Reactions, Section 9.2: Adverse Events, Appendix 6: Management Algorithms	Modified criteria for dose delay, resume, and discontinuation. Added Table 7.4.1-1. Updated treatment recommendations for infusion-related reactions. Replaced management algorithms.	Updated to align with CTCAE v5.
Section 7.4.4.2: Recommendations for Management of Hepatic Events in Nivolumab Participants with HCC, Appendix 6: Management Algorithms	Added further guidance if no response to mycophenolate mofetil in hepatocellular carcinoma (HCC) participants. Added specific information for HCC participants to Hepatic Adverse Event Management Algorithm.	Updated for clarity and to provide information specific to HCC participants.

Summary of key changes for Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.7.1: Prohibited and/or Restricted Treatments, Section 8.1.2: Nivolumab Treatment Beyond Disease Progression, Section 9: Study Assessments and Procedures, Section 9.2.1: Time Period and Frequency for Collecting AE and SAE Information, Section 9.8.4: Additional Research Collection	Updated information on prohibited and restricted treatments (corticosterioids, radiation therapy, and complementary preparations). Updated information on treatment beyond progression. Updated information regarding signs of cardiac or pulmonary toxicity. Indicated that all nonserious AEs should be collected continuously during treatment and for a minimum of 100 days following discontinuation. Updated information on additional research collection for US sites.	Updated for clarity.
Section 7.4.3: Criteria to Resume Treatment, Section 8.1: Discontinuation from Study Treatment, Section 8.1.1: Nivolumab Dose Discontinuation	Added information for resumption or discontinuation of treatment after events that lead to a prolonged delay in dosing (defined in protocol, with exceptions listed).	Updated to align with modified nivolumab clinical approaches for dose delay.
Section 9.4.4: Clinical Safety Laboratory Assessments	In Table 9.4.4-1, modified chemistry laboratory assessment panels and removed urinalysis laboratory assessment panels at screening.	Updated to align with modified nivolumab clinical safety approaches for laboratory assessments.
[redacted]		
Section 10.1: Sample Size Determination	Modified for clarity and added precision estimates for PK endpoint in Part E.	Updated for clarity and to provide statistical details on calculation of precision estimates for Part E.

Summary of key changes for Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.3.8: Interim Analyses	Added information about Interim Analysis 5, to occur when all participants in Part E have completed a minimum of 6 months of follow-up from first dose date.	Updated to provide details on Interim Analysis 5.
Appendix 2: Study Governance Considerations	In the Monitoring section, removed text indicating central review of data and scheduling of on-site visits. Provided additional details of information provided in the monitoring plan.	Updated for clarity and to allow flexibility for monitoring.
Appendix 4: Women of Childbearing Potential Definitions and Methods of Contraception	Updated information on WOCBP definition and methods of contraception. Removed contraception guidance for male participants with partners of child bearing potential.	Updated contraception guidance for participants for accuracy and clarity.

Overall Rationale for the Revised Protocol 03, 25-Oct-2019

Actual bioavailability from participants dosed at 720 mg and 960 mg SC nivolumab with rHuPH20



no clinically meaningful differences in incidence of AEs (regardless of causality or related) of any grade or Grade 3, 4, or 5 among dose treatment group, BMS considers a SC dose which provides exposures between the doses of 3 mg/kg Q2W and 10 mg/kg Q2W to have an acceptable and similar risk/benefit profile across tumors/indications.

Revised protocol 03 was warranted in order to provide updated data and dose rationale, and introduces the 1200 mg dose for Parts C & D. Primary objective of this portion of the study does not change. Purpose of Part D is to assess actual PK of 1200 mg across multiple tumors and body weight ranges in the context of continuous SC dosing. Body weight (BW) tertiles within the IV program represent a wide distribution of participants (up to 65kg, 65-90kg, >90kg), this revised

protocol also increases the number of participants in the Part D in order to enroll approximately thirty-six participants in total to represent broad range of body weights as seen in IV program (approximately ten participants within the lowest BW tertile).

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2, Table 2-1 Screening Procedural Outline; Tumor Tissue Sample	[redacted] - Updated to allow for approximately 15 participants in Part D who do not meet tissue requirements	- Clarification -Updated the number of participants in Part D that may not meet tissue requirements, as the expected total number of participants in Part D has been updated.
Section 2, Table 2-1 Screening Procedural Outline, SAE	Line item for collection of SAE added	Clarification to align table with procedures as listed in protocol.
Section 2, Table 2-2; On-Treatment Procedural Outline, Study Drug Administration	- Updated to reflect the cross-over of participants from IV dosing in Part C to 1200 mg Q4W SC nivolumab -Clarification of maximum treatment duration (regardless of IV or SC)	- Dose has been identified as 1200 mg Q4W, and protocol has been updated to reflect specific dose to be administered - Maximum treatment duration has be clarified to specify 104 weeks from first dose of nivolumab (IV or SC).
Section 3, Introduction	General update on nivolumab and SC nivolumab	Updated to reflect the most recent understanding of nivolumab and immuno-oncology.
Synopsis, Section 3.1.1, Study Rationale	Updated to reflect the identified dose of nivolumab SC	Dose has been identified as 1200 mg Q4W, and protocol has been updated to reflect specific dose to be administered
Section 3.2.2 Clinical Pharmacology of Nivolumab	Updated to provide information on SC PPK model.	Updated with data on modeling
Section 3.3 Benefit/Risk Assessment	Updated to describe results from interim analyses of Parts A and B, and the expected exposure.	Updated to include interim data
Section 4, Table 4-1 Objectives and Endpoints	Endpoint for Part C PK analyses separated from Parts A, B, and D.	This update provides clarification that only Ctau will be assessed from Part C participants. This update serves to clarify in the table, and is not a change to endpoints or analyses.
Section 5.1, Overall Design	Updated to the anticipated number or participants in Part D, and to reflect the enrollment of Parts A and B. To include the updated dose of nivolumab SC to be used in Parts C and D.	Updated to reflect Part D updates

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Updated Figure with new numbers for Part D, and identified dose included.	
Section 5.2 Number of Participants	Updated to reflect new total number of participants expected.	Number of participants for Part D was increased to 36 from 10 in the previous number. Additionally, actual enrollment of Parts A and B was reflected in this version.
Section 5.4, Scientific Rationale for Study Design	Updated to reflect the three doses under study, and that PK data from Parts A and B were used to establish the recommended dose of 1200 mg.	Updated to include the 1200 mg dose to be studied in Part C and D.
Section 5.5.2, Justification of Subcutaneous Doses of Nivolumab	Updated with PK data from 960 mg dose in Groups 3 and 4.	Updated with interim data
Section 5.5.3, Revised Protocol 03: Selection of SC Nivolumab Dose in Part D and D (1200 mg Q4W)	Updated with justification for 1200 mg Q4W dose	PK data from participants receiving the 720 mg and 960 mg nivolumab SC dose in Parts A and B, and historical nivolumab IV data across several tumor type was used to characterize the estimated exposures for the 1200 mg dose Q4W to be administered in Part D.
Section 6.1 Inclusion Criteria, h)	Updated to allow enrollment of approximately 15 participants who do not meet tissue requirements.	Based on the increased participant number planned for D, the permitted number of participants not meeting the minimum tissue requirement was also updated.
Section 7.1, Treatments Administered; Table 7.1-1: Selection and Timing of Dose	Updated with 1200 mg Q4W dose for Part D	Updated to include identified dose.
Section 7.1.3 Subcutaneous Administration of Nivolumab with rHuPH20	Updated to reflect the details of 1200 mg nivolumab SC + rHuPH20 dosing for participants in Part C and D.	Updated for 1200 mg dose.
Section 7.4.4.1 Program Safety Management Algorithms; Appendix 6	Added myocarditis to the list of algorithms provided.	Updated algorithms to align with the most recent version of the nivolumab IB
Section 8.1 Discontinuation from Study Treatment	Added Pregnancy to the list of reasons requiring discontinuation form study treatment	Updated to specify that treatment should be discontinued in the event of pregnancy.
Section 9.3 Overdose	Updated language and reporting requirements	Updated language is aligned with the reporting requirements detailed in Appendix 3.

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.4.7, Assessment of Subcutaneous Injection Site	Assessments for injection site reaction following 1200 mg dose in Parts C and D have been updated.	Included updated assessment timings for Part C and D.
Section 9.8, Biomarkers	• Description of biomarkers of interest and collections to be performed have been updated. • Collection of MDSCs has been removed. • Updated tissue requirements described for Part D.	Description of biomarkers to be studied clarified. Removed MDSC collection and updated requirements for Part D.
Section 9.10.1 Patient Experience and Preference Questionnaire; Section 9.10.2 Qualitative Patient Interviews	Updated to add collections in Part D.	Added Part D.
Section 10.1 Sample Size Determination	Updated to include rationale for 36 participants in Part D.	Updated rationale for the number of PK evaluable participants in Part D.
Section 10.3.3 Pharmacokinetic Analyses	Updated with analyses for PK	Updated to reflect that Ctau will be the primary PK parameter for Part C.
Section 10.3.8 Interim Analyses	Updated to contain details of Interim Analyses 3 and 4.	IA 3 will occur when the first 10 participants in Part D have completed 1 dose of SC nivolumab. IA4 will occur when all participants in Part D have completed a single dose of nivolumab.
Appendix 3 Adverse Events and Serious Adverse Events; Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting	Updated.	Updated to contain the reporting language.
Appendix 6, Management Algorithms	Updated to include the myocarditis algorithm.	Myocarditis algorithm was added to align with the most recent nivolumab investigator brochure.

Overall Rationale for the Revised Protocol 02, 11-Dec-2018

Part B of the study will include both assigned and randomized participants; as a result, the study design has been updated. In Part B, 30 participants will be dosed. The first 10 participants will be assigned to Group 3. The next 20 participants will be randomized 1:1 into Group 2 and Group 4.

All participants will undergo pre- and on-treatment biopsies on Cycle 1 Day 15 for Part A, Part B, and Part D. This is recommended but optional for Part A and mandatory for Part B and Part D. Timing, method of collection, and type of tumor tissue specimens from biopsy has been updated.

Up to 5 participants from each part of the trial (part A, B and D) who do not meet tissue requirements may be allowed treatment after discussion with the Medical Monitor. Other exceptions may be provided at the discretion of the Medical Monitor.

Guidelines and criteria for participants with HCC have been added that take into account the anticipated compromise of baseline liver function for these participants.

Additional changes added to provide clarity around protocol-defined populations and activities.

Revisions apply to future participants enrolled in the study, and where applicable, to all participants currently enrolled.

Summary of key changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
All	Minor formatting and typographical corrections.	Minor, therefore have not been summarized.
All	Minor clarifications throughout document for consistency across sections.	Minor, therefore have not been summarized.
Synopsis, Number of Participants and Treatment Arms and Duration Synopsis, Figure 1 Section 2 Schedule of Activities, Table 2-2 Section 5.1, Figure 5.1-1 Section 5.1 Overall Design Section 5.2 Number of participants 7.2 Method of Treatment Assignment	In Part B, 30 participants will be dosed. The first 10 participants will be assigned to Group 3. The next 20 participants will be randomized 1:1 into Group 2 and Group 4.	Change to randomization of participants in Part B
Synopsis Study Treatment Table Section 7 Treatment, Table 7-1 Footnote b	Deleted text: If needed, rHuPH20 can be obtained as local commercial product in countries if allowed by local regulations or through the investigating site's standard prescribing procedures.	[redacted] (rHuPH20) is not commercially available.
Section 2 Schedule of Activities, Table 2-1	Removed text to refer to the DM ECG study guidelines.	Document no longer available.
Section 2 Schedule of Activities, Table 2-2	Removed Inclusion/Exclusion Criteria row under Eligibility Assessments.	Inclusion/Exclusion criteria only assessed during screening visit.
Section 2 Schedule of Activities, Table 2-3 Section 5.1.3 Safety Follow-up Period	Frequency of scans for response and survival follow-up changed to every 12 weeks.	Prior text reflected continuation of on-treatment scan frequency in error.
Section 2 Schedule of Activities, Table 2-1 5.1.1 Screening period	All participants will undergo pre- and on-treatment biopsies on Cycle 1 Day 15 for Part A, Part B, and Part D. This is recommended but optional for Part A and mandatory	Timing, method, and type of tumor tissue specimens from biopsy defined, including exceptions for participants who had a biopsy in the preceding 12 months.

Summary of key changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.1 Inclusion Criteria, 2) Type of Participants and Target Disease characteristics, h) Section 9.8, Table 9.8-1 Section 9.8.1 Tumor Tissue Specimens	for Part B and Part D. Sufficient, recent tumor tissue FFPE block or unstained slides [redacted] from a metastatic tumor lesion or from an unresectable primary tumor lesion, which has not been previously irradiated, must be submitted. Up to 5 participants from each part of the trial (part A, B and D) who do not meet tissue requirements may be allowed treatment after discussion with the Medical Monitor. Other exceptions may be provided at the discretion of the Medical Monitor.	
Section 6.1 Inclusion Criteria, 2) Type of Participants and Target Disease characteristics, a), iv)	Added the following inclusion criteria for HCC participants: (1) lenvatinib added (7) Participants with chronic hepatitis B virus (HBV) infection must be on antiviral therapy and must have HBV DNA < 500 IU/mL. (8) Platelets ≥ 60 x 103/μL	The added criteria take into account anticipated compromise of baseline liver function in participants with HCC. Addition of lenvatinib reflects newly approved therapy for participants with HCC.
Section 6.1 Inclusion Criteria, 2) Type of Participants and Target Disease characteristics, a) vi)	vi) In Part B, other solid tumor types may be considered for enrollment at the discretion of the Medical Monitor.	Other solid tumor types can be enrolled in Part B at the Medical Monitor's discretion in addition to those identified in Part A.
Section 6.1 Inclusion Criteria, 2) Type of Participants and Target Disease characteristics, f)	Added text indicating that there were separate criteria for screening laboratory values for platelets, AST/ALT, and total bilirubin for HCC participants.	The added criteria take into account anticipated compromise of baseline liver function in participants with HCC.
6.2 Exclusion Criteria, 1) Medical conditions, p	Exclusion for positive urine screen for drugs of abuse is not applicable per this protocol revision.	Not applicable
6.2 Exclusion Criteria, 1) Medical conditions, q	q) Participants must not have any positive test result for HBV or hepatitis C virus (HCV) indicating presence of virus, eg, Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative). For HCC, participants with chronic HBV infection are permitted and must be on antiviral therapy and must have HBV DNA < 500 IU/mL.	Excluding participants with hepatitis B/C virus positive test results except for HCC participants with chronic HBV infection on antiviral therapy and HBV DNA < 500 IU/mL.

Summary of key changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.4.2 Dose Delay Criteria	Added dose delay criteria for participants with HCC.	The added criteria take into account anticipated compromise of baseline liver function in participants with HCC.
Section 7.4.3 Criteria to Resume Treatment	Added criteria to resume treatment for participants with HCC.	The added criteria take into account anticipated compromise of baseline liver function in participants with HCC.
Section 7.4.4.2 Management Algorithms for Immuno-Oncology Agents Section 7.4.4.1 Program Safety Management Algorithms Section 7.4.4.2 Recommendations for Management of Hepatic Events in Nivolumab Participants with HCC	Added a subsection for tumor-specific recommendations for the management of hepatic events in nivolumab participants with HCC.	The added recommendations take into account anticipated compromise of baseline liver function in participants with HCC.
Section 8.1.1 Nivolumab Dose Discontinuation	Added dose discontinuation criteria for participants with HCC	The added criteria take into account anticipated compromise of baseline liver function in participants with HCC.
Section 9.2.7 Potential Drug-induced Liver Injury (DILI)	Added definition of DILI for participants with HCC.	The added criteria take into account anticipated compromise of baseline liver function in participants with HCC.
Section 10.2 Populations for Analyses	The Evaluable PK Participants population includes all participants in the PK population who completed Cycle 1 SC and Cycle 2 IV and with adequate PK profiles for accurate estimation of PK parameters. Inadequate PK profiles are defined as 3 or more missed/unevaluable PK samples out of the 9 planned for the 2 first cycles in Part A and B and 8 planned for the 2 first cycles in Part D, including 2 or more PK samples being from Cycle 1.	Further described the Evaluable PK Participants population and defined what is considered an inadequate PK profile.
Section 10.3.3 Pharmacokinetic Analyses	Deleted Endpoint/Statistical Analysis Method table	Redundant to presented text.
Section 10.3.8 Interim Analyses	Removed reference to number of interim analyses. Details regarding interim analyses can be found in the Statistical Analysis Plan.	Removed reference to number of interim analyses to allow greater flexibility to add additional analyses if necessary.

Summary of key changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 03 Adverse Events	Updates were made to the following sections: Adverse Events Reporting of SAEs to Sponsor or Designee	BMS updated required language for the Adverse Events appendix.
Appendix 06 - 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's Brochure and nivolumab program safety parameters.
Appendix 06 - Hepatic Adverse Event Management Algorithm	Added a Hepatic Adverse Event Management Algorithm for Participants with HCC.	The added algorithm takes into account anticipated compromise of baseline liver function in participants with HCC.
Appendix 10 - Injection Site Selection and Preparation and Administration of Study Drug	Removed reference to figure. Nivolumab (BMS-986298) alone will be administered as 1 to 4 injections.	Figure not located in appendix. Added language for subcutaneous administration of nivolumab alone.

Overall Rationale for the Revised Protocol 01, 05-Jul-2018

The study will no longer include SC nivolumab Process D drug substance; as a result, the study design has been updated. Participants in Part D will receive SC nivolumab Process C drug substance with rHuPH20 manually by syringe beginning at Cycle 1 and will not receive study treatment by syringe pump.

All participants are required to have assessment of pre-treatment tumor PD-L1 expression. Results of tumor PD-L1 assessment is not required for enrollment/randomization. PD-L1 status for participants in Part A must be available prior to opening Part B for enrollment. Each treatment group [redacted] or with microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) status (for participants with colorectal cancer). Additional participants may be enrolled to meet this minimum accrual.

Additional biomarker and pharmacodynamic assessments have been added to the study.

Revisions apply to future participants enrolled in the study, and where applicable, to all participants currently enrolled.

Summary of key changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis: Overall Study Design Section 2: Schedule of Activities Section 5.1: Overall Design	Table 2.2 On-treatment Procedural Outline has been updated in Study Drug Administration.	Change in drug substance and dose regimen for study Part D.

Summary of key changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis: Overall Study Design Section 6.1: Inclusion Criteria Section 5.1: Overall Design	Added inclusion criteria 2.j. Table 2.1 Screening Procedural Outline has been updated in Eligibility Assessments.	Inclusion criteria added to require all participants to have tumor PD-L1 expression measured by IHC or prior documented MSI-H/dMMR status (for CRC) prior to study treatment.
Section 5.4	Removed Section 5.4.2 (Rationale for Inclusion of Process C and Process D Drug Substance)	Rationale for use of Process D is not needed.
Section 9.5.1	Table 2.2 On-treatment Procedural Outline has been updated in Pharmacokinetic and Immunogenicity Assessments.	Added reference to Part D PK and immunogenicity sample collection schedule table.
Section 9.4.4	Table 2.2 On-treatment Procedural Outline has been updated in Laboratory Tests.	Simplified description of clinical laboratory tests to be performed in Cycle 3 and beyond in Table 2-2. Updated list of clinical laboratory tests in Section 9.4.4.
Section 9.8: Biomarkers Section 9.8.1: Tumor Tissue Specimens	Added collection of serum [redacted] samples to Table 9.8-1.	Additional biomarker and pharmacodynamic assessments have been added to the study.
Section 3.2.2: Clinical Pharmacology of Nivolumab	Updated pharmacokinetics text.	Updated pharmacokinetics section.
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized