Official Title of Study:

A Phase 1/2 Dose Escalation and Combination Cohort Study to Evaluate the Safety and Tolerability, Pharmacokinetics, and Efficacy of BMS-986226 (anti-ICOS mAb) Alone or in Combination with Nivolumab or Ipilimumab in Patients with Advanced Solid Tumors

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CLINICAL PROTOCOL CA021002

A Phase 1/2 Dose Escalation and Combination Cohort Study to Evaluate the Safety and Tolerability, Pharmacokinetics, and Efficacy of BMS-986226 (anti-ICOS mAb) Alone or in Combination with Nivolumab or Ipilimumab in Patients with Advanced Solid Tumors

Revised Protocol 04

Study Director/Medical Monitor

[redacted]

Telephone (office): [redacted]

Fax: [redacted]

24-hr Emergency Telephone Number

USA: [redacted]

International: [redacted]

Bristol-Myers Squibb Research and Development
Route 206 & Province Line Road
Lawrenceville, NJ 08543
Avenue de Finlande 4
B-1420 Braine-l'Alleud, Belgium

promptly destroy it. All other rights reserved. References to BMS in this protocol may apply to partners to which BMS has transferred obligations, eg, a Contract Research Organization (CRO).

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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 04	31-May-2019	• Fasting glucose testing was limited to the Screening Period; on-treatment glucose testing can be non-fasting. • Guidance for premedication was added.
Revised Protocol 03	02-Dec-2018	• The eligibility criteria was modified to include additional tumor types, including but not limited to Cervical Cancer (CC), Melanoma (MEL), Renal Cell Carcinoma (RCC) and Triple Negative Breast Cancer (TNBC). • The eligibility criteria was modified to allow for up to three prior lines of systemic therapy. • The requirement for ICOS expression confirmation by IHC in pre-treatment biopsies prior to start of treatment was removed. • The protocol was modified to require tetanus booster administration 3-7 days prior to first treatment. • The protocol was modified to optimize sample collection for pharmacokinetic, pharmacodynamic [redacted] analysis. • The option for retreatment was removed from the protocol.
Revised Protocol 02	03-Apr-2018	• This protocol has been revised to modify the combination escalation of BMS-986226 with either nivolumab (Part B) or ipilimumab (Part C) to include and prioritize a Q12W dosing schedule. • On-treatment biopsy collections were changed to Q2W and Q12W. • A tetanus booster will be administered to capture pharmacodynamic activity in an antigen-specific context. • Treatment duration of BMS-986226 in combination with nivolumab or ipilimumab will be 2 years.
Revised Protocol 01	20-Jul-2017	Preliminary safety cohort added
Original Protocol	26-May-2017	Not Applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 04:

This protocol has been revised to include recommended premedication for all participants receiving BMS-986226 treatment. In addition, fasting glucose assessment was limited to Screening, while on-treatment glucose testing may be non-fasting.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-1 Screening Procedural Outline (CA021002); Table 2-2 On-treatment Procedural Outline (CA021002); Table 9.4.4-1 Clinical Laboratory Tests	Fasting glucose testing was limited to Screening. On-treatment glucose testing may be non-fasting	To clarify that fasting glucose assessment is not required for subjects while on treatment.
Synopsis; Table 2-2 On-treatment Procedural Outline (CA021002); Section 3.3 Benefit/Risk Assessment; Section 5.1.2.1 Monotherapy Dose Escalation (Preliminary Safety Cohorts and Part A); Section 5.1.2.2 BMS-986226 and Nivolumab Combination Therapy Cohort (Parts B1 and B2); Section 5.1.2.3 BMS-986226 and Ipilimumab Combination Therapy Cohort (Parts C1 and C2); Section 5.1.2.4 Combination Expansion Arms (Parts D and E); Section 7.1 Treatments Administered	Participants are recommended to receive premedication with diphenhydramine and acetaminophen to reduce risk of infusion-related reactions.	Premedication recommendation was instituted in order to reduce the risk of infusion-related reactions associated with BMS-986226 treatment.
Section 3.2.2.4 Clinical Pharmacology and Safety	Updated safety data.	Updated to provide most recent data.
Section 7.3.6 Management of Drug-related Infusion Reactions	Updated data on drug-related infusion reactions.	Updated to provide most recent data/information on drug-related infusion reactions.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Appendix 02 Study Governance Considerations	Updated potential serious breach language and included additional language updates per BMS protocol standards.	Updated per BMS protocol standards.

TABLE OF CONTENTS

[redacted]

1 SYNOPSIS

Protocol Title: A Phase 1/2 Dose Escalation and Combination Cohort Study to Evaluate the Safety and Tolerability, Pharmacokinetics, and Efficacy of BMS-986226 (anti-ICOS mAb) Alone or in Combination with Nivolumab or Ipilimumab in Patients with Advanced Solid Tumors

Study Phase: 1/2

Rationale:

Subsequent to the approval of cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and programmed death-1 (PD-1) pathway-blocking agents as anti-tumor therapies, the field of tumor immunotherapy is expanding rapidly. In addition to blocking co-inhibitory pathways, activating co-stimulatory pathways with the goal of potentiating anti-tumor immune responses are now considered a promising additional approach. With recent emerging clinical evidence that supports the significant anti-tumor activity of single-agent immunotherapies, combination therapies are now explored in an attempt to increase overall patient survival as exemplified by the combination therapy of anti-PD-1 and anti-CTLA-4 antibodies in patients with advanced melanoma. These findings raise the possibility that combining checkpoint blocking antibodies with agonistic antibodies that target T-cell co-stimulatory molecules could also be beneficial.

In this study, participants with advanced tumors will be treated with BMS-986226 (an agonistic antibody targeting inducible T-cell co-stimulator [ICOS]) in monotherapy or in combination with nivolumab (BMS-936558, PD-1 receptor blocking monoclonal antibody [mAb]) or ipilimumab (BMS-734016/MDX010; a checkpoint blocking antibody that recognizes CTLA-4).

Research hypothesis:

It is anticipated that BMS-986226, anti-ICOS mAb, administered as single agent or in combination with nivolumab (BMS-936558/MDX, anti-PD-1 antibody) or ipilimumab (BMS-734016/MDX, anti-CTLA-4 antibody), will demonstrate acceptable safety and tolerability and a favorable risk/benefit profile that will support further clinical testing. No prospective hypotheses are being formally evaluated in this study.

Study Population:

Eligible participants will have advanced solid tumors, including, but not limited to cervical cancer (CC), colorectal cancer (CRC), head and neck squamous cell carcinoma (HNSCC), melanoma (MEL), non-small cell lung cancer (NSCLC), prostate cancer (PRC), renal cell carcinoma (RCC), triple negative breast cancer (TNBC) and urothelial carcinoma (UCC). There must be histological or cytological confirmation of a malignancy that is advanced (metastatic and/or unresectable) with measureable disease as defined by Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 or Prostate Cancer Working Group 3 (PCWG 3) (prostate only), including at least 1 lesion accessible for biopsy in addition to the target lesion.

Objectives and Endpoints:

Objective	Endpoint
Primary	
To characterize the safety and tolerability of BMS-986226 administered alone and in combination with nivolumab or ipilimumab in participants with advanced solid tumors	Incidence of AEs, SAEs, AEs meeting protocol defined DLT criteria, AEs leading to discontinuation, and AEs resulting in death. Incidence of clinical laboratory test abnormalities
Secondary	
To explore the preliminary efficacy of BMS-986226 administered alone and in combination with either nivolumab or ipilimumab in participants with advanced solid tumors	ORR, median DOR, and PFS rate at 24 weeks[a]
To characterize the PK of BMS-986226 when administered alone and in combination with either nivolumab or ipilimumab in participants with advanced solid tumors	PK parameter estimates of BMS-986226
To characterize the immunogenicity of BMS-986226 when administered alone and in combination with either nivolumab or ipilimumab in participants with advanced solid tumors	Incidence of anti-drug antibodies (ADA) specific for BMS-986226
To monitor target engagement of BMS-986226 administered alone and in combination with either nivolumab or ipilimumab in participants with advanced solid tumors	Summary measures of changes from baseline (% or absolute change) in cell surface ICOS expression on T cells and ICOS-ligand + B cells
[redacted]	

[a] These endpoints will be assessed based on RECIST v1.1 or PCWG3 (prostate only) criteria and will be determined based on tumor measurements occurring every 8 weeks (± 1 week) during the treatment period and at least every 12 weeks (± 2 week) in the response and survival follow-up periods. For Part A, scans will be collected centrally and may be reviewed by BICR at a later date, or at any time during the study. For Parts B, C, D and E scans will be collected centrally to be reviewed in real time by BICR.

Abbreviations: BICR = blinded independent central review; DLT = dose-limiting toxicity; DOR = duration of response; ICOS-L = Inducible T-cell COStimulator ligand; ORR = objective response rate; PFS = progression-free survival; PK = pharmacokinetics; TIL = tumor-infiltrating lymphocytes.

Overall Design:

- This is a Phase 1/2, open-label study of BMS-986226 administered as a monotherapy or in combination with either nivolumab or ipilimumab in participants with advanced solid tumors. The study will be conducted in 3 parts: 1) dose-escalation monotherapy (Preliminary Safety Cohorts and Part A); 2) dose-escalation combination therapy with either nivolumab (Part B) or ipilimumab (Part C); 3) a dose expansion phase with either nivolumab (Part D) or ipilimumab (Part E).
- All participants receiving treatment with BMS-986226 in all study parts are recommended to receive premedication as described in Section 7.1 of the protocol.

- Monotherapy consists of 2 different cohorts as follows:
  - Preliminary Safety Cohorts with BMS-986226 administered as monotherapy at 2 mg and 8 mg once every 4 weeks (Q4W) for 24 weeks
  - Part A, with BMS-986226 administered at 25 mg, 80 mg, 200 mg, 400 mg, and 800 mg Q4W for 24 weeks
- The study will first evaluate the safety and tolerability of BMS-986226 administered Q4W, given alone, based on dose-limiting toxicities (DLTs), guided by a Bayesian Logistic Regression Model (BLRM) employing the escalation with overdose control principle.
- Parts B and C consist of different combination cohorts comprising:
  - B1: BMS-986226 administered every 12 weeks (Q12W) + nivolumab 480 mg Q4W at three dose levels of BMS-986226.
  - B2: BMS-986226 Q4W + nivolumab 480 mg Q4W at up to three dose levels of BMS-986226 evaluated in part B1.
  - C1: BMS-986226 Q12W + ipilimumab 3 mg/kg Q4W at three dose levels of BMS-986226.
  - C2: BMS-986226 Q4W + ipilimumab 3 mg/kg Q4W at up to three dose levels of BMS-986226 evaluated in part C1.
- Parts B1 and C1 will enroll concurrently. Parts B2 and C2 will enroll if additional safety, PK, or PD data is required to optimize dose and/or schedule selection, and can enroll concurrently with B1 and C1.
- BMS-986226 will be administered as a single agent (Preliminary Safety Cohorts and Part A), in combination with either nivolumab (Part B or Part D) or ipilimumab (Part C or Part E) in disease-restricted populations as follows:
  - Preliminary Safety Cohorts and Part A: CC, CRC, HNSCC, MEL, NSCLC, RCC, PRC, TNBC and UCC
  - Parts B and C: CC, CRC, HNSCC, MEL, NSCLC, RCC, PRC, TNBC and UCC
  - Parts D and E: To be determined based on safety, tolerability, PK, and PD data from Parts A, B, and C

Starting dose selection of BMS-986226 for the combination therapy cohorts will be one dose level lower than the highest monotherapy dose (Part A) that has cleared the DLT period. Subsequent doses of BMS-986226 will be determined based on all available safety (clinical and laboratory) and PK data, as well as changes in peripheral target engagement markers (eg, ICOS downregulation on T cells and ICOS + B cells) previous and completed portions of current cohorts, and BLRM-Copula model.

- The **Preliminary Safety Cohorts** consists of a single participant per dose level with BMS-986226 administered as monotherapy at 2 mg or 8 mg Q4W for up to 24 weeks of study treatment. Additional participants may be enrolled in the Preliminary Safety Cohorts per dose level as early as 5 days after the first participant is treated at each dose level to gather additional information on the safety, PK, and pharmacodynamic (PD) profile. The DLT period will be 28 days (4 weeks) in the Preliminary Safety Cohorts. Once the safety (during the 4 weeks DLT period) of 2 mg and 8 mg of BMS-986226 has been established in a single, independent

participant per dose, Part A will start. Intra-participant dose escalation is only allowed in the Preliminary Safety Cohorts as follows:

- Once the observation period of 4 weeks for 8 mg is completed, participant(s) treated at 2 mg may be offered the possibility to dose escalate at 8 mg.
- Once the DLT period of 5 weeks for 25 mg is completed, participant(s) treated at 2 mg that escalated to 8 mg or participant(s) treated with 8 mg may be offered the possibility to dose escalate at 25 mg.

- **Part A** consists of a multiple ascending dose schema that will evaluate the following dose levels of BMS-986226: 25 mg, 80 mg, 200 mg, 400 mg, and 800 mg. Enrollment in the next dose level can begin after at least 2 evaluable participants have completed 5 weeks of therapy (during the DLT evaluation) at the preceding dose level and the available safety data has been reviewed. Up to approximately 34 participants with the tumor types listed above may be treated during this part of the study (Preliminary Safety Cohorts and Part A).
- **Part B1 and Part B2** are dose escalation combination cohorts that consists of BMS-986226 administered in combination with nivolumab for duration of 2 years in the disease-restricted populations listed above. Part B1 is a combination cohort that consist of BMS-986226 administered every 12 weeks (Q12W) + nivolumab 480 mg Q4W. Part B2 is a combination cohort that consists of BMS-986226 Q4W + nivolumab 480 mg Q4W at a dose level of BMS-986226 tested in Part B1. Up to 3 different dose levels of BMS-986226 will be tested in Part B1, as determined by safety, PK and PD data. The starting dose level used in combination with nivolumab (Part B) will be one dose level lower than a monotherapy (Part A) dose that has cleared the DLT period. At each dose level, approximately 6 evaluable participants will be treated, where a sentinel participant will be enrolled in Part B1 (BMS-986226 Q12W + nivolumab 480 mg Q4W) and observed for 5 days before additional participants in Part B1 at the same dose level receive study treatment. Part B2 (BMS-986226 Q4W + nivolumab 480 mg Q4W) will be opened at dose levels evaluated in Part B1. Approximately 6-12 evaluable participants will be treated per cohort, to better characterize safety, PK, and PD of the combination. Part B2 will be utilized to provide a more granular assessment of safety and PD of BMS-986226. More than 1 dose level (no more than 3 different dose levels) may be enrolled, should additional safety, PK, and PD data be needed. Once the safety (during the DLT evaluation) of a combination of BMS-986226 and nivolumab has been established and a recommended BMS-986226 dose regimen has been selected for Part D, additional participants (up to 6 additional evaluable participants) may be treated at the recommended dose to better characterize the safety, PK, and PD profile.
- **Part C1 and Part C2** are dose escalation combination cohorts that consist of BMS-986226 administered in combination with ipilimumab for duration of 2 years in the disease-restricted populations listed above. Part C1 is a combination cohort that consists of BMS-986226 administered every 12 weeks (Q12W) + ipilimumab 3 mg/kg Q4W. Part C2 is a combination cohort that consists of BMS-986226 Q4W + ipilimumab 3 mg/kg Q4W at a dose level of BMS-986226 tested in Part C1. Part C1 aims to determine the kinetics of ICOS receptor downregulation and re-expression (and/or change in selected target engagement/[redacted]) following administration of BMS-986226 Q12W in combination with ipilimumab administered Q4W for a duration of 2 years. Continuous evaluation of toxicity events in the combination cohort will be performed throughout the enrollment. Up to 3 different dose levels of BMS-986226 will be tested in Part C1, as determined by safety, PK and PD data. At each

dose level, approximately 6 evaluable participants will be treated, where a sentinel participant will be enrolled in Part C1 (BMS-986226 Q12W + ipilimumab 3mg/kg Q4W) and observed for 5 days before additional participants in Part C1 at the same dose level receive study treatment. Part C2 (BMS-986226 Q4W + ipilimumab 3 mg/kg Q4W) will be opened at dose levels evaluated in Part C1. Approximately 6-12 evaluable participants will be treated per dose cohort, to better characterize safety, PK, and PD of the combination. Part C2 will be utilized to provide a more granular assessment of safety and PD of BMS-986226. More than 1 dose level (no more than 3 different dose levels) may be enrolled, should additional safety, PK, and PD data be needed. Once the safety (during the DLT evaluation) of a combination of BMS-986226 and ipilimumab has been established and a recommended BMS-986226 dose regimen has been selected for Part E, additional participants (up to 6 additional evaluable participants) may be treated at the recommended dose to better characterize the safety, PK, and PD profile.

- **Part D and Part E** are cohort expansion that consist of BMS-986226 in combination with either nivolumab (Part D) or ipilimumab (Part E). Continuous evaluation of toxicity events in the cohort expansions will be performed throughout enrollment in the expansion cohorts. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds 33% across all participants treated, the findings will be discussed and further enrollment will be interrupted. Depending on the nature and the grade of the toxicity, and after assessing the risk/benefit ratio, a new dose for all cohorts may be initiated at a lower dose level. The dose and schedule of BMS-986226 in Parts D and E will be determined based on all available safety, tolerability, efficacy, PK, and PD data from Parts A, B, and C. Parts D and E will enroll approximately 40 participants in each cohort. Safety, efficacy, PK, and PD data will be used to determine the precise patient population that will be enrolled in the expansion arms.
- Participants will be enrolled using the Interactive Response Technology (IRT) during the screening phase.
- For Parts A, scans will be collected centrally and may be reviewed by BICR at a later date or at any time during the study. For Parts B, C, D and E scans will be collected centrally to be reviewed in real time by BICR.

Number of Participants:

The number of participants for this study will be approximately 234. Up to approximately 34 of these participants may be treated with monotherapy (Preliminary Safety Cohorts and Part A); approximately 6 evaluable participants may be treated at each dose level for Parts B1 and C1; approximately 6-12 evaluable participants may be treated at each dose level for Parts B2 and C2; up to 6 additional evaluable participants may be treated in Parts B and/or C at a recommended BMS-986226 dose regimen for Parts D and/or E to better characterize the safety, PK, and PD profile; approximately 80 participants will be treated in combination expansion arms, Parts D and E.

Study Phases and Duration:

Screening: The screening phase will last for up to 28 days and take place prior to the first administration of study treatment for all parts. During the screening phase, the participant's initial eligibility will be established and written informed consent will be obtained. Tumor biopsies collected for all participants will be centrally evaluated for ICOS expression by

immunohistochemistry (IHC). Stool samples will be collected for baseline microbiota composition analysis. All participants will receive the tetanus booster vaccine 3-7 days prior to Cycle 1 Day 1 of first administration of study treatment. Participants will be allocated to treatment groups using the Interactive Response Technology (IRT).

Treatment Phase:

- Preliminary Safety Cohorts: The planned dose levels of BMS-986226 in the Preliminary Safety Cohorts will be 2 mg and 8 mg Q4W for 24 weeks. Following each treatment cycle, the decision to treat a participant with additional cycles of study treatment (up to a maximum of 24 weeks), will be based on safety and tolerability and tumor assessments performed every 8 weeks (±1 week).
- Part A: The initial dose level of BMS-986226 in Part A will be 25 mg Q4W for 24 weeks. Planned dose levels for dose escalation are 80, 200, 400, and 800 mg. Participants may be treated for up to 24 weeks. Following each treatment cycle, the decision to treat a participant with additional cycles of study treatment (up to a maximum of 24 weeks), will be based on safety and tolerability and tumor assessments performed every 8 weeks (± 1 week).
- Part B1: Combination therapy will consist of BMS-986226 administered every 12 weeks (Q12W) + nivolumab 480 mg administered in 4-week cycles for up to 2 years of treatment. Following each treatment cycle, the decision to treat a participant with additional cycles of study treatment, will be based on safety and tolerability and tumor assessments performed every 8 weeks (± 1 week).
- Part B2: Combination therapy will consist of BMS-986226 administered every 4 weeks (Q4W) + nivolumab 480 mg administered in 4-week cycles for up to 2 years of treatment. Following each treatment cycle, the decision to treat a participant with additional cycles of study treatment, will be based on safety, tolerability, and tumor assessments performed every 8 weeks (± 1 week).
- Part C1: Combination therapy will consist of BMS-986226 administered every 12 weeks (Q12W) + ipilimumab 3 mg/kg Q4W for up to 2 years of treatment. Following each treatment cycle, the decision to treat a participant with additional cycles of study treatment, will be based on safety, tolerability, and tumor assessments performed every 8 weeks (± 1 week).
- Part C2: Combination therapy will consist of BMS-986226 administered every 4 weeks (Q4W) + ipilimumab 3 mg/kg Q4W for up to 2 years of treatment. Following each treatment cycle, the decision to treat a participant with additional cycles of study treatment, will be based on safety, tolerability, and tumor assessments performed every 8 weeks (± 1 week).

The treatment phase in the Preliminary Safety Cohort and Part A consists of up to six 4-week treatment cycles (1 cycle = 28 days). In the Preliminary Safety Cohort and Part A, each treatment cycle will consist of BMS-986226 monotherapy for a total of 24 weeks.

In Parts B1 and C1, 4 week cycles will be used, such that BMS-986226 + nivolumab or ipilimumab will be administered starting on Cycle 1 Day 1. Nivolumab and ipilimumab will be administered on Day 1 of each cycle. BMS-986226 will be administered Q12W, or on Day 1 of every third cycle

(Cycle 1 Day1, Cycle 4, Day1, Cycle 7 Day1, etc.). Participants on Parts B1 and C1 may continue treatment for up to a total of 2 years.

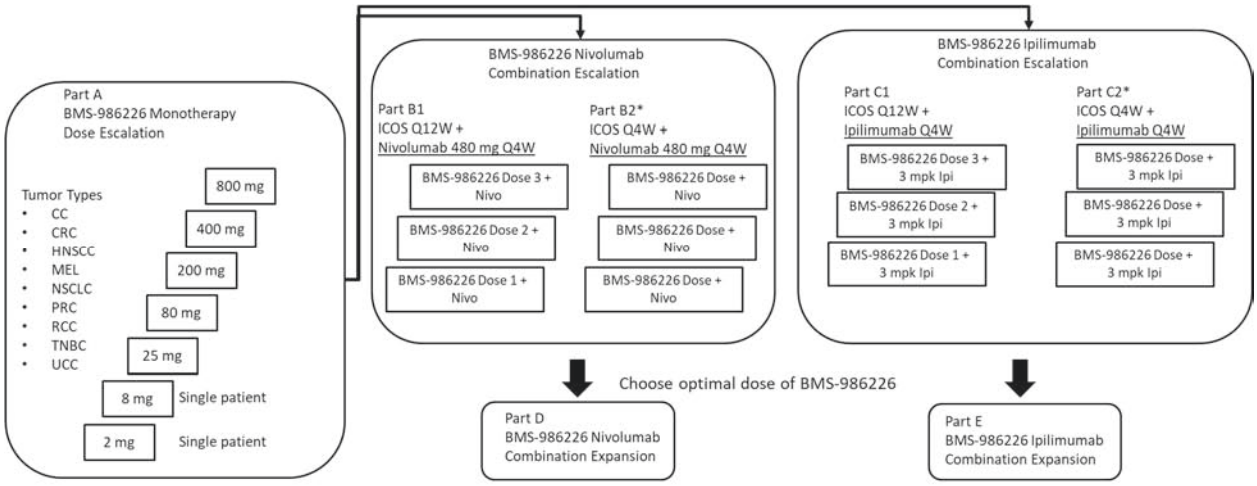
The treatment phase in Parts B2 and C2 will consist of BMS-986226 + nivolumab or ipilimumab administered on Day 1 of each cycle for up to a total of 2 years. Participants in Parts B2 and C2 will be enrolled if additional safety, PK, or PD data is required to optimize dose and/or schedule selection.

Follow-up: Safety follow-up will occur 30, 60, and 100 days (± 7 days) after either the last dose or the date of discontinuation. All participants treated with monotherapy or combination therapy will enter the survival follow-up period after the last safety visit. All participants treated with monotherapy or combination therapy with ongoing stable disease (SD), partial response (PR), or complete response (CR) will enter the response follow-up period after the last safety visit. If the participant discontinues treatment for any reason other than PD, radiological follow-up will continue until the participant receives additional treatment.

The duration of this phase is up to 2 years from the last dose of study treatment, although a longer follow-up period could be considered in selected cases if an efficacy signal is apparent. Survival follow-up will continue approximately every 3 months (12 weeks) until death, loss to follow-up or subsequent treatment, withdrawal of consent, or conclusion of the study, whichever comes first. Participants who have disease progression following the initial course of study treatment will not be evaluated for response beyond the end of treatment visit and will be allowed to receive other tumor-directed therapy as required.

A study design schematic is provided in Figure 1-1.

Figure 1-1: Study Design Schematic



* Note: Arms B2 and C2 will enroll only if additional safety, PK, and PD data are required to inform dose expansion decisions. The dose levels assessed in B2 and C2 will not exceed those evaluated in Part A, B1, or C1.

Abbreviations: CC = cervical cancer; CRC = colorectal carcinoma; HNSCC = head and neck squamous cell carcinoma; MEL = melanoma; NSCLC = non-small-cell lung cancer; RCC = renal cell carcinoma; PRC = adenocarcinoma of the prostate; RD = receptor downregulated; TNBC = triple negative breast cancer; UCC = urothelial carcinoma.

Study treatment:

Study Treatment for CA021002

Medication	Potency	IP/Non-IP
BMS-986226-01	10 mg/mL	IP
Nivolumab	10 mg/mL	IP
Ipilimumab	5 mg/mL	IP
Tetanus vaccine	Per local[a]	IP

[a] Tetanus vaccine (Tdap preferred, Td or equivalent after discussion with the Study Director/Medical Monitor (or designee)) will be obtained as local commercial product in countries if allowed by local regulations or through investigating sites standard prescribing procedures.

IP = investigational product.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA021002)

Procedure	Screening Visit (Day -28 to -1)	Day -7 to -3 Visit	Day -3 to -1 Visit	Notes
Eligibility Assessments				
Informed Consent	X			A participant is considered enrolled only when a protocol specific informed consent is signed.
IRT Participant Assignment/Treatment Assignment	X			After the participant consents, the site will use the IRT to have the participant number assigned. After the participant has completed all screening procedures, IRT will be used for treatment assignment or discontinuing the participant. Subsequent visits will need to be registered into the IRT system for drug supply.
Inclusion/Exclusion Criteria	X			
Medical History	X			Includes history of any toxicities or allergy related to previous treatments, irAEs, cardiac signs/symptoms/disease, and immunization (eg, influenza vaccine).
Prior Systemic Therapies	X			
Tobacco History/Status	X			Document participant's history and current status of tobacco use.
Archived Tumor Tissue Sample	X			Additional archival tumor tissue samples, if available, may be provided for participants in all parts as 1 paraffin block or 15-20 FFPE unstained slides. Samples must be shipped to central laboratory.
Fresh Pretreatment Tumor Biopsy	X			**All participants require a mandatory pretreatment biopsy[a] during screening.** **Archival specimens may not be substituted for this baseline specimen (See Section 6.1 for exceptions) but can be submitted to help understand the evolution of the tumor (ie, ICOS expression changes over time).** Tumor tissue to be sent for assessment of tumor content and ICOS expression.
[redacted]				

Table 2-1: Screening Procedural Outline (CA021002)

Procedure	Screening Visit (Day -28 to -1)	Day -7 to -3 Visit	Day -3 to -1 Visit	Notes
				and C4D1-pre-dose. The biopsy after dose escalation will be optional in participants in the Preliminary Safety Cohorts who intra-dose escalate up to 8 and/or 25 mg
Safety Assessments				
Full Physical Exam (PE)	X			If the screening physical examination is performed within 24 hours prior to dosing on Cycle 1 Day 1, then a single examination may count as both the screening and pre-dose evaluation.
Physical Measurements	X			Includes height and weight.
ECOG Performance Status	X			See Appendix 7.
Vital Signs	X			Includes body temperature, respiratory rate, as well as seated blood pressure and heart rate. Blood pressure, respiratory rate, and heart rate should be measured after the participant has been seated for at least 5 minutes.
12-lead ECG	X			12-lead electrocardiograms should be recorded after the participant has been supine for at least 5 minutes. All screening ECG tests should be performed as a single ECG.
Laboratory Tests				Laboratory tests listed below must be completed within 2 weeks of Cycle 1Day 1 unless otherwise noted.
Chemistry	X			See Section 9.4.4, Table 9.4.4-1. Includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, carbon dioxide, phosphorus, BUN, creatinine, creatinine kinase, CrCl (screening only), fasting glucose (screening only; on-treatment assessments do not require fasting), total protein, albumin, amylase, lipase, CRP, LDH, AST, ALT, total bilirubin, direct bilirubin (reflex only), ALP, GGT (reflex only), and Testosterone (PRC only).
CBC with Differential and Platelets	X			
Urinalysis	X			Urine to be checked for protein, glucose, blood, leukocyte esterase, specific gravity, and pH. Microscopic examination of sediment if positive for blood, protein, or leukocyte esterase on dipstick.

Table 2-1: Screening Procedural Outline (CA021002)

Procedure	Screening Visit (Day -28 to -1)	Day -7 to -3 Visit	Day -3 to -1 Visit	Notes
Thyroid Function Tests	X			TSH with reflex to free T3 and T4.
[redacted]				
Serum Tumor Markers	X			Should be performed for tumor types, included in this study, with known serologic markers (eg, CEA, CA19-9, and PSA)
Viral Status	X			HNSCC and CC only: Sites should submit and document prior human papillomavirus (HPV) status within 28 days of dosing.
Serology Tests	X			Within 28 days of dosing: hepatitis B surface antigen and hepatitis C antibody (if positive reflex to hepatitis C RNA) or hepatitis C RNA. Note: Testing for HIV-1 and HIV-2 must be performed at sites, only where mandated by local requirements.
Pregnancy Test			X	For WOCBP only; serum/urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) at screening and within 24 hours prior to dosing. The serum pregnancy test may be completed on the first day of treatment provided that the results are available before the start of study treatment. If performed within 24 hours of dosing on Cycle 1 Day 1, then Cycle 1 Day 1 pregnancy test is not required.
Follicle-stimulating Hormone	X			Women only, if needed to document postmenopausal status (refer to Appendix 4).
Tetanus booster		X		To be performed on all participants in preliminary safety cohort, Parts A, B1, B2, C1, C2, D and E, using an approved tetanus vaccine. The tetanus booster must be administered between Day -7 and Day -3, prior to dosing. A tetanus booster does not have to be administered if the participant received a tetanus booster within 6 weeks of starting study drug.
AE Reporting and Concomitant Medication Assessments				
Clinical Complaints	X			Complaints related to the disease under study collected during the 2 weeks prior to dosing.

Table 2-1: Screening Procedural Outline (CA021002)

Procedure	Screening Visit (Day -28 to -1)	Day -7 to -3 Visit	Day -3 to -1 Visit	Notes
Concomitant Medications	X			All concomitant medications taken within 4 weeks prior to study treatment administration must be recorded on the CRF.
Monitor for SAEs	X			All SAEs must be collected from the date of participant's written consent until 100 days after last dose of study drug. eSAEs should be approved in the electronic capture system within 5 business days of entry.
Efficacy Assessments				
Body Imaging	X			See Section 9.1.
Brain Imaging	X			See Section 9.1. As clinically indicated (eg, participants with history or symptoms of brain metastasis).
Bone Scan	X			See Section 9.1. As clinically indicated (eg, participants with history or symptoms of bone metastases). Bone scans will not be considered a modality for assessment for measurable disease.

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

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C1 = Cycle 1; CA19-9 = cancer antigen 19-9; CBC = complete blood count; CEA = cancer embryonic antigen; CrCl = creatinine clearance; CRF = Case Report Form; CRP = C-reactive protein; D1 = Day 1; [redacted] ECOG = Eastern Cooperative Oncology Group; eSAE = electronic serious adverse event; FFPE = formalin-fixed paraffin-embedded; GGT = gamma-glutamyl transferase; HIV = human immunodeficiency virus; ICOS = Inducible T-cell COStimulator; IRT = Interactive Response Technology; LDH = lactate dehydrogenase; NSCLC = non-small-cell lung cancer; PD-L1 = programmed death ligand 1; PSA = prostate-specific antigen; RNA = ribonucleic acid; SAE = serious adverse event; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

Table 2-2: On-treatment Procedural Outline (CA021002)

Procedures for Safety Cohort, and Parts A, B, C, D and E[a,b]	C1					C2 to beyond	C2 Only	C2 Only		Notes
Procedure	**D1**	**D2**	**D8 ± 1 days**	**D15 ± 1 days**	**D22 ± 1 days**	**D1**	**D2**	**D8 ± 1 days**	**EOT c,d,e**	
Safety Assessments										
Full PE	X								X	Pre-dose (Cycle 1 Only)
Symptom-directed PE		X	X	X	X	X				To include signs and symptoms
Physical measurements	X					X				Includes weight only. Should be collected on Day 1 of every cycle, prior to start of treatment.
ECOG Performance Status	X					X			X	ECOG score (Appendix 7).
Vital Signs	X					X			X	See note in Table 2-1. For BMS-986226, vital signs will be obtained before the infusion and then every 15 minutes (± 5 minutes) until 4 hours after completion of the infusion on Cycle 1 Day 1. For cycle 2 Day 1 and every infusion thereafter, vital signs will be obtained before the infusion and then every 15 minutes (± 5 minutes) for 60 minutes after the completion of the infusion, For nivolumab or ipilimumab, vital signs will be obtained before the infusion and then every 30 minutes (± 10 minutes) until the start of BMS-986226 infusion or per institution guidelines for administration of nivolumab or ipilimumab. The 30-minute post nivolumab or ipilimumab infusion vital signs may correspond to the pre-infusion BMS-986226

Table 2-2: On-treatment Procedural Outline (CA021002)

Procedures for Safety Cohort, and Parts A, B, C, D and E[a,b]	C1					C2 to beyond	C2 Only	C2 Only		Notes
Procedure	D1	D2	D8 ± 1 days	D15 ± 1 days	D22 ± 1 days	D1	D2	D8 ± 1 days	EOT [c,d,e]	
										vital signs. In the event BMS-986226 administration is delayed, nivolumab or ipilimumab vital signs will be obtained until 60 minutes after completion of the infusion. If any vital sign is abnormal (based on clinician assessment) at the final check, the participant must be observed further for a period of time, as clinically indicated.
[redacted]										

Table 2-2: On-treatment Procedural Outline (CA021002)

Procedures for Safety Cohort, and Parts A, B, C, D and E[a,b]	C1					C2 to beyond	C2 Only	C2 Only		Notes
Procedure	**D1**	**D2**	**D8 ± 1 days**	**D15 ± 1 days**	**D22 ± 1 days**	**D1**	**D2**	**D8 ± 1 days**	**EOT c,d,e**	
Laboratory Tests										See Section 9.4.4. On-study laboratory tests (including pregnancy testing) to be done on site/local within 72 hours prior to dosing on Day 1 of each cycle.
Chemistry	X	X	X	X	X	X	X	X	X	See note in Table 2-1. On-treatment Glucose is not required to be fasting. Every cycle on Day 1. For parts B1 and C1, Cycle 2 Day 2 only and Cycle 2 Day 8 only, assessments should take place on Cycle 4 Day 2 and Cycle 4 Day 8.
CBC with Differential and Platelets	X	X	X	X	X	X	X	X	X	Should also be collected at each time point where samples [redacted] are collected [redacted] For parts B1 and C1, Cycle 2 Day 2 only and Cycle 2 Day 8 only assessments should take place on Cycle 4 Day 2 and Cycle 4 Day 8.
Thyroid Function Tests	X					X (see notes)				To include TSH with reflex testing (free T3 and free T4), if applicable. Results should be examined by the investigator or appropriate designee within 48 hours of dose administration. To be performed during odd cycles (eg, Cycles 1, 3, and 5) only.

Table 2-2: On-treatment Procedural Outline (CA021002)

Procedures for Safety Cohort, and Parts A, B, C, D and E[a,b]	C1					C2 to beyond	C2 Only	C2 Only		Notes
Procedure	**D1**	**D2**	**D8 ± 1 days**	**D15 ± 1 days**	**D22 ± 1 days**	**D1**	**D2**	**D8 ± 1 days**	**EOT c,d,e**	
Urinalysis			As clinically indicated.							See note in Table 2-1. See Section 9.4.4.
Pregnancy Test (WOCBP)	X					X			X	Serum/urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study treatment. If the pregnancy test result is positive, hold all study treatments and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue all study treatment and immediately notify BMS Medical Monitor/Study Director or designee (see Section 9.2.5).
AE Reporting and Concomitant Medication Assessments										
Concomitant Medication Assessments	X									Review prior to dosing.
Monitor for Non-serious AEs	X									Non-serious AEs will be collected starting with the first dose of study treatment and through 100 days after last dose of study drug, or until new anti-cancer treatment is initiated, whichever comes first.
Monitor for SAEs	X									See note in Table 2-1.

Table 2-2: On-treatment Procedural Outline (CA021002)

Procedures for Safety Cohort, and Parts A, B, C, D and E[a,b]	C1					C2 to beyond	C2 Only	C2 Only		Notes
Procedure	**D1**	**D2**	**D8 ± 1 days**	**D15 ± 1 days**	**D22 ± 1 days**	**D1**	**D2**	**D8 ± 1 days**	**EOT c,d,e**	
Sample Collection										
PK Assessments			See Table 9.5-1, Table 9.5-2, Table 9.5-3, and Table 9.5-4							See Section 9.5. To be performed in all participants.
Immunogenicity Assessments			See Table 9.5-1, Table 9.5-2, Table 9.5-3, and Table 9.5-4.							[redacted]
[redacted]										

Table 2-2: On-treatment Procedural Outline (CA021002)

Procedures for Safety Cohort, and Parts A, B, C, D and E[a,b]	C1					C2 to beyond	C2 Only	C2 Only		Notes
Procedure	**D1**	**D2**	**D8 ± 1 days**	**D15 ± 1 days**	**D22 ± 1 days**	**D1**	**D2**	**D8 ± 1 days**	**EOT c,d,e**	
Efficacy Assessments										
Body Imaging						Every 8 weeks (± 1 week) prior to dosing at C3 and C5			X	See Section 9.1.
Brain Imaging			For participants with history of brain metastases, surveillance scans to be done per standard of care frequency, or sooner if clinically indicated.							See Section 9.1.
Bone Scan			As clinically indicated.							See Table 2-1. See Section 9.1.
Study Treatment Administration										Details regarding preparation and administration are provided in site training materials. In all study parts, participants will be observed for at least 60 minutes following the completion of BMS-986226 infusion due to the potential risk of, and to monitor for, infusion reactions.

Table 2-2: On-treatment Procedural Outline (CA021002)

Procedures for Safety Cohort, and Parts A, B, C, D and E[a,b]	C1					C2 to beyond	C2 Only	C2 Only		Notes
Procedure	**D1**	**D2**	**D8 ± 1 days**	**D15 ± 1 days**	**D22 ± 1 days**	**D1**	**D2**	**D8 ± 1 days**	**EOT c,d,e**	
All Parts: Premedication	X					X				In all study parts, participants are recommended to receive premedication 30 minutes prior to infusion of any study drug, to reduce the risk of infusion-related reactions, as described in Section 7.1 and Section 7.3.6. Any modification to the recommended regimen must be discussed and agreed upon with BMS Medical Monitor/Study Director.
All Parts: BMS-986226 Administration	X					X				Use vials assigned per IRT. Safety Cohort and Part A BMS-986226 will be administered every 4 weeks on the first day of each cycle Parts B1 and C1: BMS-986226 will be administered on Day 1 every 12 weeks (Cycle 1 Day1, Cycle 4 Day1, Cycle 7 Day 1, etc) Parts B2 and C2: BMS-986226 will be administered every 4 weeks on the first day of each cycle Parts D and E: The dose and schedule of BMS-986226 will be determined based on available data from Parts A, B1, B2, C1 and C2.

Table 2-2: On-treatment Procedural Outline (CA021002)

Procedures for Safety Cohort, and Parts A, B, C, D and E[a,b]	C1					C2 to beyond	C2 Only	C2 Only		Notes
Procedure	**D1**	**D2**	**D8 ± 1 days**	**D15 ± 1 days**	**D22 ± 1 days**	**D1**	**D2**	**D8 ± 1 days**	**EOT c,d,e**	
Parts B1, B2, and D **ONLY**: Nivolumab Administration	X					X				Use vials assigned per IRT. Nivolumab is administered ONLY for those participants enrolled in Parts B1, B2, and D.
Parts C1, C2, and E **ONLY**: Ipilimumab Administration	X					X				Use vials assigned per IRT. Ipilimumab is administered ONLY for those participants enrolled in Parts C1, C2 and E.

[a] The procedural outline for participants who receive additional cycles are outlined in Table 2-4.

[b] Participants taking 2 or 8 mg of BMS-986226 in the Preliminary Safety Cohorts will follow the same procedure schedule as in Part A. In the event that participants taking 2 or 8 mg of BMS-986226 should be permitted to intra-dose escalate up to 8 and/or 25 mg, the sampling schedule should be restarted at Cycle 1 Day 1 at each dose escalation, and an additional tumor biopsy may be optionally re-collected at C1D15.

[c] EOT is defined as the visit where a decision is made to discontinue the participant from treatment.

[d] For participants who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit (eg, Cycle 6 Day 175) and the start of the Week 1 safety follow-up visit.

[e] For participants who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data) and does not need to be repeated, and it will be considered the start of the Week 1 safety follow-up visit.

Abbreviations: AE = adverse event; C1 = Cycle 1; C2 = Cycle 2; C3 = Cycle 3; C5 = Cycle 5; C6 = Cycle 6; CBC = complete blood count; [redacted]; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; D1 = Day 1; D2 = Day 2; D4 = Day 4; D8 = Day 8; D15 = Day 15; D21 = Day 21; hCG = human chorionic gonadotropin; IRT = Interactive Response Technology; PE = physical examination; PK = pharmacokinetic; PD = pharmacodynamic; Q12W = every 12 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

Table 2-3: Follow-up Procedural Outline (CA021002)

Procedure	Safety Follow-up[a]			Survival/Response Long-term Follow-up	Notes
	FU 1 30 days (± 7 days)	FU 2 60 days (± 7 days)	FU 3 100 days (± 7 days)	Begins After Completion of Safety Follow-up Q12W (Q12W ± 2 weeks) Until 2 Years After Last Dose of Study Treatment	
Safety Assessments					
Symptom-directed PE	X	X	X		Symptom-directed only.
ECOG Performance Status	X	X	X		ECOG score (Appendix 7)
Vital Signs	X	X	X		See note in Table 2-1.
Laboratory Tests					See note in Table 2-1.
Chemistry	X	X	X		See note in Table 2-1.
CBC with Differential and Platelets	X	X	X		See note in Table 2-2.
Thyroid Function Tests	X	X	X		See note in Table 2-2.
Urinalysis	As clinically indicated.				See Section 9.4.4. See note in Table 2-1.
Pregnancy Test	X	X	X		See note in Table 2-2.
AE Reporting					
Concomitant Medication Assessments	X	X	X		
Monitor for Non-serious AEs	X	X	X		See note in Table 2-2.
Monitor for SAEs	X	X	X		See note in Table 2-1.
Sample Collection					
PK Assessments	See Table 9.5-1, Table 9.5-2, Table 9.5-3, and Table 9.5-4				See Section 9.5.

Table 2-3: Follow-up Procedural Outline (CA021002)

Procedure	Safety Follow-up[a]			Survival/Response Long-term Follow-up	Notes
	FU 1 30 days (± 7 days)	FU 2 60 days (± 7 days)	FU 3 100 days (± 7 days)	Begins After Completion of Safety Follow-up Q12W (Q12W ± 2 weeks) Until 2 Years After Last Dose of Study Treatment	
Immunogenicity (eg, ADA) Assessments					
Efficacy Assessments					
Body Imaging			X	X[b]	See Section 9.1. Participants should undergo tumor assessment via CT/MRI scans at least Q12W during the survival follow-up period until beginning a new anti-cancer therapy.
Brain Imaging	For participants with history of brain metastases, surveillance scans to be done per standard of care frequency, or sooner if clinically indicated.				See Section 9.1.
Bone Scan	As clinically indicated.				See Section 9.1.
Assessment of Participant Survival Status				X	Participant status will be assessed by either a clinic visit or a telephone contact.
New Anti-cancer Therapies	X	X	X	X	Any new anti-cancer therapies (including surgery and radiotherapy) will be recorded.

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

[b] Only participants with SD, PR, or CR at the EOT visit.

Abbreviations: ADA = anti-drug antibody; AE = adverse event; CBC = complete blood count; CR = complete response; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; FU = follow-up; MRI = magnetic resonance imaging; PE = physical examination; PK = pharmacokinetic; PD = pharmacodynamic; PR = partial response; Q12W = every 12 weeks; SAE = serious adverse event; SD = stable disease.

Table 2-4: Additional Treatment Procedural Outline (CA021002)

Procedure	Additional Cycles	EOT[a,b,c]	Notes
	D1		
Safety Assessments			
Full PE	X		Cycle 1 only.
Symptom-directed PE	X	X	Cycles 2 and beyond. To include signs and symptoms.
Physical Measurements	X		Includes weight.
ECOG Performance Status	X	X	ECOG score (See Appendix 7).
Vital Signs	X	X	For BMS-986226, vital signs will be obtained before the infusion and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the infusion.
Laboratory Test			See Section 9.4.4. On-study laboratory tests (including pregnancy testing) to be done on site/local within 72 hours prior to dosing.
Chemistry	X	X	See Section 9.4.4, Table 9.4.4-1. Includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, carbon dioxide, phosphorus, BUN, creatinine, creatinine kinase, CrCl, fasting glucose, total protein, albumin, amylase, lipase, CRP, LDH, AST, ALT, total bilirubin, direct bilirubin (reflex only), ALP, and GGT (reflex only).
CBC with Differential and Platelets	X	X	
Thyroid Function Tests	X	X	To include TSH with reflex testing (free T3 and free T4), if applicable. Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Urinalysis	X	X	See Section 9.4.4.
Pregnancy Test (WOCBP)	X	X	Serum/urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study treatment.

Table 2-4: Additional Treatment Procedural Outline (CA021002)

Procedure	Additional Cycles	EOT[a,b,c]	Notes
	D1		
			If the pregnancy test is positive, hold all study treatments and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue all study treatment and immediately notify BMS Medical Monitor/Study Director or designee (see Section 9.2.5).
AE Reporting and Concomitant Medication Assessments			
Clinical Complaints	X		To be completed within 2 weeks of Day 0 only if participant entered survival follow up.
Concomitant Medication Assessments	X		Review prior to dosing.
Monitor for Non-serious AEs	X		Non-serious AEs will be collected starting with the first dose of study medication and through 100 days after last dose of study drug.
Monitor for SAEs	X		See note in Table 2-1.
Efficacy Assessments			
Body Imaging	Every 8 weeks (± 1 week) prior to dosing at C3 and C5	X	See Section 9.1.
Brain Imaging	For participants with history of brain metastases, surveillance scans to be done per standard of care frequency, or sooner if clinically indicated.		See Section 9.1.
Bone Scan	As clinically indicated.		See Section 9.1.
Study Treatment Administration			Details regarding preparation and administration are provided in site training materials.
All Parts: BMS-986226 Administration	X		Use vials assigned per IRT. Safety Cohort and Part A BMS-986226 will be administered every 4 weeks on the first day of each cycle

[a] EOT is defined as the visit where a decision is made to discontinue the participant from treatment.

[b] For participants who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit (eg, Cycle 6 Day 175) and the start of the Week 1 safety follow-up visit.

[c] For participants who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data) and does not need to be repeated, and it will be considered the start of the Week 1 safety follow-up visit.

Abbreviations: AE = adverse event; D1 = Day 1; C = Cycle; CBC = complete blood count; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; hCG = human chorionic gonadotropin; IRT = Interactive Response Technology; min = minutes; PE = physical examination; PK = pharmacokinetic; Q12W = every 12 weeks; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

Table 2-5: Additional Treatment Follow-up Procedural Outline (CA021002)

Procedure	Safety Follow-up[a]			Survival/Response Long-term Follow-up	
	FU 1 30 days (± 7 days)	FU 2 60 days (± 7 days)	FU 3 100 days (± 7 days)	Begins After Completion of Safety Follow-up Q12W (± 2 weeks) Until 2 years After Last Dose of Study Treatment	Notes
Safety Assessments					
PE	X	X	X		Symptom-directed only.
ECOG Performance Status	X	X	X		ECOG score (Appendix 7)
Vital Signs	X	X	X		See note in Table 2-1.
Laboratory Tests					See note in Table 2-1.
Chemistry	X	X	X		See note in Table 2-1.
CBC with Differential and Platelets	X	X	X		See note in Table 2-2.
Thyroid Function Tests	X	X	X		See note in Table 2-2.
Urinalysis	X	X	X		See note in Table 2-1.
Pregnancy Test	X	X	X		See note in Table 2-2.
AE Reporting and Concomitant Medication Assessments					
Monitor for Non-serious AE	X				See note in Table 2-2.
Monitor for SAE	X				See note in Table 2-1.
Concomitant Medication Assessments	X				
Efficacy Assessments					
Body Imaging			X	X[b]	See Section 9.1.

Table 2-5: Additional Treatment Follow-up Procedural Outline (CA021002)

Procedure	Safety Follow-up[a]			Survival/Response Long-term Follow-up	
	FU 1 30 days (± 7 days)	**FU 2 60 days (± 7 days)**	**FU 3 100 days (± 7 days)**	**Begins After Completion of Safety Follow-up Q12W (± 2 weeks) Until 2 years After Last Dose of Study Treatment**	**Notes**
Brain Imaging	For participants with history of brain metastases, surveillance scans to be done per standard of care frequency, or sooner if clinically indicated.				See Section 9.1.
Bone Scan	As clinically indicated.				See Section 9.1.
Assessment of Participant Survival Status				X	Participant status will be assessed by either a clinic visit or a telephone contact.
New Anti-cancer Therapies	X	X	X	X	Any new anti-cancer therapies (including surgery and radiotherapy) will be recorded.

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

[b] Except for participants who start new anti-cancer therapies, participants with SD, PR, or CR at the EOT visit should undergo tumor assessment via CT/MRI scans at least Q12W during the survival follow-up period until progression.

Abbreviations: ADA = anti-drug antibody; AE = adverse event; CBC = complete blood count; CR = complete response; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FU = follow-up; PE = physical examination; PK = pharmacokinetic; PD = pharmacodynamic; PR = partial response; Q12W = every 12 weeks; SAE = serious adverse event; SD = stable disease.

In the event of multiple procedures are required at a single time point, the ECG may be obtained up to 15 minutes earlier, vital signs may be obtained up to 10 minutes earlier or later, and clinical laboratory sample may be obtained up to 5 minutes earlier than the nominal time point, ensuring the PK samples can be collected on time.

3 INTRODUCTION

CA021002 is a Phase 1/2, first-in-human (FIH), ascending, multiple-dose study of BMS-986226, an Inducible T-cell - COStimulator (ICOS; cluster of differentiation [CD]278) agonist monoclonal antibody (mAb), in humans with advanced/metastatic solid tumors as monotherapy or in combination with either nivolumab (programmed death 1 [PD-1] receptor blocking mAb) or ipilimumab (cytotoxic T lymphocyte-associated antigen-4 [CTLA-4], an activation-induced T-cell surface molecule that binds CD80 and CD86).

This study will evaluate the safety profile, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of intravenous (IV) doses of BMS-986226 administered as monotherapy or in combination with either nivolumab or ipilimumab in participants with advanced solid tumors, including but not limited to, cervical cancer (CC), colorectal cancer (CRC), head and neck squamous cell carcinoma (HNSCC), melanoma (MEL), non-small cell lung cancer (NSCLC), adenocarcinoma of the prostate (PRC), renal cell carcinoma (RCC), triple negative breast cancer (TNBC) and urothelial carcinoma (UCC).

3.1 Study Rationale

Antibody-based therapy for cancer has become established in recent years and is now one of the most successful and important strategies for treating patients with hematological malignancies and advanced solid tumors.[1] Aside from targeting antigens that are involved in cancer cell proliferation and survival, antibodies can also function to either activate or inactivate immunological pathways that are important in cancer immune surveillance.[2] It is now clear that an antigen-specific anti-cancer immune response is the result of a complex dynamic interplay between antigen presenting cells (APCs), T lymphocyte cells (T cells), and the target cancer cells. The critical balance of T-cell activity that dictates whether endogenous anti-tumor immune responses will be effective are largely understood to be controlled by antigen-specific stimuli sensed by the T-cell receptor and by the combined activity of both positive (co-stimulatory) and negative (co-inhibitory) T-cell surface molecules.[3] Within the past decade, antibodies against these key receptors have been designed and evaluated in the clinic with impressive results, heralding the onset of immunotherapy as a key pillar of anti-cancer therapy.[4]

The most extensively studied immunotherapies in cancer target the negative regulatory receptors CTLA-4 or PD-1.[5] Inhibition of these negative regulatory receptors, referred to as immune checkpoint blockade, results in the enhanced activation of T-cell responses and potent anti-tumor activity in nonclinical models. Studies with CTLA-4 blockade provided the first clinical evidence of improvement in overall survival (OS) with immune modulatory anti-cancer therapy in patients with metastatic melanoma.[6,7] Following that, Topalian et al showed that anti-PD-1 antibody

therapy resulted in objective responses in patients with melanoma, NSCLC, and renal cell carcinoma (RCC).[8]

Subsequent to the success of anti-tumor treatment with CTLA-4 and PD-1 pathway-blocking agents, the field of tumor immunotherapy is expanding rapidly. In addition to blocking co-inhibitory pathways, activating co-stimulatory pathways to potentiate anti-tumor immune responses is being considered as a promising approach.[9] With recent emerging clinical evidences of significant anti-tumor activity of single-agent immunotherapies, combination therapies are now explored because they could lead to greater depth of response and OS. This has been observed with the combination therapy of anti-PD-1 and anti-CTLA-4 antibodies in patients with advanced melanoma. It also raises the possibility that combining checkpoint blocking antibodies with agonistic antibodies targeting T-cell co-stimulatory molecules could be beneficial. Nonclinical data evaluating this type of treatment combination in mouse tumor models indicate that combination treatment indeed leads to enhanced anti-tumor activity compared with single-agent- treatment.

Administration of ipilimumab has been shown to up-regulate ICOS expression on the surface of CD4 and CD8 effector T cells in patients with superficial bladder cancer and advanced melanoma.[10] Patients with ≥ 2-fold increase in percentage of circulating $CD4^{+}ICOS^{hi}$ expression that was sustained at Week 12 showed clinical benefit, while patients with < 2-fold increase did not, thus suggesting a role for ICOS+ T cells in supporting anti-tumor activity after administration of ipilimumab (n = 14).

Nivolumab treatment results in increased ICOS gene expression in tumor biopsies in patients with both RCC and melanoma.[11,12] The increase in ICOS expression after both ipilimumab and nivolumab treatment suggests that the ICOS pathway is an appealing target for an agonist antibody in combination with either nivolumab or ipilimumab, alone or as a combination.

ICOS costimulation potently induces T-cell activation and cytokine production, and agonism of ICOS on T-effector cells (Teffs) should further enhance antitumor activity. The activity of an ICOS agonist may provide the most benefit in combination with checkpoint inhibitors that induce ICOS expression (eg, ipilimumab or nivolumab) and in patients whose T cells are not receiving an optimal costimulatory signal through ICOS due to low expression of Inducible T-cell COStimulator ligand (ICOS-L) at the tumor site.

In this study, participants with advanced tumors will be treated with BMS-986226 (an agonistic antibody targeting ICOS) monotherapy or BMS-986226 in combination with nivolumab (a checkpoint blocking antibody [anti-PD-1 antibody]) or ipilimumab (a checkpoint blocking antibody [anti-CTLA-4 antibody]) to take advantage of this enhanced anti-tumor effect.

3.1.1 Research Hypothesis

It is anticipated that an anti-ICOS mAb (BMS-986226) administered as a single agent or in combination with nivolumab (BMS-936558/MDX1106, anti-PD-1 antibody) or ipilimumab (BMS-734016/MDX010, anti-CTLA-4 antibody) demonstrates adequate safety and tolerability, as well as a favorable risk/benefit profile, to support further clinical testing.

3.2 Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of BMS-986226 is provided in the Investigator's Brochure (IB).

3.2.1 Indication Background

It is hypothesized that tumors with more frequent ICOS-expressing tumor infiltrating immune cells and less frequent or non-proximal ICOS-L-expressing cells will respond to ICOS agonist mAb (BMS-986226) therapy. In addition, the presence of FcγRII (CD32), particularly the FcγRIIB (CD32B) isoform, will be required for cross-linking and the anti-tumor activity of BMS-986226. To explore which tumor types may respond better to ICOS mAb therapy, immunohistochemistry (IHC) assessment of ICOS, ICOS-L, and CD32B expression using commercial mAbs against these proteins was performed on adjacent formalin-fixed paraffin-embedded (FFPE) sections. Several tumors were analyzed, including CRC, HNSCC, melanoma, NSCLC-adenocarcinoma type (NSCLC-AD), NSCLC-squamous cell type (NSCLC-SQC), PRC, RCC, and UCC.

As expected, specific ICOS staining was observed in cells morphologically resembling small lymphocytes. CD32B staining was observed in cells with a morphology of either a plasma cell or a small lymphocyte. While ICOS-expressing and CD32B-expressing cells were primarily distributed in tumor stroma, ICOS-L staining was seen in cells with the morphology of a small lymphocyte or tumor cells in a subset of cases. Automated image analysis using HALO software on whole slide images revealed a relatively high expression of ICOS and CD32B and low expression of ICOS-L in HNSCC, melanoma, and NSCLC-AD, and relatively high expression of ICOS and low ICOS-L and CD32B expression in UCC, but relatively low ICOS and CD32B expression and high ICOS-L expression in CRC, PRC, and RCC. NSCLC-SQC demonstrated a relatively low ICOS and high ICOS-L and CD32B expression.

External evaluation of ICOS gene expression in a variety of epithelial solid tumors demonstrated similar results, with HNSCC, NSCLC, TNBC, gastric carcinoma and CC exhibiting highest ICOS mRNA expression.[13] Based on the aforementioned hypothesis, these preliminary datasets support initial development of BMS-986226 in multiple advanced tumors, including HNSCC, NSCLC, TNBC, CC and MEL. However, ICOS is also known to be upregulated upon treatment with ipilimumab.[10] Therefore, tumors that have baseline low expression of ICOS, may become more favorable to co-stimulation in the presence of anti-CTLA-4 or anti-PD-1 therapy. Given this observation, in this study testing of BMS-986226 will be expanded to all advanced epithelial solid tumors, including previously identified low-ICOS expressing tumors, such as CRC, PRC, RCC, and UCC.

3.2.2 BMS-986226

3.2.2.1 Pharmacology of BMS-986226

The nonclinical pharmacology of BMS-986226 was evaluated in vitro, including binding to cells characterized by flow cytometry and Scatchard analysis and binding to human FcγRs characterized by surface plasmon resonance. In vitro functional assays elevated activation of T cells, antibody-driven effector function in antibody-dependent cellular cytotoxicity assays, and complement

binding assays. Cytokine release from whole blood was not observed following BMS-986226 treatment. BMS-986226 was evaluated for binding to human and cynomolgus tissues and ICOS expression was characterized by flow cytometry on human tumor-infiltrating lymphocytes (TILs). BMS-986226 was found to overcome T-regulatory cell (Treg) activity in in vitro suppression assays. In vivo, surrogate mouse binding ICOS agonists were evaluated for anti-tumor activity and PD effects in syngeneic mouse tumor models.

Further information on the pharmacology of BMS-986226 is detailed in the IB.[14]

3.2.2.2 Toxicity of BMS-986226

The nonclinical safety of BMS-986226 was evaluated in vitro in a human tissue cross-reactivity study and in cytokine-release and lymphocyte-activation assays in human cells. In vivo, BMS-986226 was evaluated in exploratory repeat-dose IV toxicity studies in rats and cynomolgus monkeys. In addition, an exploratory single- and repeat-dose (2-week) IV toxicity study was conducted in mice using BMS-986246, a surrogate anti-mouse ICOS agonistic antibody with identical complementarity-determining regions (hamster-derived) as BMS-986226, with mouse Fc domains, and with comparable affinity for mouse ICOS.

In a Good Laboratory Practice (GLP)compliant tissue cross-reactivity study in normal human tissues, staining was consistent with known ICOS expression on T cells and demonstrated binding of BMS-986226- fluorescein isothiocyanate (FITC) on the membrane of a subset of mononuclear cells (consistent with lymphocytes) in lymphoid tissues and other tissues with mononuclear infiltrates. BMS-986226 did not induce cytokine release or increase the expression of activation markers on human T, B, or natural killer (NK) cells.

The mouse, rat, and cynomolgus monkey were evaluated in toxicology studies because BMS-986226 binds to ICOS receptors expressed on activated T cells from mice, rats, and cynomolgus monkeys with comparable affinity as ICOS expressed on activated human T cells (concentration required for 50% efficacy values of 0.13 nM to 0.87 nM), and is pharmacologically active.

To explore the feasibility of pivotal rodent studies, single-dose (mouse only) and repeat-dose exploratory studies in rats with BMS-986226 and in mice with BMS-986246 were conducted. BMS-986226 and BMS-986246 resulted in mortality in rats and mice, respectively, after repeated administration. These mortalities were considered secondary to anti-drug antibody (ADA)-mediated hypersensitivity reactions based on the nature and timing of clinical signs, presence of serum ADA in affected animals, and elevated serum cytokine levels and evidence of complement activation in rats. Therefore, rodent species were considered not suitable for further toxicity assessment in pivotal studies. It should be noted that as described in International Conference on Harmonisation (ICH) S6, the induction of ADA formation in animals is not predictive of a potential for ADA formation in humans.

In the GLP 1-month IV toxicity study in cynomolgus monkeys, doses of 0, 1.5 mg/kg (every 3 weeks [Q3W], 2 total doses), and 15 mg/kg or 75 mg/kg (once every week (Q1W), 5 total doses), were administered as a slow bolus injection. BMS-986226 was clinically well tolerated at all doses

without any adverse effects. No significant irritation or local tolerance issues were observed at the injection sites following repeated IV administration of BMS-986226 as a slow bolus injection at ≤ 75 mg/kg in cynomolgus monkeys.

BMS-986226-related findings were limited to PD and immunomodulatory effects at all doses that included ICOS receptor expression (RE)/receptor occupancy (RO) changes (for CD4 helper T cells), suppression of T-dependent antigen response to keyhole limpet hemocyanin, decreased levels of T cells (including total T cells, CD4 helper T cells, CD4 Tregs, central memory CD4 T cells, and central memory CD8 T cells), decreased CD4 T-cell activation, and decreased percentages of antigen-specific CD8 T cells. Many of these changes persisted up to the end of the recovery period at ≥ 15 mg/kg Q1W consistent with continued BMS-986226 exposure throughout the recovery period and the subsequent sustained ICOS receptor downregulation at these doses. In general, ICOS RE levels inversely correlated with serum BMS-986226 concentrations. Based on the lack of adverse findings, the high dose of 75 mg/kg (Q1W, mean sex-combined area under the concentration-time curve (AUC) from time zero to 168 hours [AUC(0-168h)=452,000 μg•h/mL]) was considered the no-observed-adverse-effect level (NOAEL). In addition, for determination of the human maximum recommended starting dose (MRSD), 75 mg/kg was also considered the highest nonseverely toxic dose (HNSTD). The HNSTD/NOAEL of 75 mg/kg in cynomolgus monkeys is 250× higher than the proposed starting dose in humans (0.3 mg/kg) with a corresponding plasma AUC multiple of 102× the projected human AUC at the starting dose (approximately 4425 μg•h/mL; see Section 5.4.1).

Overall, the nonclinical toxicology assessment of BMS-986226 has demonstrated an acceptable safety profile, supporting clinical use in oncology patients. Additional details are provided in the BMS-986226 IB.

3.2.2.3 Nonclinical Metabolism and Pharmacokinetics of BMS-986226

This section summarizes the data available from a series of in vivo PK and PD studies that were conducted with BMS-986246 (ICOS.4-mIgG1, an anti-mouse surrogate antibody being used as a rodent surrogate for BMS-986226) and BMS-986226 in mice and cynomolgus monkeys, respectively.

In mice, following a single IV bolus dose of 1 mg/kg, the serum concentrations of BMS-986246 exhibited a bi-exponential decline.[15] The serum clearance was 1.8 mL/h/kg and the apparent terminal half-life in serum (T-HALF) was 0.65 hours. After a single intraperitoneal dose of 0.1, 1, or 10 mg/kg, BMS-986246 was slowly absorbed, with a time of maximum observed plasma concentration (Tmax) of 6 to 24 hours, and the absolute bioavailability was 38%, > 100%, and > 100%, respectively; reasons for the higher bioavailability at higher doses are not known. Over this dose range, increases in exposure were more than dose proportional; with a dose ratio of 1:10:10, respectively, and the maximum observed plasma concentration (Cmax) and AUC from time zero extrapolated to infinite time values increased in the proportion of 1:13:177 and 1:33:599, respectively.

After IV dosing to cynomolgus monkeys, the systemic exposure of BMS-986226 increased in a dose-proportional manner between 1 and 10 mg/kg.[15] Extracellular distribution was limited in both mice and cynomolgus monkeys.

No in vitro or in vivo metabolism studies have been conducted with BMS-986226. In accordance with the regulatory guidelines for biotechnology-derived pharmaceuticals,[16] the expected in vivo degradation of mAbs is to small peptides and amino acids via biochemical pathways that are generally understood and independent of typical small-molecule, drug-metabolizing enzymes.

In accordance with regulatory guidelines for biotechnology-derived pharmaceuticals,[16] no mass balance studies with BMS-986226 were conducted in animals.

3.2.2.4 Clinical Pharmacology and Safety

BMS-986226 has been administered to 21 participants between October 2017 and 28-March-2019, in doses ranging from 2 mg to 200 mg. All described data are preliminary and subject to change. Nineteen of 21 treated participants received BMS-986226 monotherapy. Monotherapy treatment was well tolerated. Grade 1/2 infusion reactions have been reported in 7 of 19 participants, and have been clinically manageable. A Grade 3 drug-related hypersensitivity was reported for a participant in the 80 mg cohort during BMS-986226 infusion after the above data cut-off date. Two participants have been treated with BMS-986226 in combination with ipilimumab, with no adverse events (AEs) reported as of the 28-March-2019 data cut-off date.

Given the small number of participants treated with BMS-986226, the subsequent more detailed evaluation of safety is based on information from nonclinical studies, as described in Section 3.2.2, as well as preliminary clinical study data.

As described in ICH S6, the induction of ADA formation in animals is not predictive of a potential for ADA formation in humans. Since BMS-986226 is a humanized mAb, it is expected to be less immunogenic in humans; however, it has the potential to induce the development of ADAs following administration. Preliminary data suggests that ADAs are formed in participants treated with BMS-986226. The relationship between the incidence of infusion reactions and emergence of ADAs is currently unknown based on the small number of treated participants. However, most infusion reactions are occurring during the first infusion of BMS-986226, while the ADAs are detected 2-4 weeks following the initial BMS-986226 administration. Additionally, because BMS-986226 will be evaluated in combination with either nivolumab or ipilimumab, it is possible that this combination may increase the development of BMS-986226 ADA versus BMS-986226 monotherapy. In combination therapy, BMS-986226 may potentiate immune-related adverse reactions caused by nivolumab or ipilimumab. Potential safety concerns and recommended management guidelines regarding nivolumab- or ipilimumab-induced AEs are summarized in the nivolumab IB[17] and ipilimumab IB.[18]

Immuno-modulatory antibodies, which provide activation signals to T cells, also have the potential to cause cytokine release. Nonclinical data indicate that BMS-986226 does not induce cytokine release when incubated with human peripheral blood mononuclear cells (PBMC). In addition, administration of nivolumab and/or ipilimumab monotherapy or combination therapy in clinical

studies did not produce AEs related to cytokine release syndrome. There is no evidence that BMS-986226 will induce cytokine release syndrome when administered in combination.

BMS-986226 did not cause cytokine release or activation of lymphocytes when incubated with human PBMCs, and tissue cross-reactivity studies revealed staining of only mononuclear cells in various tissues (no off-target binding). Thus, the expected effects are anticipated to be limited to activated CD4 and CD8 T lymphocytes and T regs.

3.2.2.5 Pharmacokinetics of BMS-986226

BMS-986226 has been administered to 12 participants to date, at four different doses; therefore, insufficient data are available to clearly characterize human pharmacokinetics. Based on nonclinical data, the PK of BMS-986226 are expected to be similar to those of other mAbs. The predicted PK estimates for total plasma clearance (CL), volume of distribution, and T-HALF of BMS-986226 following IV administration are 0.079 mL/h/kg, 0.066 L/kg, and 25 days, respectively. All projected human exposures are expected to be less than those exposures deemed safe in the nonclinical toxicology studies.

3.2.3 Nivolumab

3.2.3.1 Pharmacology and Mechanism of Action of Nivolumab

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[19,20,21] 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.[22] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA-4, ICOS, and B- and T-lymphocyte attenuator (BTLA). [23] PD-1 signaling has been shown to inhibit CD-28-mediated up-regulation of interleukin (IL)-2, IL-10, IL-13, interferon-γ (IFN-γ) and Bcl-xL. PD-1 expression also been noted to inhibit T-cell activation and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[24] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands programmed death ligand-1 (PD-L1) and programmed

death ligand-2 (IC50 1.04 nM and 0.97 nM, respectively). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction. Using a cytomegalovirus (CMV) re-stimulation assay with human PBMC, the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV-specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and results in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[25]

3.2.3.2 Clinical Pharmacology and Safety of Nivolumab

The PK of nivolumab were studied in participants over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. The geometric mean (coefficient of variation [CV]%) CL was 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state was 8.0 L (30.4%), and geometric mean elimination T-HALF was 26.7 days (101%). 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-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered Q2W. The clearance of nivolumab increased with increasing body weight. The population pharmacokinetic (PPK) analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline lactate dehydrogenase, PD-L1, solid tumor type, baseline tumor size, and hepatic impairment.

Although Eastern Cooperative Oncology Group (ECOG) status, baseline glomerular filtration rate (GFR), albumin level, and body weight had an effect on nivolumab CL, the effect was not clinically meaningful. When nivolumab is administered in combination with ipilimumab, the CL of nivolumab was increased by 24%, whereas there was no effect on the clearance of ipilimumab. Additionally, PPK and exposure response analyses have been performed to support use of 240 mg Q2W dosing in addition to the 3 mg/kg Q2W regimen. Using the PPK model, exposure of nivolumab at a 240-mg flat dose was identical to a dose of 3 mg/kg for participants weighing 80 kg, which was the approximate median body weight in nivolumab clinical studies.

Full details on the clinical pharmacology aspects of nivolumab can be found in the nivolumab IB.[17]

3.2.4 Ipilimumab

3.2.4.1 Pharmacology and Mechanism of Action of Ipilimumab

CTLA-4, an activation-induced T-cell surface molecule, is a member of the CD28:B7 immunoglobulin (Ig) superfamily that competes with CD28 for B7. CTLA-4-mediated signals are inhibitory and turn off T-cell-dependent immune responses.[26] Ipilimumab is a fully human monoclonal IgG1κ that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. The proposed mechanism of action for ipilimumab is interference of the

interaction of CTLA-4 with B7 molecules on APCs, with subsequent blockade of the inhibitory modulation of T-cell activation promoted by the CTLA-4/B7 interaction.

Additional details are provided in the current version of the ipilimumab IB.[18]

3.2.4.2 Clinical Pharmacology and Safety

Phase 3 programs are ongoing in melanoma, PRC, and lung cancer. The safety profile of ipilimumab is generally consistent across these studies with (a) the majority of AEs being inflammatory in nature, which is consistent with the proposed mechanism of action of ipilimumab; (b) the same types of such immune-mediated events in the gastrointestinal (GI) tract, skin, liver, and endocrine system being reported; and (c) most of these events being manageable with immune suppressive therapies.

In addition, a completed, large, Phase 2 study (Study CA184041) has investigated the addition of ipilimumab to carboplatin and paclitaxel using 2 different schedules (concurrent and phased) in participants with NSCLC or small cell lung cancer.

Ipilimumab offers a clinically meaningful and statistically significant survival benefit to participants with pretreated advanced melanoma (as 3 mg/kg monotherapy compared with the melanoma peptide vaccine gp100) and previously untreated advanced melanoma (at 10 mg/kg in combination with dacarbazine [DTIC] compared with DTIC alone), and there was evidence of clinical activity in randomized studies in other tumor types.

The PK of ipilimumab has been extensively studied in participants with melanoma at the 3- and 10-mg/kg dose administered as an IV infusion. The mean CL (± standard deviation [Std. Dev.]) value after IV administration of 10 mg/kg was 18.3 ± 5.88 mL/h, and the mean steady-state volume of distribution (± Std. Dev.) value was 5.75 ± 1.69 L. The PPK of ipilimumab was studied in participants with advanced melanoma in 4 Phase 2, 1 Phase 3, and 1 Phase 1 studies. The PPK analysis demonstrated that the PK of ipilimumab was linear, the exposures were dose proportional across the tested dose range of 0.3 to 10 mg/kg, and the model parameters were time invariant, similar to those determined by noncompartmental analyses.

Additional details are provided in the current version of the ipilimumab IB.[18]

3.3 Benefit/Risk Assessment

Participants who have advanced solid tumors have a poor prognosis, few treatment options, and the majority will die of disease.

Immunotherapy with ipilimumab or nivolumab has demonstrated clinical activity in a percentage of participants with MEL, NSCLC, RCC, HNSCC, and other tumors. Treatment-related AEs include those associated with autoimmune activation, such as colitis, pneumonitis, thyroiditis, hepatitis, and adrenal insufficiency.

Overall, the safety profile of nivolumab monotherapy as well as in combination with ipilimumab is manageable and generally consistent across completed and ongoing clinical studies with no MTD reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) AEs with relatively few related, high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence,

severity, or causality of AEs with respect to nivolumab dose level. A pattern of immune-related AEs has been defined, for which management algorithms have been developed; these are provided in Appendix 6. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

Additional details on the safety profile of nivolumab and ipilimumab, including results from other clinical studies, are available in the respective IBs.

Preclinical Toxicology

Three anti-ICOS antibodies have entered the clinic for evaluation in humans (NCT02520791, NCT02904226, and NCT02723955), however, published safety data are not available. Since no anti-ICOS class of compounds has been marketed, and BMS-986226 has never been administered to humans, data to inform the safe conduct of FIH studies are mainly based on the toxicology studies in monkeys.

The safety of BMS-986226 has been extensively evaluated in nonclinical models. Based on nonclinical data in cynomolgus monkeys, administration of single or multiple doses of BMS-986226 is expected to be well tolerated at all the doses proposed for this FIH clinical study. Efficacy of the anti-ICOS mAb has been evaluated as monotherapy or in combination with either anti-PD-1 or anti-CTLA-4 in multiple tumor-bearing mouse models. Based on the nonclinical data, the combination of BMS-986226 and nivolumab or ipilimumab is expected to exert anti-tumor activity across multiple tumor types.

In the absence of clinical studies with BMS-986226, the evaluation of risk is based on information from nonclinical studies with BMS-986226 in cynomolgus monkeys (Section 3.2.2.2), and potential effects are based on the proposed mechanism of action and clinical evidence from nivolumab or ipilimumab therapy.

The nonclinical GLP toxicology assessment of BMS-986226 has demonstrated a dose-related toxicity profile of immune-related AEs (irAEs) and cytokine-release potential compatible with the expected mechanism of action. Overall, there were no adverse findings observed in the nonclinical toxicology studies that identify specific safety concerns for using BMS-986226 in the proposed clinical study as a single agent. The nonclinical safety of BMS-986226 was evaluated in vitro in a human tissue cross-reactivity study and in cytokine-release and lymphocyte-activation assays in human cells. In vivo, BMS-986226 was evaluated in exploratory repeat-dose IV toxicity studies in rats (≤ 30 mg/kg) and cynomolgus monkeys (≤ 75 mg/kg; pivotal study). In addition, an exploratory single- and repeat-dose (2-week) IV toxicity study was conducted in mice using BMS-986246, a surrogate anti-mouse ICOS agonistic antibody with identical complementarity-determining regions (hamster-derived) as BMS-986226 with mouse Fc domains, and with comparable affinity for mouse ICOS. While toxicities associated with ADA formation limited the usefulness of this animal model, the results are not expected to be predictive of human response to ADA. As described in ICH S6, the induction of ADA formation in animals is not predictive of a potential for ADA formation in humans. A detailed explanation of the nonclinical toxicology program for BMS-986226 is described in Section 3.2.2.2 and in the IB.

Overall Risk/Benefit for Combination with Nivolumab or Ipilimumab

In combination therapy of BMS-986226 and nivolumab or ipilimumab, as observed in the combination of ipilimumab and nivolumab, it is possible that a higher incidence of irAEs may occur with the combination of the 2 antibodies. The safety profiles of nivolumab and ipilimumab monotherapy and the combination of ipilimumab and nivolumab are well defined based on experience with more than 12,300 patients evaluated in clinical studies. The frequency and types of immune-mediated adverse reactions are similar across multiple types of tumors and are described in the Reference Safety Information in the current IBs for nivolumab[17] and ipilimumab[18]. Unanticipated side effect events may also occur.

Summary

The proposed clinical study of BMS-986226 has been designed to minimize the overall risk to participants; thus, measures will include:

- A sentinel participant will be utilized for all dose escalation cohorts in monotherapy (Preliminary Safety Cohorts and Part A) and all cohorts in combination therapy (Parts B and C; see Section 5.1.2).
- Continuous safety assessments will be utilized by the investigators and Sponsor to determine whether dose modification, additional safety measures, or termination of the study is required at any time. In addition, AEs and SAEs will be reviewed on an ongoing basis by the Bristol-Myers Squibb (BMS) Medical Monitor/Study Director (or designee) and Global Pharmacovigilance and Epidemiology representatives to monitor for any safety signals or trends. As BMS-986226 is an experimental agent, it is possible that unforeseen, unknown, or unanticipated reactions may occur. However, based on the nonclinical safety profile of BMS-986226 and the 250-fold exposure margin (based on the nonclinical HNSTD of 75 mg/kg in cynomolgus monkeys) built into the planned starting dose of 25 mg (flat dose), the potential safety risks are expected to be minimized.
- The administration will occur at infusion centers with medical monitoring and the capability to manage infusion reactions or anaphylaxis. Premedications are recommended to be administered prior to BMS-986226 infusion, as described in Section 7.1 and 7.3.6. Participants will be observed for at least 60 minutes following the completion of BMS-986226 infusion due to the potential risk of, and to monitor for, infusion reactions. The protocol provides a treatment algorithm for infusion reactions (see Section 7.3.6 and Appendix 6). In addition to conventional safety measures for infusion of biologic agents, all participants will undergo observation and assessment for signs of infusion reaction post-infusion after all infusions of BMS-986226.
- Furthermore, to assess for potential effects of lymphocyte activation, dose-limiting toxicities (DLTs) will be recorded for all the cohorts in monotherapy and in combination with nivolumab or ipilimumab.
- Management algorithms for nivolumab- and ipilimumab-induced AEs involving GI, renal, pulmonary, hepatic, endocrine, skin, and neurologic systems are included in the protocol (see Section 7.3.3).
- Participants who develop irAEs may require prolonged treatment with high-dose corticosteroids and other immunosuppressive agents. This could increase the risk of

opportunistic infections. IrAE management algorithms in the protocol recommend antibiotic prophylaxis against opportunistic infections in such situations.

- Complete blood counts and chemistry (including liver enzyme) tests will be carried out prior to administration of study treatment and on a weekly basis during the first 4 weeks of treatment in monotherapy or in combination between BMS-986226 and nivolumab or ipilimumab. In addition, a complete physical examination (PE) will be conducted on Cycle 1 Day 1 along with weekly symptom-directed targeted PEs during the first 5 to 6 weeks of treatment. Due to the potential risk of exaggerated inflammatory response, participants with autoimmune disorders, chronic hepatitis, or who are at risk for flare of autoimmunity will be excluded.

In conclusion, there may be no direct benefit to participants treated with BMS-986226, and the potential exists for study treatment-related toxicity. However, there may be potential direct benefit to participants in this study including the following: both single-agent and combined therapy with these investigational agents may result in a greater proportion of participants with stabilization of disease, objective response, or increased DOR than those observed with standard therapy or other investigational immunotherapy. It is also possible that both single-agent and combined therapy may reverse T-cell exhaustion and achieve responses in 1) tumors refractory to anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibody therapy; and/or 2) tumors with high Treg infiltrate.

The potential benefit described above supports evaluating BMS-986226 both as single agent and in combination with nivolumab or ipilimumab in this Phase 1/2 clinical study with risk mitigation and clinical monitoring described above.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To characterize the safety and tolerability of BMS-986226 administered alone and in combination with nivolumab or ipilimumab in participants with advanced solid tumors	Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and AEs resulting in death. Incidence of clinical laboratory test abnormalities
Secondary	
To explore the preliminary efficacy of BMS-986226 administered alone and in combination with either nivolumab or ipilimumab in participants with advanced solid tumors	ORR, mDOR, and PFS rate at 24 weeks[a]
To characterize the PK of BMS-986226 when administered alone and in combination with nivolumab or ipilimumab in participants with advanced solid tumors	PK parameter estimates of BMS-986226
To characterize the immunogenicity of BMS-986226 when administered alone and in combination with nivolumab or ipilimumab in participants with advanced solid tumors	Incidence of ADAs specific for BMS-986226

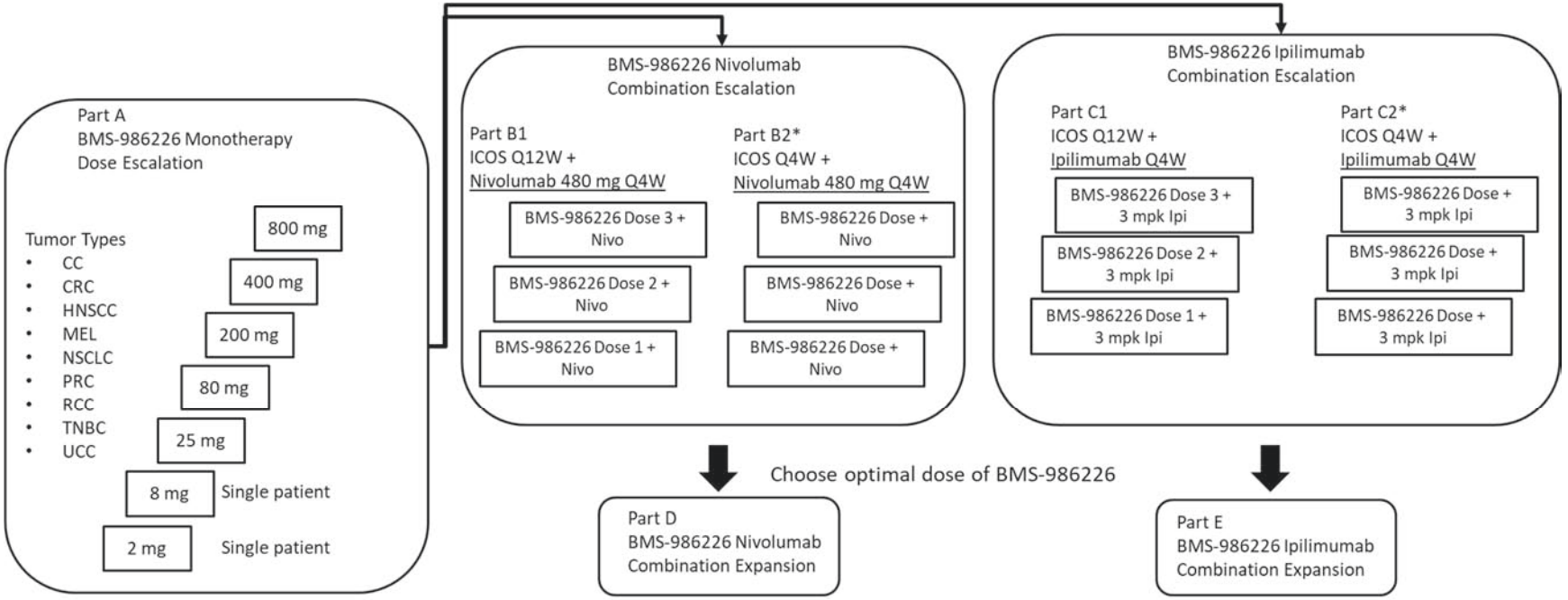
Table 4-1: Objectives and Endpoints	
Objectives	**Endpoints**
To monitor target engagement of BMS-986226 administered alone and in combination with either nivolumab or ipilimumab in participants with advanced solid tumors	Summary measures of changes from baseline (% or absolute change) in cell surface ICOS expression on T cells and ICOS-ligand+ B cells
[redacted]	

[a] These endpoints will be assessed based on RECIST v1.1 or PCWG3 (prostate only) criteria and will be determined based on tumor measurements occurring every 8 weeks (± 1 week) during the treatment period and at least every 12 weeks (± 2 week) in the response and survival follow-up periods. For Part A, scans will be collected centrally and may be reviewed by BICR at a later date or at any time during the study. For Parts B, C, D and E, scans will be collected centrally to be reviewed in real time by BICR.

Abbreviations: ADA = anti-drug antibody; BICR = blinded independent central review; DLT = dose limiting toxicity; DOR = duration of response; [redacted] mDOR = median duration of response; ORR = objective response rate; [redacted] PK = pharmacokinetics; [redacted] RECIST = Response Evaluation Criteria In Solid Tumors; TIL = tumor-infiltrating lymphocytes.

5 STUDY DESIGN

Figure 5-1: Study Design Schematic



* Note: Arms B2 and C2 will enroll only if additional safety, PK, and PD data are required to inform dose expansion decisions. The dose levels assessed in B2 and C2 will not exceed those evaluated in Part A, B1, or C1.

5.1 Overall Design

This is a Phase 1/2, open-label study of BMS-986226 administered as a monotherapy or in combination with either nivolumab or ipilimumab in participants with advanced solid tumors. The study will be conducted in 3 parts: 1) dose-escalation monotherapy (Preliminary Safety Cohorts and Part A); 2) dose-escalation combination therapy with either nivolumab (Part B) or ipilimumab (Part C); 3) a dose expansion phase with either nivolumab (Part D) or ipilimumab (Part E).

Monotherapy consists of 2 different parts as follows:

- Preliminary Safety Cohorts with BMS-986226 administered as monotherapy at 2 mg and 8 mg once every 4 weeks (Q4W) for 24 weeks
- Part A, with BMS-986226 administered at 25 mg, 80 mg, 200 mg, 400 mg, and 800 mg Q4W for 24 weeks

Parts B and C consist of different combination cohorts comprising:

- B1: BMS-986226 administered every 12 weeks (Q12W) + nivolumab 480 mg Q4W at a starting dose level of BMS-986226 one dose level lower than a monotherapy dose (Part A) that has cleared the DLT period.
- B2: BMS-986226 Q4W + nivolumab 480 mg Q4W at a starting dose level of BMS-986226 tested in part B1.
- C1: BMS-986226 Q12W + ipilimumab 3 mg/kg Q4W at a starting dose level of BMS-986226 one dose level lower than a monotherapy dose (Part A) that has cleared the DLT period.
- C2: BMS-986226 Q4W + ipilimumab 3 mg/kg Q4W at a starting dose level of BMS-986226 tested in Part C1.

Parts B1 and C1 will enroll concurrently. Parts B2 and C2 will enroll if preliminary data from Part A or Parts B1 and C1 suggest a more frequent dose regimen than Q12W and if additional safety, PK, or PD data are required to optimize dose and/or schedule selection (see Section 5.1.2.2 [Parts B1 and B2] and Section 5.1.2.3 [Parts C1 and C2]). Parts B1/C1 and B2/C2 can enroll concurrently and participants will be alternately assigned to all open cohorts.

The doses of BMS-986226 for Parts B and C (combination with nivolumab or ipilimumab) will be determined using all available safety (clinical and laboratory), PK, and target engagement/PD [redacted] data, as well as modeling recommendations within the Bayesian hierarchical modeling framework, ie, the BLRM-Copula model, by incorporating single-agent toxicity profiles of both BMS-986226 (Preliminary Safety Cohorts and Part A) and nivolumab or ipilimumab[18] and any available combination toxicity data from Parts B and C (for subsequent doses of BMS-986226 in Parts B and C), PK/PD modeling, and will not exceed the maximum administered dose (MAD) of BMS-986226 monotherapy in the Preliminary Safety Cohorts and Part A (see Section 5.1.2.1).

At no point will the dose of BMS-986226 administered in combination with nivolumab or ipilimumab (Parts B and C) exceed the dose of BMS-986226 that has been demonstrated previously to be safe in the monotherapy dose-escalation arm (Part A), nor at any point during

combination therapy in Parts B and C will the BMS-986226 dose exceed the highest dose determined to be tolerated in the monotherapy dose-escalation arm (Part A). In addition, the starting dose level of BMS-986226 used in combination with nivolumab or ipilimumab (Parts B and C) will be one dose level lower than a monotherapy (Part A) dose that has cleared the DLT period.

Parts B and C will consist of combination dose escalation cohorts aimed to explore the kinetics of ICOS-receptor downmodulation and re-expression (and/or change in selected target engagement/PD [redacted]) following administration of BMS-986226 in the presence of multiple doses of nivolumab Q4W (Part B) or ipilimumab (Q4W) (Part C). Up to 3 different doses of BMS-986226 will be administered in each of Parts B1 and C1 and an additional 6-12 participants will be enrolled in up to 3 different dose cohorts in Parts B2 and C2:

- Doses that induce or are predicted to induce different levels of ICOS receptor downmodulation, including at least one dose that induces near-complete receptor downmodulation (and/or change in selected target engagement/PD [redacted]) for a duration of at least 4 weeks. These dose levels will allow characterization of the ICOS receptor re-expression kinetics after near-complete downmodulation for a period of time equal to, less than, and/or exceeding the dosing intervals used in Part A. Understanding ICOS receptor kinetics will help inform testing BMS-986226 dosing intervals in future study(ies). Subsequent doses will also be evaluated by BLRM-Copula for toxicity.

Dose levels will be determined based on all available safety (clinical and laboratory) and PK data, as well as changes in peripheral target engagement markers (eg, ICOS down regulation on T cells and ICOS + B cells) from previous and completed portions of current cohorts and/or the BLRM/BLRM-Copula model whenever applicable.

Table 5.1-1: Study Cohorts per Part

Study Part	Study Treatment	Cohorts
Preliminary Safety Cohorts and Part A	BMS-986226 monotherapy	• CC • CRC • HNSCC • MEL • NSCLC • PRC • RCC • TNBC • UCC • Other Advanced Epithelial Solid Tumors
Parts B and C	BMS-986226 + nivolumab or ipilimumab	• CC • CRC • HNSCC • MEL

Table 5.1-1: Study Cohorts per Part

Study Part	Study Treatment	Cohorts
		• NSCLC • PRC • RCC • TNBC • UCC • Other Advanced Epithelial Solid Tumors
Parts D and E	BMS-986226 + nivolumab or ipilimumab	• To be determined based on safety, tolerability, PK, and PD data from Parts A, B, and C

For Parts A, scans will be collected centrally and may be reviewed by BICR at a later date or at any time during the study. For Parts B, C, D and E scans will be collected centrally to be reviewed in real time by BICR.

Physical examinations, vital sign measurements, 12-lead electrocardiogram (ECG), and clinical laboratory evaluations will be performed at selected times throughout the dosing interval. Participants will be closely monitored for AEs throughout the study. Blood will be collected at 30, 60, and 100-day follow-up visits (Section 9.5) after study treatment administration for PK analysis.

Participants will complete up to 4 phases of the study: screening, treatment, safety follow-up, and response/survival follow-up, as described below. Total duration of participation in the study is approximately 4 years.

The study design schematic is presented in Figure 5-1.

5.1.1 Screening

The screening phase will last for up to 28 days and take place prior to the first administration of study treatment. During the screening phase, the participant's initial eligibility will be established, and written informed consent will be obtained. Tumor biopsies will be collected for all participants and sent for central evaluation of ICOS expression by immunohistochemistry, and all participants will receive the tetanus booster vaccine 3-7 days prior to Cycle 1 Day 1 of first administration of study treatment. Stool will be collected for microbiota composition analysis. Participants will be enrolled using the Interactive Response Technology (IRT). The screening assessments are shown in Table 2-1.

5.1.2 Treatment Phase

The treatment phase in the Preliminary Safety Cohort and Part A consists of up to six 4-week treatment cycles (1 cycle = 28 days). In the Preliminary Safety Cohort and Part A, each treatment cycle will consist of BMS-986226 monotherapy for a total of 24 weeks.

Dose levels for Parts B and C will be determined based on all available safety (clinical and laboratory) and PK data, as well as changes in peripheral target engagement markers (eg, ICOS

downregulation on T cells and ICOS + B cells) from previous and completed portion of current cohorts, and will be guided by the BLRM/BLRM-Copula model whenever applicable.

In Parts B1 and C1, 4 week cycles will be used, such that BMS986226 + nivolumab or ipilimumab will be administered starting on Cycle 1 Day 1. Nivolumab and ipilimumab will be administered on Day 1 of each cycle. BMS-986226 will be administered Q12W, or on Day 1 of every third cycle (Cycle 1 Day1, Cycle 4, Day1, Cycle 7 Day1, etc.). Participants on Parts B1 and C1 may continue treatment for up to a total of 2 years.

The treatment phase in Parts B2 and C2 will consist of BMS-986226 + nivolumab or ipilimumab administered on Day 1 of each cycle and will be enrolled if additional safety, PK, or PD data is required to optimize dose and/or schedule selection. In parts B2 and C2 BMS-986226 will be administered Q4W and participants may continue treatment for a total of 2 years.

Following each treatment cycle, the decision to treat a participant with additional cycles of study treatment will be based on tumor assessment evaluations performed every 8 weeks (Q8W ± 1 week) and completed before the first dose in the next cycle. Tumor progression or response endpoints will be assessed using Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 (Appendix 5) or PCWG3, for prostate only (Appendix 11).

Treatment beyond progression with additional cycles of study treatment may be allowed for up to a maximum of 24 weeks for Part A and 2 years for Parts B, C, D, and E in select participants with initial RECIST v1.1 or PCWG3 (prostate only) defined progressive disease after discussion and agreement between the Principal Investigator and the BMS Medical Monitor/Study Director (or designee) that the benefit/risk assessment favors continued administration of the study treatment (eg, participants are continuing to experience clinical benefit as assessed by the investigator, tolerating treatment, and meeting other criteria specified in Section 8.1.2).

Participants with a response of unconfirmed progressive disease, SD, PR, or CR at the end of a given cycle will continue to the next treatment cycle. Participants will generally be allowed to continue study treatment until the first occurrence of 1) completion of the maximum number of cycles, 2) confirmed progressive disease, 3) clinical deterioration suggesting that no further benefit from treatment is likely, 4) intolerability to therapy, or 5) a participant meeting criteria for discontinuation of study treatment as outlined in Section 8.1. Individual participants with confirmed CR will be given the option to discontinue study treatment on a case-by-case basis after specific consultation and agreement between the investigator and BMS Medical Monitor/Study Director (or designee) in settings where benefit/risk justify discontinuation of study treatment.

5.1.2.1 Monotherapy Dose Escalation (Preliminary Safety Cohorts and Part A)

Up to approximately 34 participants may be treated during the monotherapy dose escalation (Preliminary Safety Cohorts and Part A).

Expected dose levels for monotherapy dose escalation (Preliminary Safety Cohorts and Part A) are provided in Table 5.1.2.1-1. All participants treated with BMS-986226 monotherapy are recommended to receive premedications, as described in Section 7.1, in order to reduce the risk of infusion-related reactions.

Preliminary Safety Cohorts

The Preliminary Safety Cohorts will evaluate the safety of BMS-986226 following monotherapy administration of 2 dose levels, 2 mg and 8 mg.

A single new participant per cohort will be administered an IV BMS-986226 as follows:

- BMS-986226 2 mg Q4W in 4-week cycles for up to 24 weeks of study treatment
- BMS-986226 8 mg Q4W in 4-week cycles for up to 24 weeks of study treatment

For the purpose of guiding dose escalation, dose-limiting toxicities (DLTs) will be defined based on the incidence, intensity, and duration of AEs for which no clear alternative cause is identified. The DLT period will be 28 days (4 weeks) in the Preliminary Safety Cohorts. Any toxicities that occur beyond the 4-week DLT period will also be considered in dose-level decisions. For the purpose of participant management, any AE that meets DLT criteria (Section 7.3.2), regardless of the cycle in which it occurs, will lead to discontinuation of study treatment. Participants who discontinue study treatment during the 4-week DLT evaluation period for reasons other than a DLT may be replaced with a new participant at the same dose level. AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03[27].

Once the safety (during the 4 weeks DLT period) of 2 mg and 8 mg of BMS-986226 has been established in a single, independent participant per dose, Part A will start.

Additional participants may be enrolled in the Preliminary Safety Cohorts per dose level as early as 5 days after the first participant is treated at each dose level to gather additional information on the safety, PK, and PD profile.

Intra-participant dose escalation is only allowed in the Preliminary Safety Cohorts as follows:

- Once the observation period of 4 weeks for 8 mg is completed, participant(s) treated at 2 mg may be offered the possibility to dose escalate at 8 mg.
- Once the DLT period of 5 weeks for 25 mg is completed, participant(s) treated at 2 mg that escalated to 8 mg or participant(s) treated with 8 mg may be offered the possibility to dose escalate at 25 mg

The decision to dose escalate may be allowed in select participants after discussion and agreement with the BMS Medical Monitor/Study Director (or designee), as long as the participant is tolerating treatment.

The decision to treat a participant with additional cycles of study treatment (up to a maximum of 24 weeks), will be based on safety, tolerability, and tumor assessment Q8W (± 1 week) prior to dose administration in the next cycle.

Part A

Dose escalation decisions in Part A of the study will be guided by Bayesian Logistic Regression Model (BLRM). Each participant will be administered IV doses of BMS-986226 per the cohort assignment as follows:

- 25 mg flat dose Q4W in 4-week cycles for up to 24 weeks of study treatment
- 80 mg flat dose Q4W in 4-week cycles for up to 24 weeks of study treatment
- 200 mg flat dose Q4W in 4-week cycles for up to 24 weeks of study treatment
- 400 mg flat dose Q4W in 4-week cycles for up to 24 weeks of study treatment
- 800 mg flat dose Q4W in 4-week cycles for up to 24 weeks of study treatment

A sentinel participant will be used for all cohorts of monotherapy in Part A and combination therapy in Parts B and C. The first participant in each cohort will receive the Cycle 1 Day 1 dose of study treatment and be observed for 5 days before additional participants (ie, Participant 2 onward) in that cohort receive study treatment.

The decision to treat a participant with additional cycles of study treatment (up to a maximum of 24 weeks), will be based on safety, tolerability, and tumor assessment Q8W (± 1 week) prior to dose administration in the next cycle.

Planned dose levels may be modified or intermediate dose levels added guided by the BLRM analysis with consideration of all available safety, PK, and PD data.

Once the safety (during the DLT evaluation) of a dose level has been established, additional participants (up to a total of 12) may be added at that dose level to better characterize the safety, PK, and PD profile.

Dose Escalation Decisions for Part A

The dose-escalation phase of the study will evaluate the safety and tolerability of BMS-986226 monotherapy based on DLTs using a BLRM model.

During the dose-escalation phase, a set of approximately 3 participants will be treated initially at each specified dose level. Cohort tolerability assessment and subsequent dose recommendation will occur when at least 2 evaluable participants within a cohort have completed a 5-week DLT period. Any toxicities that occur beyond the 5-week DLT period will be accounted for in making dose level decisions and/or dose level modifications.

If the potential DLT occurring in the third evaluable participant regarding the specific dose level does not influence the dose recommendation by BLRM, the next dose level may proceed without waiting for the third participant to complete the corresponding DLT observation period after discussion and agreement between the Sponsor and investigators. Continuous re-assessment of dose recommendation, by BLRM in the monotherapy escalation phase, will be carried out for each dose level. Planned dose levels for dose escalation are provided in Table 5.1.2.1-1. Planned dose levels may be modified, or additional intermediate dose levels added, based upon the BLRM

analysis. Once the safety (during the DLT evaluation) of a monotherapy dose level has been established (Preliminary Safety Cohorts and Part A), additional participants (up to 12 total) may be added at that dose level to better characterize the safety, PK, and PD profile.

Table 5.1.2.1-1: Dose Escalation (Preliminary Safety Cohorts and Part A)

Dose Level	BMS-986226
1	2 mg (Preliminary Safety Cohorts)
2	8 mg (Preliminary Safety Cohorts)
3	25 mg (Part A)
4	80 mg (Part A)
5	200 mg (Part A)
6	400 mg (Part A)
7	800 mg (Part A)

Dose-limiting Toxicities in Part A

For the purpose of guiding dose escalation, DLTs will be defined based on the incidence, intensity, and duration of AEs for which no clear alternative cause is identified. The DLT period will be 35 days (5 weeks) in Part A. Any toxicities that occur beyond the 5-week DLT period will also be considered in dose-level decisions.

For the purpose of participant management, any AE that meets DLT criteria (Section 7.3.2), regardless of the cycle in which it occurs, will lead to discontinuation of study treatment. Participants who withdraw from the study during the DLT evaluation period for reasons other than a DLT may be replaced with a new participant at the same dose level. The incidence of DLT(s) during the DLT evaluation period will be used in dose escalation decisions in Part A and guide dose recommendations in Parts B and C. AEs occurring after the 5-week DLT evaluation period will be considered for the purposes of defining any BLRM recommended dose upon agreement between the Sponsor, Medical Monitor/Study Director (or designee), and investigators, if the AEs are determined to have no clear alternative cause and are not related to disease progression.

AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03.[27]

5.1.2.2 BMS-986226 and Nivolumab Combination Therapy Cohort (Parts B1 and B2)

The purpose of combination cohort with nivolumab is to gather safety, tolerability, PK, and PD information regarding the administration of BMS-986226 in combination with nivolumab 480 mg flat dose Q4W. Part B1 aims to determine the kinetics of ICOS receptor downmodulation and re-expression (and/or change in selected target engagement/PD [redacted]) following administration of BMS-986226 Q12W in combination with nivolumab 480 mg administered Q4W for a duration

of 2 years. Continuous evaluation of toxicity events in the combination cohort will be performed throughout the enrollment. All participants treated with BMS-986226 in combination with nivolumab are recommended to receive premedications, as described in Section 7.1, in order to reduce the risk of infusion-related reactions.

Up to 3 different dose levels of BMS-986226 will be tested in Part B1, as determined by safety, PK and PD data. The starting dose level used in combination with nivolumab (Part B) will be one dose level lower than a monotherapy (Part A) dose that has cleared the DLT period. At each dose level, approximately 6 evaluable participants will be treated. A sentinel participant will be enrolled in Part B1 (BMS-986226 Q12W + nivolumab 480 mg Q4W) and observed for 5 days before additional participants in Parts B1 at the same dose level receive study treatment.

Part B2 (BMS-986226 Q4W + nivolumab 480 mg Q4W) will be opened at dose levels evaluated in at least one participant in Part B1. Approximately 6-12 evaluable participants will be treated per cohort, if enrolled, to better characterize safety, PK, and PD of the combination. For instance, Part B2 will begin enrollment if the re-expression of ICOS on circulating T cells is observed 4 weeks after the first dose of BMS-986226 in Parts A or B1. Part B2 would therefore be utilized to provide a more granular assessment of safety and PD of BMS-986226. More than 1 dose level (no more than 3 different dose levels) may be enrolled, should additional safety, PK, and PD data be needed.

Once the safety (during the DLT evaluation) of a combination of BMS-986226 and nivolumab has been established and a recommended BMS-986226 dose regimen has been selected for Part D, then additional participants (up to 6 additional evaluable participants) may be treated at the recommended dose to better characterize the safety, PK, and PD profile.

5.1.2.3 BMS-986226 and Ipilimumab Combination Therapy Cohort (Parts C1 and C2)

The purpose of combination cohort with ipilimumab is to gather safety, tolerability, PK, and PD information regarding the administration of BMS-986226 in combination with ipilimumab at 3 mg/kg Q4W. Part C1 aims to determine the kinetics of ICOS receptor downmodulation and re-expression (and/or change in selected target engagement/PD [redacted]) following administration of BMS-986226 Q12W in combination with ipilimumab administered Q4W for a duration of 2 years. Continuous evaluation of toxicity events in the combination cohort will be performed throughout the enrollment. All participants treated with BMS-986226 in combination with ipilimumab are recommended to receive premedications, as described in Section 7.1, in order to reduce the risk of infusion-related reactions.

Up to 3 different dose levels of BMS-986226 will be tested in Parts C1, as determined by safety, PK and PD data. The starting dose level used in combination with ipilimumab (Part C) will be one dose level lower than a monotherapy (Part A) dose that has cleared the DLT period. At each dose level, approximately 6 evaluable participants will be treated, where a sentinel participant will be enrolled in Part C1 (BMS-986226 Q12W + ipilimumab 3mg/kg Q4W and observed for 5 days before additional participants in Parts C1 at the same dose level receive study treatment.

Part C2 (BMS-986226 Q4W + ipilimumab 3 mg/kg Q4W) will be opened at dose levels evaluated in at least one participant in Part C1. Approximately 6-12 evaluable participants will be treated per

dose cohort, if enrolled, to better characterize safety, PK, and PD of the combination. For instance, Part C2 will begin enrollment if the re-expression of ICOS on circulating T cells is observed 4 weeks after the first dose of BMS-986226 in Part A or C1. Part C2 would therefore be utilized to provide a more granular assessment of safety and PD of BMS-986226. More than 1 dose level (no more than 3 different dose levels) may be enrolled, should additional safety, PK, and PD data be needed.

Once the safety (during the DLT evaluation) of a combination of BMS-986226 and ipilimumab has been established and a recommended BMS-986226 dose regimen has been selected for Part E, then additional participants (up to 6 additional evaluable participants) may be treated at the recommended dose to better characterize the safety, PK, and PD profile.

Dose-limiting Toxicities in Combination Cohorts (Parts B and C)

For the purpose of ensuring safety, DLTs will be defined based on the incidence, intensity, and duration of AEs for which no clear alternative cause is identified. The DLT period will be 35 days (5 weeks) in Parts B and C.

For the purpose of participant management, any AE that meets DLT criteria (Section 7.3.2), regardless of the cycle in which it occurs, will lead to temporary hold of study treatment.

Participants who withdraw from the study during the DLT evaluation period for reasons other than a DLT may be replaced with a new participant at the same dose level.

Re-challenge of participants experiencing a DLT will be evaluated on a case-by-case basis, once the AE returns to baseline or Grade 1, after specific consultation and agreement between the investigator and BMS Medical Monitor/Study Director (or designee) in settings where benefit/risk justify re-administration of study treatment (see Section 7.3.5).

AEs will be graded according to the NCI CTCAE v4.03.[27]

5.1.2.4 Combination Expansion Arms (Parts D and E)

The purpose of the cohort expansion is to gather additional safety, tolerability, preliminary efficacy, PK, and PD information regarding BMS-986226 in combination with either nivolumab (Part D) or ipilimumab (Part E). Continuous evaluation of toxicity events in the cohort expansions will be performed throughout enrollment in the expansion cohorts. All participants treated with BMS-986226 in combination with either nivolumab or ipilimumab are recommended to receive premedications, as described in Section 7.1, in order to reduce the risk of infusion-related reactions. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds 33% across all participants treated the findings will be discussed and further enrollment will be interrupted. Depending on the nature and grade of the toxicity, and after assessing the risk/benefit ratio, a new dose for all cohorts may be initiated at a lower dose level.

The dose and schedule of BMS-986226 in Parts D and E will be determined based on all available safety, tolerability, efficacy, PK, and PD data from Parts A, B, and C. Parts D and E will be implemented following the revised protocol to define dose, schedule, and population.

Approximately 40 participants will be enrolled in each of Parts D and E. Safety, efficacy, PK, and PD data will be used to determine the precise patient population that will be enrolled in the expansion arms.

Participants with a response of unconfirmed progressive disease, stable disease, partial response, or complete response, at the end of a given cycle will continue to the next treatment cycle. Participants will be allowed to continue study treatment until the first occurrence of any of the following:

- Completion of the maximum number of cycles
- Confirmed progressive disease
- Clinical deterioration suggesting that no further benefit from treatment is likely
- Intolerability to therapy
- Participant meets the criteria for discontinuation of study treatment as shown in Section 8.2.

5.1.3 Follow-up

5.1.3.1 Safety Follow-up

Upon completion of 24 weeks of study treatment for Part A (or up to a maximum of 48 weeks if applicable) or 2 years for Parts B, C, D, and E, once the decision is made to discontinue the participant from study treatment (e.g., at end of treatment [EOT]), all participants will enter the safety follow-up period.

For participants who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit and the start of the Week 1 safety follow-up visit. For participants who do not complete all scheduled cycles of study treatment, the EOT visit will be the most recent on-treatment visit (with all available safety and response data), does not need to be repeated, and will be considered the start of the safety follow-up visit.

After the EOT visit, all participants will be evaluated for any new AEs for at least 100 days after the last dose of study treatment. Follow-up visits to monitor for AEs should occur at Days 30, 60, and 100 after the last dose or on the date of discontinuation (± 7 days). All participants will be required to complete the 3 clinical safety follow-up visits regardless of whether or not they start new anti-cancer treatment, except those participants who withdraw consent for study participation.

5.1.3.2 Survival Follow-up

After completion of the safety follow-up visits, all participants treated with monotherapy and combination therapy will enter the survival follow-up period. Participants will be followed approximately every 3 months (12 weeks) until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first. The duration of this phase is up to 2 years from the last dose of study treatment, although a longer follow-up period could be considered in selected cases if an efficacy signal is apparent.

5.1.3.3 Response Follow-up

After completion of the Safety Follow-up period, participants with ongoing SD, PR, or CR at the EOT visit will enter the Response Follow-up period. This period will occur simultaneously with the Survival Follow-up period for the mentioned participants. Participants will continue to have radiologic and clinical tumor assessments approximately every 3 months (12 weeks) until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first. Radiological tumor assessments for participants who have ongoing clinical benefit may continue to be collected after participants complete the survival phase of the study. Participants who have disease progression following initial course of study treatment will not be evaluated for response beyond the EOT visit and will be allowed to receive other tumor-directed therapy as required. If the participant discontinues treatment for any reason other than progressive disease, radiological follow-up will continue until the participant receives additional treatment.

5.1.4 Treatment with Additional Cycles

All participants will be treated for 24 weeks of monotherapy or for 2 years for combination therapy unless criteria for study treatment discontinuation are met earlier. Only participants completing treatment in the monotherapy (Part A) cohort, with ongoing disease control (CR, PR, or SD), or unconfirmed progressive disease, may be eligible for an additional 24 weeks of study treatment on a case-by-case basis after careful evaluation and discussion with the BMS Medical Monitor/Study Director (or designee) to determine whether the risk/benefit ratio supports administration of further study treatment. Upon completion of the additional study treatment period all participants will enter safety follow-up period.

5.1.5 Treatment Beyond Progression

Treatment beyond progression may be allowed in select participants with initial RECIST v1.1 or PCWG3 (prostate only) defined progressive disease after discussion and agreement with the BMS Medical Monitor/Study Director (or designee) that the benefit/risk assessment favors continued administration of study treatment (eg, participants are continuing to experience clinical benefit as assessed by the investigator, tolerating treatment, and meeting other criteria specified in (Section 8.1.2).

Participants must be re-consented with an informed consent form (ICF) addendum to continue treatment beyond progression. Treatment beyond progression will require continued tumor assessments.

5.1.6 Data Monitoring Committee and Other External Committees

As this is an early stage, first-in-human study, a data monitoring committee will not be used.

BMS has developed a multi-layered process to ensure safety monitoring through close collaboration of study site investigators, the BMS study team, and the BMS Global Pharmacovigilance and Epidemiology (GPVE)-led Medical Surveillance Team. Study safety will be evaluated continuously in real time by representatives of BMS GPVE, who operate independently from the clinical team and monitor safety across all BMS protocols. AEs will be monitored continuously by the medical monitor(s) and GPVE. Safety, PK, and PD data are

reviewed during teleconferences between investigators and the BMS clinical team, which will be held regularly. The decision to escalate or expand the dose will be based on the aforementioned review with investigators.

5.2 Number of Participants

The number of participants for this study will be approximately 234. Up to approximately 34 of these participants may be treated with monotherapy (Preliminary Safety Cohorts and Part A); approximately 6 evaluable participants may be treated at each dose level for Parts B1 and C1; approximately 6-12 evaluable participants may be treated at each dose level for Parts B2 and C2; up to 6 additional evaluable participants may be treated in Parts B and/or C, at a recommended BMS-986226 dose regimen for Parts D and/or E to better characterize the safety, PK, and PD profile; approximately 80 participants will be treated in combination expansion arms, Parts D and E.

Additional information on sample size determination can be found in Section 10.1.

5.3 End of Study Definition

The start of the study is defined as the first visit for the first participant screened.

The end of study is defined as the last visit or scheduled procedure shown in the Schedule of Activities (Section 2) for the last participant. Study completion is defined as the final date on which data for the primary endpoint were or are expected to be collected if they are not the same.

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for BMS-986226 First-in-Human Dose (Preliminary Safety Cohorts and Part A Monotherapy)

The selection of the BMS-986226 starting dose is based on the pivotal repeat-dose IV toxicology study in cynomolgus monkeys and the mouse CT26 colon adenocarcinoma tumor efficacy model. These approaches reflect the goal of adequately ensuring patient safety while limiting the number of advanced-stage cancer patients from receiving sub-pharmacologically active doses.

In the pivotal repeat-dose (5 doses/week) IV toxicity study, the dose of 75 mg/kg (AUC[0-168h] ≤ 452,000 μg•h/mL) was considered to be the NOAEL and was also considered the HNSTD to determine potential MRSD as per ICH S9.[28] Using a standard milligram per kilogram conversion to the human equivalent dose and a safety factor of 6-fold, the potential MRSD was calculated to be 12.5 mg/kg.

The anti-tumor efficacy of hamster anti-mouse ICOS agonist mAb (BMS-986246) was studied in the mouse CT26 colon adenocarcinoma model as a single agent or in combination with an anti-mouse PD-1 mAb.[29] In this study, improved anti-tumor efficacy of BMS-986246 was noted in combination with an anti-murine PD-1 mAb relative to single-agent treatment. The AUC and percent tumor growth inhibition (%TGI) relationship in this study was used to project human starting and efficacious doses. Peak %TGI was reached at 3 mg/kg dose of BMS-986246 in combination with anti-mPD1 (corresponding Cmax at first week of 84 μg/mL and AUC from 0 to 1 week of 450 μg•day/mL). Accordingly, the 4.6-mg/kg dose of BMS-986226 (368 mg assuming

80 kg human body weight) is projected to achieve these targeted exposures in humans and is considered the targeted efficacious dose. Negligible anti-tumor activity (no improvement over anti-murine PD-1 mAb alone) in mice was noted at 0.3 mg/kg. To achieve comparable systemic exposures as the 0.3 mg/kg dose in mice, 25 mg was selected as the first dose level for Part A. The projected exposures (eg, AUCs) following administration of 25 mg are 102-fold lower than the exposures observed in cynomolgus monkeys at the NOAEL dose.

Other considerations to select the starting dose included ICOS expression in humans and comparisons of the projected concentrations relative to those used in the in vitro cytokine-release assay. Unlike high-risk targets, eg, CD28 receptor, which is constitutively expressed, normal ICOS expression is limited, with the majority of high-expressing cells found to be activated T cells.[30] The dose of BMS-986226 that is projected to result in approximately 80% to 85% ICOS binding to activated T cells at Cmax is 2 mg. This dose would be expected to engage ICOS in activated T cells, but not expected to have appreciable clinical activity and thus will be used as the starting dose in the Preliminary Safety Cohorts.

Collectively, these data support using a starting dose of 2 mg BMS-986226 in the Preliminary Safety Cohorts to allow safe administration of BMS-986226 at a dose projected to not have appreciable clinical activity. The first dose level in Part A is 25 mg BMS-986226, as it is expected to have pharmacologic activity and reasonable safety in the cancer patient population.

5.4.2 Rationale For Treatment Duration

5.4.2.1 Rationale for 24-week Duration of BMS-986226 Monotherapy

While immunotherapies are rapidly making great strides in the treatment of cancer, the optimal duration of treatment to obtain and maintain deep and durable responses is a matter of ongoing clinical investigation. Emerging clinical data on time to response with immunotherapies in cancer suggest that a majority of participants who responded did so within the first 24 weeks on treatment.

5.4.2.2 Rationale for 2-year Duration of BMS-986226 in Combination with Nivolumab or Ipilimumab

The optimal duration of immunotherapy is an important question and continues to be investigated. In study 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 progression-free survival (PFS) compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached vs 10.3 months, respectively; HR=0.42 (95% 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 HR = 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (i.e., 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years.[31] Moreover, accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long term benefit. In study 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 participants with NSCLC), specified a maximum treatment duration of 2 years. Among 16 participants with NSCLC who discontinued nivolumab after completing 2 years of treatment, 12 participants were alive > 5 years and remained progression-free without any subsequent therapy. In the CA209003 NSCLC cohort, the OS curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years.[32] 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).[33]

Taken together, the data suggest 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. Also, 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.

Although there is no data available for 2 year treatment regimen of ipilimumab, the mechanism of action of the negative regulators of T cell activation is similar to that of nivolumab. Therefore, CA021002 will evaluate the safety and tolerability of ipilimumab (Q4W) in combination with BMS-986226 for up to 2 years.

Collectively, these data suggest that there is minimal if any benefit derived from continuing I-O treatment beyond two years in advanced tumors. However, even though immunotherapy is well tolerated, patients will be at risk for additional toxicity with longer term treatment. Therefore in study CA021002, treatment with BMS-986226 in combination with nivolumab or ipilimumab will not be extended beyond 2 years.

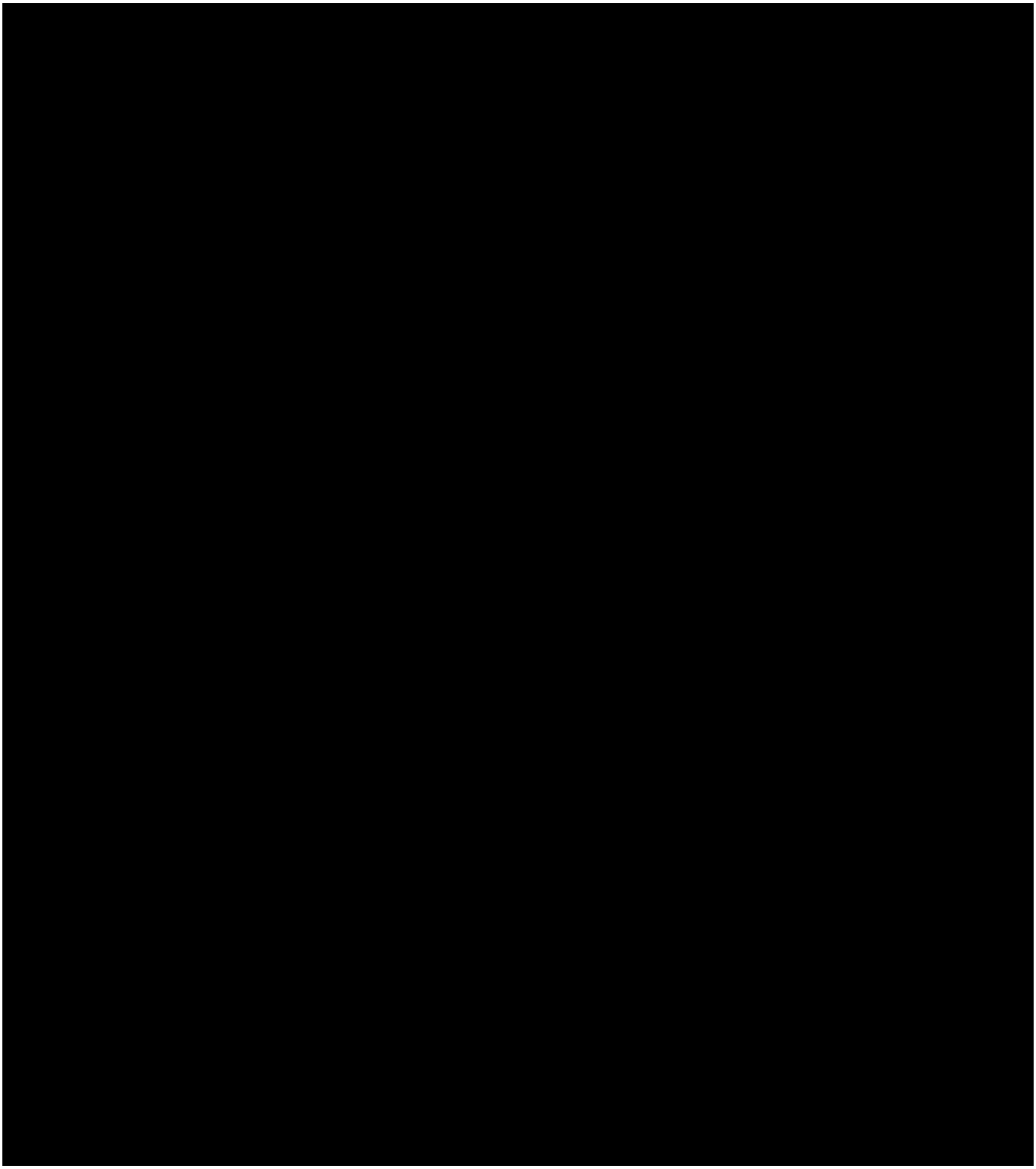
5.4.3 Rationale for Treatment Beyond Progression

Immunotherapeutic agents produce atypical clinical response patterns that are not usually observed in conventional chemotherapy. Accumulating clinical evidence indicates that some participants treated with immune system-stimulating agents may develop disease progression by the conventional response criteria before demonstrating clinical objective responses and/or SD.

Two distinct nonconventional patterns have been reported: 1) a reduction in target tumor burden despite the appearance of new lesion(s) and 2) a transient increase in target tumor burden in an initial phase followed by subsequent tumor shrinkage.

This phenomenon was observed in the Phase 2 study of nivolumab (Study CA209003) in solid tumor patients. Two hypotheses explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size, which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease, leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. Therefore, it is important to avoid premature discontinuation of the study treatment that might induce a nonconventional response pattern in some participants.

The decision to continue treatment beyond investigator-assessed progression should be discussed with the BMS Medical Monitor/Study Director (or designee) and documented in the study records. The assessment of clinical benefit should take into account whether the participant is clinically deteriorating and unlikely to receive further benefit from continued treatment.



5.5 Justification for Dose and Schedules for BMS-986226, Nivolumab, and Ipilimumab

5.5.1 Rationale for BMS-986226 Flat Dosing and Schedule

Therapeutic mAb doses have been routinely calculated on a body size basis with a perception that this approach may reduce inter-participant variability in drug exposure compared with a flat dose approach. However, recent analyses of marketed experimental mAbs have demonstrated that body weight-based dosing did not always offer advantages over flat dosing in reducing exposure variability. Because the magnitude of the impact of body weight on the human PK of BMS-986226 is not yet determined and it is unknown if body size-based dosing would increase or decrease inter-participant variability, this study will utilize a flat dose in the escalation and combination phases as a more convenient approach and which is more likely to reduce the potential for dosing errors.

The starting dose of BMS-986226 in combination with either nivolumab 480 mg Q4W or ipilimumab 3 mg/kg Q4W will be determined based on the expected activity at this dose range and the expected tolerability and safety profile of BMS-986226 in the monotherapy dose escalation (Part A). At no point will the dose of BMS-986226 administered in combination with nivolumab or ipilimumab- exceed doses of BMS-986226 that have been demonstrated previously to be tolerated in the monotherapy dose escalation arm (Part A). Accordingly, additional intermediate

or lower doses or less frequent dosing of BMS-986226 may be tested, if none of the planned doses/schedule is found to be tolerated when combined with nivolumab or ipilimumab.

The BMS-986226 dose for Parts B and C will be based on evaluating the most up-to-date data available in all dosed participants, including clinical and laboratory safety assessments as well as PK, PD, and efficacy data from all treated participants at each dose level up to the MAD.

For the Preliminary Safety Cohorts and Parts A, B2 and C2, BMS-986226 will be administered at a dose schedule of Q4W. This schedule is based on predicted human PK using nonclinical data. The projected T-HALF for BMS-986226 in humans is 25 days (Section 3.2.2.5), allowing for dosing at an interval of 4 weeks.

Parts B1 and C1 will be conducted to help inform safety and possible alternative dosing schedules by utilizing PK and target engagement/PD markers, including but not limited to ICOS downregulation and re-expression. In Parts B1 and C1, participants will be administered BMS-986226 Q12W at the dose that induces or is predicted to induce near-complete receptor downregulation (and/or change in selected target engagement/PD [redacted]) in the presence of nivolumab Q4W or ipilimumab Q4W. PK and PD data will be generated and analyzed to understand the duration of effect of BMS-986266 on the kinetics of ICOS downregulation and re-expression, and/or the kinetics of other appropriate PD markers.

5.5.2 Rationale for Nivolumab Dose Selection

Currently, nivolumab 240 mg Q2W or nivolumab 3 mg/kg Q2W are approved in various regions for the treatment of melanoma, NSCLC, RCC, classical Hodgkin's lymphoma, and UCC.

The safety and efficacy of the nivolumab 480 mg Q4W flat dose are expected to be similar to the approved nivolumab dose of 240 mg or nivolumab 3 mg/kg Q2W. The nivolumab dose of 480 mg Q4W was selected based on clinical data and modeling and simulation approaches using PPK and exposure-response analyses of data from studies in multiple tumor types (melanoma, NSCLC, and RCC) where body weight-normalized dosing (mg/kg) has been used. The PPK analyses have shown that exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered Q2W, and no clinically meaningful differences in PK across ethnicities and tumor types were observed. Nivolumab clearance and volume of distribution were found to increase as body weight increases but less than proportionally with increasing weight, indicating that milligram-per-kilogram dosing represents an over-adjustment for the effect of body weight on nivolumab PK. Using the PPK model, the overall distributions of average nivolumab steadystate exposures are comparable after treatment with either nivolumab 3 mg/kg Q2W or nivolumab 480 mg Q4W, although the flat dose regimen of 480 mg Q4W is predicted to result in approximately 40% higher steadystate peak concentration (-Cmaxss-) and approximately 20% lower steady-state trough concentrations compared to the reference regimen of 3 mg/kg Q2W. Across the various tumor types in the clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy and safety has been found to be relatively flat. Although nivolumab Cmaxss is predicted to be higher following 480 mg Q4W, these exposures are predicted to be lower than or within the exposure ranges observed at doses up to 10 mg/kg Q2W used in the

nivolumab clinical program and are not considered to put participants at increased risk. The exposures predicted following administration of nivolumab 480 mg Q4W are on the flat part of the exposure response curves for previously investigated tumors (melanoma and NSCLC) and are not predicted to affect efficacy. Based on these data, nivolumab 480 mg Q4W is expected to have similar efficacy and safety profiles to nivolumab- 3 mg/kg Q2W.

5.5.3 Rationale for Ipilimumab Dose Schedule

Ipilimumab 3 mg/kg Q4W will be tested in combination with BMS-986226 during the study in Parts C1 and C2. Ipilimumab is currently approved in the US for administration in unresectable or metastatic melanoma following monotherapy administration and in combination with nivolumab at a dose of 3 mg/kg Q3W for a total of 4 doses. Ipilimumab is also approved in the US for the treatment of adjuvant melanoma at a dose of 10 mg/kg Q3W for 4 doses, followed by 10 mg/kg Q12W for up to 3 years or until documented disease recurrence or unacceptable toxicity.[37] Finally, ipilimumab is being studied in combination with nivolumab at various doses, including 1 and 3 mg/kg, and at dosing intervals up to Q12W. Benefit may be gained from dosing ipilimumab for a longer duration than the dosing interval of Q3W dosing for a total of 4 doses. Further, in the combination setting, less frequent dosing has shown to be beneficial to the tolerability and response profile of ipilimumab.[38] While ipilimumab Q4W dosing has not been tested previously, it may offer benefit to enhance the tolerability of ipilimumab versus Q3W dosing, and to allow for prolonged dosing duration versus the 4-dose schedule when administered in combination with BMS-986226.

5.5.4 Rationale for Dose-escalation Phase Design

The BLRM with an overdose control principle escalation was selected as an appropriate design for this study. It offers more accuracy and efficiency in determining the true MTD/MAD compared to rule-based methods (such as 3 + 3 design) by incorporating external information from nonclinical studies as well as historical clinical studies. The escalation with overdose control (EWOC) principle limits the risk of exposing participants in the next cohort to an unsafe or toxic dose. Hence, it ensures that safety is not compromised during dose escalation. Simulation results demonstrate that BLRM allows fast escalation when the expected toxicity is very low and with participants treated at sub-therapeutic doses, which is attributed to the adaptive Bayesian learning from previous doses. In addition, BLRM has greater applicability to the combination therapy setting compared to other model-based methods. All available treatment related adverse events obtained from the monotherapy phase (Preliminary Safety Cohorts and Part A) will be characterized and incorporated as prior knowledge into the drug combination phase of the study (Parts B, C, D, and E) or used in future studies.

6 STUDY POPULATION

For entry into the study, the following criteria MUST be met prior to dosing on Day 1. No exceptions will be granted.

6.1 Inclusion Criteria

1) Signed Written Informed Consent

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

b) The participant must sign the consent for pretreatment and on-treatment tumor biopsy samples at acceptable clinical risk, as judged by the investigator.

i) Participants will be eligible to receive treatment upon completion of pre-treatment biopsy collection and confirmation that the biopsy sample has been sent for central analysis.

ii) The solid tumor tissue specimen must be a core needle, excisional, or incisional biopsy. [redacted] Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable.

iii) Biopsied lesions should be distinct from index lesion(s) being evaluated for radiological response.

iv) An FFPE (block) sample must be sent for central analysis. [redacted]

v) If a participant had a biopsy in the preceding 90 days with no intervening anti-cancer therapy, participants can be enrolled without needing a repeat biopsy after discussion with the BMS Medical Monitor/Study Director (or designee) and upon confirmation of the availability of FFPE blocks. Participants will be required to undergo on-treatment biopsies at acceptable clinical risk as judged by the investigator in all arms.

2) Type of Participant and Target Disease Characteristics

a) Participants must be at least 18 years old and have histological or cytological confirmation of metastatic and/or unresectable malignancy, including but not limited to CC, CRC, HNSCC, MEL, NSCLC, PRC, RCC, TNBC, and UCC with measureable disease per RECIST v1.1 (see Appendix 5) or PCWG3 (prostate only) (see Appendix 11) and have at least 1 lesion accessible for biopsy in addition to the target lesion.

b) Presence of at least 1 lesion with measurable disease as defined by RECIST v1.1 or PCWG3 (prostate only) for solid tumors for response assessment. Participants with lesions in a previously irradiated field as the sole site of measurable disease will be permitted to enroll provided the lesion(s) have demonstrated clear progression and can be measured

c) Participants must have received, and then progressed or been intolerant to, at least 1 standard treatment regimen in the advanced or metastatic setting, if such a therapy exists, and have been considered for all other potentially efficacious therapies prior to enrollment. Participants who are ineligible for standard therapy (due to medical factors such as co-morbid illness, age, etc.) will be allowed to enroll provided the reason for their ineligibility is documented in their medical records.

d) Participants with prior exposure to therapy with any agent specifically targeting checkpoint pathway inhibition (such as anti-PD-1, anti-PD-L1, or anti-CTLA-4) are permitted after a washout period of any time greater than 4 weeks from the last treatment.

e) For all parts (A, B1, B2, C1, C2, D, and E):

i) Participants with CC, CRC, HNSCC, MEL, NSCLC, PRC, RCC, TNBC, and UCC will be permitted. Participants with other solid tumor histologies may be considered and

eligibility should be discussed with BMS Medical Monitor/Study Director (or designee).

f) For all parts (A, B1, B2, C1, C2, D, and E)
   i) The participant must consent for pretreatment and sequential treatment (2 weeks after first dose of study treatment and 12 weeks after first dose) tumor biopsy samples.
   ii) The pretreatment and sequential biopsy samples should be from the same lesion, if possible. Thus, lesion that is > 3 cm at baseline should be considered for collecting biopsy samples. A different lesion may be used to collect on-treatment biopsies should the original lesion not be available.

g) As per revised protocol 02 this criteria is now combined with criteria f).

h) Participants who experienced prior Grade 1 to 2 immunotherapy therapy-related immune-mediated AEs must have confirmed recovery from these events at the time of study entry, other than endocrinopathies treated with supplementation, as documented by resolution of all related clinical symptoms, abnormal findings on physical examination, and/or associated laboratory abnormalities. Where applicable, these participants must also have completed steroid tapers for treatment of these AEs by a minimum of 14 days prior to commencing treatment with study treatment.

i) Eligibility of participants with prior Grade ≥ 3 checkpoint therapy-related immune AEs will be considered on a case-by-case basis after discussion with the BMS Medical Monitor/Study Director (or designee) (eg, asymptomatic isolated Grade 3 lipase elevations without clinical or radiological features of pancreatitis will be permitted to enroll).

j) *"Not applicable as per revised protocol 02"* In an effort to limit confounding factors, for all cohorts where applicable, no more than 5 participants previously found to be "rapid progressors" (time to treatment failure ≤ 2 months) on anti-PD-1, anti-PD-L1, or anti-CTLA-4 therapy should be enrolled per cohort.

k) ECOG performance status ≤ 2

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

3) The following tumor types will be explored:

a) CRC

   i) Participants must have histologically confirmed CRC that is metastatic or recurrent with documented disease progression.
   ii) Document microsatellite instability (MSI), mismatch repair (MMR), KRAS, and BRAF status if known.
   iii) Prior therapy requirement: Participants must have received at least 1, but no more than 3, prior systemic therapies for metastatic and/or unresectable disease (or have progressed within 6 months of adjuvant therapy).
   iv) Participant must have incurable metastatic disease (ie, participants with disease that is potentially curable by surgical resection are not eligible for treatment).
   v) Participants must have been offered and/or have received or refused at least 1 prior approved immune therapy regimen, that is considered standard of care for their disease

stage and condition, in the country where they are receiving treatment, if such a regimen exists. Reason(s) for refusal should be documented.

b) HNSCC (oral cavity, pharynx, larynx)

i) Participants must have histologically confirmed incurable, locally advanced, recurrent, or metastatic HNSCC (oral cavity, pharynx, larynx), Stage III or IV and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy).

ii) Participants should have documented HPV status (can be inferred by p16 staining) and, if known, subtype (HPV16/18).

iii) *"Not applicable as per revised protocol 03"* Participants must have received and then progressed or have been intolerant or refractory to at least 1 but no more than 2 prior systemic therapies (eg, platinum-based chemotherapy) regimen for the treatment of metastatic or locally advanced unresectable disease.

iv) Prior curative radiation therapy must have been completed at least 4 weeks prior to study treatment administration. Prior focal palliative radiotherapy must have been completed at least 2 weeks before study treatment administration.

v) Participants must have been offered and/or have received or refused at least 1 prior approved immune therapy regimen, that is considered standard of care for their disease stage and condition, in the country where they are receiving treatment, if such a regimen exists. Reason(s) for refusal should be documented.

vi) Participants must have received and then progressed or have been intolerant or refractory to at least 1 but no more than 3 prior systemic therapies (eg, platinum-based chemotherapy) regimen for the treatment of metastatic or locally advanced unresectable disease

c) NSCLC

i) Participants must have histologic or cytologic confirmation of NSCLC (per the seventh International Association for the Study of Lung Cancer [IASLC]) with squamous or nonsquamous histology that is advanced (metastatic and/or unresectable).

ii) "Not applicable as per revised protocol 03" Participants must have had at least 1, but not more than 2, prior systemic therapies for NSCLC. Maintenance, adjuvant, or neoadjuvant (chemotherapy or chemoradiation) therapy do not count as an additional line of treatment.

iii) Participants should have been offered a platinum-based chemotherapy for NSCLC. The platinum-based chemotherapy may have been in the adjuvant, neoadjuvant, or chemoradiation setting. Participants with recurrent/metastatic disease that has recurred within 6 months of completing such treatment are considered eligible for study treatment. Prior adjuvant or neoadjuvant chemotherapy is permitted as long as the last administration of the prior regimen occurred at least 4 weeks prior to enrollment.

iv) Prior definitive chemoradiation for locally advanced disease is also permitted as long as the last administration of chemotherapy or radiotherapy (whichever was given last) occurred at least 4 weeks prior to enrollment.

v) Participants with known EGFR mutations or ALK rearrangements must have received EGFR or ALK inhibitors, respectively. EGFR, ALK, KRAS, and ROS1 mutational status must be documented, if known.

vi) Participants must have been offered and/or have received or refused at least 1 prior approved immune therapy regimen, that is considered standard of care for their disease stage and condition, in the country where they are receiving treatment, if such a regimen exists. Reason(s) for refusal should be documented.

vii) Participants must have had at least 1, but not more than 3 prior systemic therapies for NSCLC. Maintenance, adjuvant, or neoadjuvant (chemotherapy or chemoradiation) therapy do not count as an additional line of treatment.

d) PRC

i) Participants must have histologic or cytologic confirmation of adenocarcinoma of the prostate.

ii) *"Not applicable as per revised protocol 02"* Participants have been treated by orchiectomy or are receiving a luteinizing hormone-releasing hormone analog, and have a testosterone level ≤ 50 ng/dL.

iii) *"Not applicable as per revised protocol 02"* Metastatic disease by any 1 of the following modalities: computerized tomography (CT), magnetic resonance imaging (MRI), and bone scan.

a. Participants with bone-only disease should have progression confirmed as per PCWG3 criteria and require confirmatory scans.

iv) Participants must have received abiraterone or enzalutamide.

v) *"Not applicable as per revised protocol 02"* Progression during hormonal treatment. For eligibility purposes, progressive disease is defined as:

(1). Rising prostate-specific antigen values at a minimum of 1-week intervals and a 2.0-ng/mL minimum starting value OR;

(2). Progression per bone scan: the appearance of 2 or more new lesions, OR;

(3). Progression per target lesions/measurable disease: nodal progression, per modified RECIST v1.1. Only lymph nodes > 2 cm will be considered to assess a change in size qualifying for disease progression.

vi) Anti-androgens (bicalutamide, flutamide, nilutamide) or adrenal androgen production inhibitors (aminoglutethamide or ketoconazole) should be discontinued 28 days prior to starting study treatment. Note: bicalutamide or nilutamide must be discontinued within 6 weeks of study arm assignment.

(1). Participants with a history of response to an anti-androgen or adrenal androgen production inhibitor and subsequent progression while on that anti-androgen should be assessed for anti-androgen withdrawal response for 4 weeks, and must demonstrate progression.

(2). For participants who have never responded to anti-androgens, observation for anti-androgen withdrawal response is not necessary; however, a 2-week washout period is required prior to start of study treatment.

vii) Evidence of M1 metastatic disease on previous bone, CT, and/or MRI scan.

viii) Ongoing ADT with a gonadotropin-releasing hormone (GnRH) analogue or bilateral orchiectomy (ie, surgical or medical castration) confirmed by testosterone levels of 1.73 nmol/L (≤ 50 ng/dL) at the screening visit. Castrate levels of testosterone must be maintained by surgical or medical means (leuteinizing

hormone-releasing hormone (LHRH / GnRH analogues) throughout the conduct of the study.

ix) Documented prostate cancer progression as per PCWG3 criteria[39] (see Appendix 11) with one of the following:

(1). PSA progression* defined by a minimum of 2 rising PSA levels with an interval of ≥ 1 week between each determination with either (a) soft tissue disease progression or (b) bone disease progression or both (a) and (b). The PSA value at the screening visit should be ≥ 2µg/L (2 ng/mL).

(2). Soft tissue disease progression defined by RECIST v1.1. Participants whose disease spread is limited to regional pelvic lymph nodes will be considered eligible.

(3). Bone disease progression with 2 or more new lesions on bone scan.

*Participants who received an anti-androgen must have progression after withdrawal (≥ 4 weeks since last flutamide administration or ≥ 6 weeks since last bicalutamide or nilutamide administration)

x) Participants with bone-only disease may not be eligible if a soft tissue fresh pre-treatment and on-treatment tumor biopsies cannot be provided.

xi) *"Not applicable as per revised protocol 03*" Participants must have received 1 but not more than 2 prior regimens for castration-resistant disease. If docetaxel chemotherapy is used more than once, this will be considered as one regimen.

xii) Participants must have received 1 but not more than 3 prior regimens for castration-resistant disease. If docetaxel chemotherapy is used more than once, this will be considered as one regimen.

xiii) Participants must have been offered and/or have received or refused at least 1 prior approved immune therapy regimen, that is considered standard of care for their disease stage and condition, in the country where they are receiving treatment, if such a regimen exists. Reason(s) for refusal should be documented.

e) UCC

i) Participants must have histological or cytological evidence of metastatic or surgically unresectable transitional cell carcinoma of the urothelium involving the bladder, urethra, ureter, or renal pelvis. Minor histologic variants (< 50% overall) are acceptable.

ii) Participants must have metastatic or surgically unresectable disease.

iii) Participants must have progression or recurrence after treatment:

(1). *"Not applicable as per revised protocol 03"* With at least 1 platinum-containing chemotherapy regimen (if platinum eligible) but no more than 2 for metastatic or surgically unresectable locally advanced urothelial cancer, or

(2). Within 12 months of peri-operative (neo-adjuvant or adjuvant) treatment with a platinum agent in the setting of cystectomy for localized muscle-invasive urothelial cancer.

(3). With at least 1 platinum-containing chemotherapy regimen (if platinum eligible) but no more than 3 for metastatic or surgically unresectable locally advanced urothelial cancer.

iv) Sequential chemotherapy given as a planned sequence to optimize response will count as 1 regimen.

v) Participants must have been offered and/or have received or refused at least 1 prior approved immune therapy regimen, that is considered standard of care for their disease stage and condition, in the country where they are receiving treatment, if such a regimen exists. Reason(s) for refusal should be documented.

f) CC

i) Participants must have histologically confirmed CC that is unresectable, metastatic, or recurrent with documented disease progression.

ii) Document tumor HPV status if known. If tumor HPV status is unknown, participants must consent to allow their submitted archived tumor tissue sample (block or unstained slides) to be tested.

iii) Participants must have been offered and/or have received or refused at least 1 prior platinum-based therapy for metastatic and/or unresectable disease. Reason(s) for refusal should be documented.

iv) Participants must have not received more than 3 prior systemic therapies.

v) Concurrent chemotherapy administered with primary radiation and adjuvant chemotherapy given following completion of radiation therapy do not count as systemic therapies, though participants who progressed less than 6 months from primary platinum-based therapy are eligible.

vi) Participants must have been offered and/or have received or refused at least 1 prior approved immune therapy regimen, that is considered standard of care for their disease stage and condition, in the country where they are receiving treatment, if such a regimen exists. Reason(s) for refusal should be documented.

g) MEL

i) Participants must have histologically confirmed recurrent or metastatic melanoma not amenable to local therapy with curative intent (surgery with or without chemotherapy)

ii) Participants must have known BRAF and NRAS mutation status.

iii) Participants must have received and progressed/been intolerant of at least 1 but no more than 3 prior systemic therapies for metastatic and/or unresectable disease and have been considered for all other potentially efficacious therapies.

iv) Participants must have been offered and/or have received or refused at least 1 prior approved immune therapy regimen, that is considered standard of care for their disease stage and condition, in the country where they are receiving treatment, if such a regimen exists. Reason(s) for refusal should be documented.

h) RCC

i) Participants must have histologically confirmed advanced or metastatic RCC with a clear cell component, not amenable to curative surgery.

ii) Must have received at least 1 but not more than 3 prior systemic therapies in the advanced or metastatic setting. Systemic therapies may include anti-angiogenic therapy regimens (including but not limited to sunitinib, sorafenib, pazopanib, axitinib, tivozanib, and bevacizumab), cytokine therapy (eg, IL-2, IFN-α), vaccine therapy, or treatment with cytotoxics.

iii) Participants must have evidence of progression on or after the last treatment regimen received and within 6 months prior to study enrollment.

iv) Participants must have been offered and/or have received or refused at least 1 prior approved immune therapy regimen, that is considered standard of care for their disease stage and condition, in the country where they are receiving treatment, if such a regimen exists. Reason(s) for refusal should be documented.

i) TNBC

i) Participants must be women with histologically or cytologically confirmed breast carcinoma.

ii) Tumor must be "triple receptor negative" defined as ER/progesterone negative per local lab and HER-2 negative defined as HER-2 0 or 1+ by IHC, or IHC 2+ and ISH not amplified, or ISH-non amplified.

iii) Participants must have progression or refractory disease.

iv) Participants must have had at least 1 and not more than 3 systemic chemotherapeutic, targeted or investigational regimens for the treatment of metastatic or locally advanced and unresectable disease.

v) Participants may refuse chemotherapy for their disease. Participants actively refusing chemotherapy must have had best response of stable disease, or progression or refractory disease to other treatment options such as radiotherapy, targeted agents, or investigational therapy prior to starting study treatment. The participant's refusal must be thoroughly documented. The investigator will discuss each individual participant refusing chemotherapy with the sponsor's Medical Monitor/Study Director (or designee) to confirm eligibility.

vi) Participants must have been offered and/or have received or refused at least 1 prior approved immune therapy regimen, that is considered standard of care for their disease stage and condition, in the country where they are receiving treatment, if such a regimen exists. Reason(s) for refusal should be documented.

4) Physical and laboratory test findings

a) Adequate hematologic function

i) White blood cells ≥ 2,000/μL

ii) Neutrophils ≥ 1,500/μL (stable off any growth factor within 4 weeks of first study treatment administration)

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

iv) Hemoglobin ≥ 9.0 g/dL (transfusion to achieve this level is not permitted within 2 weeks of first study treatment administration)

b) Adequate hepatic function

i) ALT and AST ≤ 3× upper limit of normal (ULN)

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

c) Normal thyroid function or stable on hormone supplementation per investigator assessment

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

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

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

e) Ability to comply with treatment, PK and PD sample collection, and required study followup.

f) Participant re-enrollment: This study permits the re-enrollment of a participant who has discontinued the study as a pretreatment failure (eg, participant has not been treated). If re-enrolled, the participant must be re-consented.

5) Age and Reproductive Status

a) Males and females, ages ≥18 years at the time of informed consent.

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

c) Women must not be breastfeeding.

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment with nivolumab or ipilimumab and 5 months after the last dose of study treatment (ie, 30 days [duration of ovulatory cycle] plus the time required for the investigational drug to undergo approximately 5 half-lives).

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment with nivolumab or ipilimumab and 7 months after the last dose of study treatment (ie, 90 days [duration of sperm turnover] plus the time required for the investigational drug to undergo approximately five half-lives). In addition, male participants must be willing to refrain from sperm donation during this time.

f) Due to potential presence of study drugs in seminal fluid, azoospermic males who are sexually active must use condoms for all sexual activity during study treatment. Additionally, condoms must continue to be used for 4 months after the participants' final treatment. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

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

6.2 Exclusion Criteria

1) Target Disease Exceptions

a) Participants with active central nervous system (CNS) metastases, untreated CNS metastases, or with the CNS as the only site of disease are excluded. However, participants with controlled brain metastases will be allowed to enroll. Controlled brain metastases are defined as no radiographic progression for at least 4 weeks following radiation and/or surgical treatment (or 4 weeks of observation if no intervention is clinically indicated), off steroids for at least 2 weeks, and no new or progressive neurological signs and symptoms.

b) Participants with carcinomatous meningitis.

2) Prohibited Treatments

a) Cytotoxic agents, unless at least 4 weeks have elapsed from last dose of prior anti-cancer therapy and initiation of study treatment.

b) Non-cytotoxic agents, unless at least 4 weeks or 5 half-lives (whichever is shorter) have elapsed from the last dose of prior anti-cancer therapy and the initiation of study treatment. If 5 half-lives is shorter than 4 weeks, agreement with the Sponsor/Medical Monitor/Study Director (or designee) is mandatory.

c) Prior immunotherapy treatments, unless at least 4 weeks or 5 half-lives (whichever is shorter) have elapsed from the last dose of immune therapy and initiation of study treatment.

d) Prior therapy with any agent specifically targeting T-cell co-stimulation pathways, such as anti-OX40 antibody, anti-CD137, anti-GITR antibody, and anti-CD27.

e) Prior therapy with anti-ICOS antibody.

f) No prior adverse reaction to tetanus toxoid-containing vaccines.

g) Participants with known allergies to egg products, neomycin, or tetanus toxoid are also considered ineligible

3) Medical History and Concurrent Diseases

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 prostate, cervix, or breast.

b) Prior organ allograft.

c) Toxicity (except for alopecia) related to prior anti-cancer therapy and/or surgery, unless the toxicity is either resolved, returned to baseline or Grade 1, or deemed irreversible.

i) Any active neuropathy Grade > 2 (NCI CTCAE v4.03[27]).

d) Participants with the following:

i) Active, known, or suspected autoimmune disease.

(1). Participants with well-controlled asthma and/or mild allergic rhinitis (seasonal allergies) are eligible.

(2). Participants with the following disease conditions are also eligible:

a. Vitiligo.

b. Type 1 diabetes mellitus.

c. Residual hypothyroidism due to autoimmune condition only requiring hormone replacement.

d. Euthyroid participants with a history of Grave's disease (participants with suspected autoimmune thyroid disorders must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid-stimulating Ig prior to the first dose of study treatment).

e. Psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger.

e) History of life-threatening toxicity related to prior immune therapy (eg, anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (eg, hormone replacement after adrenal crisis).

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

g) Conditions requiring systemic treatment with either corticosteroids > 10 mg daily prednisone equivalents or other immunosuppressive medications within 14 days of study treatment administration, except for adrenal replacement steroid doses ≤ 10 mg daily prednisone equivalent in the absence of active autoimmune disease.

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

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

i) Myocardial infarction or stroke/transient ischemic attack within the past 6 months.

ii) Uncontrolled angina within the past 3 months.

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

iv) History of other clinically significant heart disease (eg, myocarditis, cardiomyopathy, congestive heart failure with New York Heart Association functional classification III to IV [Appendix 9], pericarditis, or significant pericardial effusion).

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

vi) QT interval corrected for heart rate using Fridericia's formula (QTcF) prolongation > 480 msec, except for right bundle branch block.

i) History of chronic hepatitis as evidenced by the following:

i) Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, eg, hepatitis B surface antigen (Australia antigen) positive, or hepatitis C antibody positive (except if hepatitis C ribonucleic acid [RNA] negative).

j) Evidence of active infection that requires systemic antibacterial, antiviral, or antifungal therapy ≤ 7 days prior to the first dose of study treatment (except for viral infections that are presumed to be associated with the underlying tumor type required for study entry).

k) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome.

Note: Testing for HIV-1 and HIV-2 must be performed at sites where mandated by local requirements.

l) Any major surgery within 4 weeks of the first dose of study treatment. Participants must have recovered from the effects of a major surgery or significant traumatic injury at least 14 days before the first dose of study treatment.
   i) Participants who have received a live / attenuated vaccine within 30 days of first treatment.
      (1). The use of inactivated seasonal influenza vaccines (eg, Fluzone®) will be permitted on study without restriction.

m) Receipt of packed red blood cells or platelet transfusion within 2 weeks of the first dose of study treatment.

n) Any known or underlying medical or psychiatric condition and/or social reason that, in the opinion of the investigator or Sponsor, could make the administration of study treatment hazardous to the participants or could adversely affect the ability of the participant to comply with or tolerate the study.

o) WOCBP who are pregnant or breastfeeding.

4) Allergies and Adverse Drug Reaction

a) History of allergy to study treatment components.

b) History of severe hypersensitivity reaction to any mAb.

5) Other Exclusion Criteria

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

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

c) Participants with serious or uncontrolled medical disorders

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

There are no lifestyle restrictions applicable for this study given that the participants will receive the study investigational products (IPs) intravenously.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized/entered 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 (see Appendix 8), and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any SAEs.

6.4.1 Retesting During Screening

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

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

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

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

7 TREATMENT

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

Study treatment includes IPs/investigational medicinal products (IMPs) and non-IPs/IMPs and can consist of the following:

- BMS-986226
- Nivolumab
- Ipilimumab
- Tetanus Vaccine

An IP, also known as IMP in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently from the authorized form, 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-IPs.

Table 7-1: Study Treatments for CA021002

Product Description / Dosage Form	Potency	IP/NonIMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per Label)
BMS-986226-01 Solution for Injection	10 mg/mL	IP	Open	Vial	2 to 8 °C, Protect from light
Nivolumab Solution for Injection	10 mg/mL	IP	Open	Vial	2 to 8 °C, Protect from light and freezing
Ipilimumab Solution for Injection	5 mg/mL	IP	Open	Vial	2 to 8 °C, Protect from light and freezing
Tetanus vaccine	Per local[a]	IP	Open	Various packaging configuration	Refer to the label on container and/or pharmacy manual

Abbreviations: IP = investigational product

[a] Tetanus vaccine (Tdap preferred, Td or equivalent after discussion with the Medical Monitor/Study Director or designee) will be obtained as local commercial product in countries if allowed by local regulations or through investigating sites standard prescribing procedures.

7.1 Treatments Administered

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

Table 7.1-1: Selection and Timing of Dose per Part

Study Treatment	Dose Level	Frequency of Administration	Route of Administration	Infusion time (Minute)
Preliminary Safety Cohorts and Part A				
BMS-986226	2, 8, 25, 80, 200, 400, 800 mg	Q4W	IV	30
Part B1				
Nivolumab	480 mg	Q4W	IV	30
BMS-986226	3 Doses evaluated by BLRM-copula, PK/PD	Q12W		30
Part B2				
Nivolumab	480 mg	Q4W	IV	30
BMS-986226	3 Doses evaluated by BLRM-copula, PK/PD	Q4W	IV	30
Part C1				
Ipilimumab	3 mg/kg[a]	Q4W	IV	30
BMS-986226	3 Doses evaluated by BLRM-copula, PK/PD	Q12W		30

Table 7.1-1: Selection and Timing of Dose per Part

Study Treatment	Dose Level	Frequency of Administration	Route of Administration	Infusion time (Minute)
Part C2				
Ipilimumab	3 mg/kg[a]	Q4W	IV	30
BMS-986226	3 Doses evaluated by BLRM-copula, PK/PD	Q4W		30
Part D				
Nivolumab	480 mg	Q4W	IV	30
BMS-986226	PK/PD from Part B	TBD		30
Part E				
Ipilimumab	3 mg/kg[a]	Q4W	IV	30
BMS-986226	PK/PD from Part C	TBD	IV	30

[a] Weight collected at baseline/screening should be used to calculate ipilimumab dose unless weight has changes more than +/- 10% from baseline on C1D1

Note: In Parts B, C, D, and E a 30-minute infusion of either nivolumab or ipilimumab will be followed by a 30-minute observation period, followed by a 30-minute infusion of BMS-986226. In all parts, participants will be observed for at least 60 minutes following the completion of BMS-986226 infusion due to the potential risk of, and to monitor for, infusion reactions.

In order to reduce the risk of infusion-related reactions, participants enrolled in all study parts are recommended to receive premedication 30 minutes prior to initiation of study treatment. Recommended premedications include a H1 histamine antagonist, such as diphenhydramine 50 mg (or equivalent), and an antipyretic, such as acetaminophen/paracetamol 325 to 1000 mg (or equivalent). Premedication should be administered prior to infusion of any study drug, and should comply with the permitted medications and dosing described in Section 7.6. Any alternative premedication regimen must be discussed with, and approved by the BMS Medical Monitor/Study Director prior to administration of any study treatment. Medical management of any infusion reactions occurring irrespective of whether premedication was administered, remain at the discretion of the investigator. Guidelines for management of infusion reactions are described in Section 7.3.6.

7.1.1 Method of Treatment Assignment

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

The participant identification number (PID) will ultimately be composed of the site number and participant number. For example, the first participant screened (e.g., enrolled) at site number 1, will have a PID [redacted]. Specific instructions for using the IRT will be provided to the investigational sites in a separate instruction manual.

Once it is determined that the participant meets the eligibility criteria following the screening visit, the assigned treatment group and dose level will be provided to the site study team through the IRT prior to the first study treatment administration. The participant will be informed of one of the following:

- Assigned to a part (Preliminary Safety Cohorts and Part A) and dose cohort in the dose escalation portion of the study.
- Assigned to a part (Part B1, B2, C1, or C2) in the combination portion of the study.
- Assigned to the expansion portion of the study (Parts D and E)

During dose escalation, all participants will be assigned to the Preliminary Safety Cohorts, then Part A until the decision is made to start the combination with either nivolumab or ipilimumab. If there are no openings available in the part to which the participant would be assigned by this algorithm, then the participant will be assigned to the next open part/cohort. In the event that multiple cohorts are open in Parts B and/or C simultaneously, participants will be assigned to those cohorts in an alternating fashion.

During dose escalation (Preliminary Safety Cohorts and Part A), participants who are not evaluable for DLT determination may be replaced (see Section 5.1.2.1). Replacement participants will be assigned to the same part (Part A) and dose, but will be assigned a new participant number. Please refer to the IRT manual for complete details on replacement of participants.

Participants in Parts A, B and C may be replaced if adequate paired pretreatment and on-treatment biopsy specimens are not obtained. The replacement participant will receive the same treatment as that for the participant being replaced, but a new participant number will be assigned (see Section 5.1.2.2 and 5.1.2.3).

7.2 Blinding

This is a non-randomized, open-label study; blinding procedures are not applicable.

7.3 Dosage Modification

With the exclusion of the Preliminary Safety Cohorts, intra-participant dose escalation or reduction of BMS-986226, nivolumab, or ipilimumab is not permitted in this study in order to allow better evaluation of the safety and efficacy at individual dose levels and schedules.

7.3.1 Treatment Delay

Participants who experience a DLT must have the study treatment held. Participants who are required to permanently discontinue both study treatments are listed in Section 8.1. In addition, all Grade 2 hepatic, pulmonary, renal, GI, and neurological AEs should be evaluated and managed per the toxicity management algorithms (Appendix 6). Participants not meeting guidelines for

permanent discontinuation will be permitted to resume study treatment based on the criteria specified below in Section 8.1.1. Participants eligible to resume study treatment will resume study treatment at the visit following their last received dose.

In all cohorts, if there is a delay in dosing of BMS-986226 alone or in combination with nivolumab or ipilimumab, between 1 and 12 days, the procedures at the original scheduled visit should be performed as soon as possible. If the delay is more than 12 days, the visit and dose will be considered missed; the procedures at the next scheduled visit should be performed, and subsequent BMS-986226 doses will follow every 4 weeks.

Extensions to the period of dose delays may be granted for individual participants on a case-by-case basis after specific consultation and agreement between the investigator and BMS Medical Monitor/Study Director (or designee) in settings where benefit/risk may justify continued study treatment (eg, participant deriving clinical benefit who requires prolonged steroid taper for the management of non-DLT -drug-related- AEs or experiences delays for the management of a nondrug-related AE).

The end of cycle tumor assessments (ie, CT/MRI, PET, etc) will continue on a Q8W schedule relative to the participant's first dose regardless of any study treatment delay incurred.

7.3.2 BMS-986226 Dose-limiting Toxicities

For the purpose of guiding dose escalation, DLTs will be defined based on the incidence, intensity, and duration of AEs for which no clear alternative cause is identified. The DLT period will be 35 days (5 weeks).

In the Preliminary Safety Cohorts, participants who have received 1 dose of BMS-986226 and have completed, or who discontinued due to a DLT in the 4-week DLT period, will be considered as DLT-evaluable participants for BMS-986226 monotherapy.

In Part A, participants who have received 2 doses of BMS-986226 and have completed, or who discontinued due to a DLT in the 5-week DLT period, will be considered as DLT-evaluable participants for BMS-986226 monotherapy.

In Parts B, C, D and E, participants receiving either 1 dose of BMS-986226 or 2 doses of either nivolumab or ipilimumab, or participants who discontinued due to a DLT in the 5-week combination treatment DLT period, will be considered as DLT-evaluable participants for combination treatment. Participants who withdraw from the study during the DLT evaluation period or have received less than 2 doses for reasons other than a DLT in the monotherapy (Part A) or 1 dose in combination therapy (Parts B, C, D, E), will not be considered as DLT-evaluable participants and may be replaced with a new participant at the same dose level. Participants in Part A, who are dose delayed during the DLT evaluation period for reasons other than a DLT could be considered as DLT-evaluable participants if they receive at least 2 doses of therapy.

For the purpose of participant management, any AE that meets DLT criteria, regardless of the cycle in which it occurs, will lead to discontinuation of study treatment (except as defined in Section 7.3.5). Participants who withdraw from the study during the 5-week DLT evaluation period for reasons other than a DLT may be replaced with a new participant at the same dose

level. The incidence of DLT(s) during the 5-week DLT evaluation period will be used in dose escalation decisions through application of the BLRM/BLRM-Copula model. AEs occurring after the DLT period will be considered to enhance the robustness of BLRM/BLRM-Copula prediction, upon agreement between the Sponsor, Medical Monitor/Study Director (or designee), and investigators.

Participants experiencing a DLT will enter the safety follow-up period of the study. DLTs occurring after the 4-week DLT observation period for the Preliminary Safety Cohorts or 5-week DLT observation period for Parts A, B and C will be accounted for in determining the MAD for the combination part.

AEs will be graded according to the NCI CTCAE v4.03[27], as listed below:

A. Hepatic Non-hematological DLT

Any one of the following study treatment-related events will be considered a hepatic DLT:

- Any Grade ≥ 3 elevation of AST, ALT, or total bilirubin.
- Grade 2 AST or ALT with symptomatic liver inflammation (eg, right upper quadrant tenderness, jaundice, pruritus).
- AST or ALT > 3× ULN and concurrent total bilirubin > 2× ULN without initial findings of cholestasis (elevated serum alkaline phosphatase [ALP] [eg, findings consistent with Hy's law or FDA definition of potential drug-induced liver injury or potential drug-induced liver injury [p-DILI]). Note that this special category of DLT uses ULN rather than Common Toxicity Criteria (CTC) grade for definition.

B. Non-hepatic Non-hematological DLT

Any of the following events will be considered a non-hepatic non-hematological DLT:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity ≤ 2 weeks *or* requires systemic treatment.
- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, myocarditis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration will require discontinuation.
- Any Grade 3 or greater nondermatologic, nonhepatic nonhematological study treatment-related toxicity will be considered a DLT, with the following specific exceptions:
  - Grade 3 or Grade 4 electrolyte abnormalities that are not complicated by associated clinical adverse experiences, last ≤ 72 hours, and either resolve spontaneously or respond to conventional medical intervention
  - Grade 3 nausea, vomiting, or diarrhea that lasts less than 72 hours (without steroid therapy) and either resolves spontaneously or responds to conventional medical intervention
  - Isolated Grade 3 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis
  - Isolated Grade 3 fever not associated with hemodynamic compromise (eg, hypotension, clinical or laboratory evidence of impaired end-organ perfusion or with other symptoms of infusion-related reactions that returns to ≤ Grade 1 with standard treatment in ≤ 1 hour

- Grade 3 endocrinopathy that is well controlled by hormone replacement
- Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor)
- Grade 3 fatigue for ≤ 7 days
- Grade 3 infusion reaction that returns to Grade 1 in ≤ 1 hour

C. Dermatologic DLT

- Grade 3/4 rash if no improvement (ie, resolution to Grade ≤ 1) after a 1-week to 2-week infusion delay. Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Grade 4 rash of any duration

D. Hematologic DLT

- Grade 4 neutropenia ≥ 5 days in duration
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with clinically significant bleeding or any requirement for platelet transfusion
- Grade 4 anemia not explained by underlying disease
- Grade 4 febrile neutropenia
- Grade 3 febrile neutropenia that lasts > 48 hours
- Grade ≥ 3 hemolysis (i.e., requiring transfusion or medical intervention such as steroids)

7.3.3 Management Algorithms for Immuno-oncology Agents

Immuno-oncology (I-O) agents are associated with irAEs that can differ in severity and duration from AEs caused by other therapeutic classes. BMS-986226, nivolumab, and ipilimumab are considered I-O agents in this protocol. Early recognition and management of irAEs associated with I-O agents may mitigate severe toxicity. Management algorithms have been developed from extensive experience with I-O agents to assist investigators in assessing and managing the following groups of irAEs:

- GI
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological

The clinical nature of AEs noted with BMS-986226 will determine the role of the algorithms for use in toxicities related to its use in this study. The algorithms recommended for the management of irAEs in this protocol are in Appendix 6.

7.3.4 Dose Delays Due To Toxicity

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

- Potential DLTs, until DLT relatedness is defined.
- Select AEs and laboratory abnormalities:
  - Grade ≥ 1 pneumonitis
  - Grade ≥ 2 abnormality in AST, ALT, or total bilirubin
  - Grade ≥ 2 abnormality in creatinine
  - Grade ≥ 2 diarrhea or colitis
  - Grade ≥ 2 neurological AE
  - AE, laboratory abnormality, or concurrent illness that, in the judgment of the investigator, warrants delaying study treatment administration.

Criteria for participants who are required to permanently discontinue both study treatments are listed in Section 8.1. Participants not meeting guidelines for permanent discontinuation will be permitted to resume therapy based on the criteria specified below in Section 7.3.5. Participants eligible to resume study treatment will resume study treatment at the nominal treatment visit following their last received study treatment dose.

The end of cycle tumor assessments, such as CT, MRI, or positron emission tomography (PET), will continue on a once Q8W schedule relative to the participant's first dose, regardless of any treatment delay incurred.

7.3.5 Exceptions to Permanent Discontinuation Criteria

Any drug-related AE occurring at any time that meets DLT criteria as outlined in Section 7.3.2 will require permanent discontinuation. Exceptions to permanent discontinuation are listed in Section 8.1.

Study treatment may be re-initiated in participants experiencing non-life-threatening AEs that meet DLT criteria and that have been resolved to Grade 1 or baseline. Consideration to resume treatment will be made on a case-by-case basis in a discussion between the investigator and BMS Medical Monitor/Study Director (or designee) and approval of the sponsor, taking into account the overall benefit/risk ratio for the individual participant and the following factors:

- A 2-week washout period is required after completing the immune suppressive treatment used to manage the AE (eg, steroids). The AE should not recur/worsen during the washout period.
- Evidence for clinical or radiographic benefit must be present, which can include improvement of physical symptoms (eg, ECOG status, shortness of breath), symptomatic improvement in combination with assessment of SD, or radiographic response.

In the event of recurrence of the AE that met the DLT criteria, study treatment will be permanently discontinued for the participant.

Additionally, consideration to permanently discontinue study treatment for participants with any severe Grade 3 drug-related AE that recurs will be made on a case-by-case basis in a discussion between the investigator and BMS Medical Monitor/Study Director (or designee).

All participants who discontinue IP should comply with protocol-specified follow-up procedures as outlined in Section 5.1.3. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (eg, imprisonment or involuntarily incarceration 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 Case Report Form (CRF) page.

7.3.6 Management of Drug-related Infusion Reactions

BMS-986226 is a humanized mAb and has the potential to induce hypersensitivity reactions following administration. As of 28-March-2019, 7 of 19 (36.8%) participants treated with BMS-986226 monotherapy experienced a Grade 1 or Grade 2 infusion-related reaction. One participant experienced Grade 3 hypersensitivity during BMS-986226 infusion after the data cut-off date of 28 March 2019. When such reactions occur, they may manifest with fever, chills, rigors, headache, flushing, rash, urticaria, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor/Study Director (or designee) and reported as an SAE. Infusion reactions should be graded according to NCI CTCAE v4.03[27] guidelines.

Premedications are recommended as per section 7.1.

Treatment recommendations for infusion reactions are provided below 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 acetaminophen/paracetamol 325 to 1,000 mg at least 30 minutes before study treatment administrations.

For Grade 2 symptoms: Moderate reaction requiring therapy or infusion interruption but responding promptly to symptomatic treatment (eg, antihistamines, nonsteroidal-anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, or IV fluids); prophylactic medications indicated for ≤ 24 hours.

- Remain at the bedside and monitor participant until resolution of symptoms**.** Monitor participant closely.
- Stop the study treatment infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and acetaminophen/paracetamol 325 to 1,000 mg.
- 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. The amount of study treatment infused must be recorded on the CRF.
- If symptoms recur, then no further BMS-986226, nivolumab, or ipilimumab will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and acetaminophen/paracetamol 325 to 1,000 mg should be administered at least 30 minutes before study treatment infusions. 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 other clinical sequelae (eg, renal impairment or pulmonary infiltrates); Grade 4: life-threatening; pressor or ventilatory support indicated.

- Remain at bedside and monitor participant until recovery of the symptoms.
- 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 1:1,000 solution for intramuscular or subcutaneous 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.
- Participant should be monitored until the investigator is comfortable that the symptoms will not recur. Study treatment will be permanently discontinued except for a Grade 3 infusion reaction that returns to Grade 1 in less than 6 hours. Investigators should follow their institutional guidelines for the treatment of anaphylaxis.

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).

7.4 Preparation/Handling/Storage/Accountability

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

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

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

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

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

7.4.1 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

7.5 Treatment Compliance

Study treatment will be administered in the clinical facility by trained medical personnel. Treatment compliance will be monitored by drug accountability as well as by recording BMS-986226, nivolumab, and ipilimumab administration in participants' medical records and in the CRF.

7.6 Concomitant Therapy

7.6.1 Prohibited and/or Restricted Treatments

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

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

- Immunosuppressive agents (except as stated in Section 7.6.2)
- Concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy (except where otherwise indicate), immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents) Herbal prescriptions including, but not limited to, cannabis and other recreational drugs
- Any live / attenuated vaccine (eg varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella (MMR) during treatment and until 100 days post last dose.

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

7.6.1.1 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen for each participant. Imaging contraindications and contrast risks should be considered in this assessment. Participants with renal insufficiency should be assessed as to whether or not they should receive contrast and, if so, what type and dose of contrast are appropriate. MRI contrast should not be given to participants with severe renal insufficiency (eg, estimated GFR < 30 mL/min/1.73 m^2) because of increased risk of nephrogenic systemic fibrosis in this participant population. In these participants, alternative imaging tests or MRI without gadolinium should be considered. In addition, participants should be excluded from MRI if they have uncontrollable claustrophobia, metallic implants, pacemakers, and so on.

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 (EC).

7.6.2 Permitted Therapy

Participants are permitted the use of the following treatments:

- Topical, ocular, intra-articular, intra-nasal, and inhalational corticosteroids (with minimal systemic absorption).
- Adrenal replacement steroid doses ≤ 10 mg daily prednisone equivalent.
- 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).
- Bisphosphonates and RANKL directed-therapies for bone metastases are permitted.

Systemic immunosuppressive agents and the use of systemic corticosteroids are permitted in the context of treating AEs. Participants receiving corticosteroids for treatment of drug-related AEs must be receiving < 10 mg/day prednisone equivalent for < 5 days up to 7 days prior to re-initiation of study treatment. Participants may continue to receive hormone replacement therapy.

7.6.3 Palliative Local Therapy

Palliative and supportive care for disease-related symptoms may be offered to all participants on the study after the DLT evaluation period. Limited radiation therapy or surgery to control isolated lesions is permitted for participants who have investigator-assessed clinical benefit following consultation with the BMS Medical Monitor/Study Director (or designee).

Participants should not receive study treatment during radiation, as the potential for overlapping toxicities with radiotherapy and BMS-986226 or BMS-986226 in combination with nivolumab or ipilimumab is currently not known. Anecdotal data suggest that radiotherapy administered to participants while receiving nivolumab or ipilimumab therapy is tolerable. However, because concurrent radiotherapy and immunotherapies in cancer have not been formally evaluated, in cases where palliative radiotherapy is required for a tumor lesion, BMS-986226 alone or in combination with nivolumab or ipilimumab should be withheld for at least 1 week before, during, and 1 week

after radiation. Participants should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs related to radiotherapy should resolve to Grade 1 prior to resuming study treatment.

Participants who have received palliative local therapy will be documented as having had disease progression for the purpose of efficacy analyses.

7.7 Treatment After the End of the Study

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

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

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

- Participant's request to stop study treatment
- Any clinical AE, laboratory abnormality, or intercurrent illness that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- Pregnancy
- Documented and confirmed disease progression as defined by RECIST v1.1 (see Appendix 5) or PCWG3 (prostate cancer only) (see Appendix 11) unless participant meets criteria for treatment beyond progression (Section 8.1.2)
- Clinical deterioration while receiving active study treatment that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Discretion of the investigator
- Inability to comply with the protocol requirements
- Individual participants with confirmed CR will be given the option to discontinue study treatment on a case-by-case basis after specific consultation and agreement between the investigator and BMS Medical Monitor/Study Director (or designee) in settings where benefit/risk justifies discontinuation of study treatment
- Any Grade 4 drug-related AE or laboratory abnormality (including, but not limited to, creatinine, AST, ALT, or total bilirubin), except for the following events that do not require discontinuation:

  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia, leukopenia, or asymptomatic amylase or lipase abnormalities
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy AEs, such as hyperthyroidism or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor/Study Director (or designee).
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage study treatment-related AEs are allowed
  - Dosing delays lasting > 6 weeks from the previous dose that occur for nondrug-related reasons may be allowed if approved by the BMS Medical Monitor/Study Director (or designee).
- The assessment for discontinuation of nivolumab or ipilimumab should be made separately from the assessment made for discontinuation of BMS-986226. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for BMS-986226 but not for nivolumab or ipilimumab, treatment with nivolumab or ipilimumab may continue even if BMS-986226 is discontinued.
- If a participant in any of the nivolumab or ipilimumab/BMS-986226 combination arms meets criteria for discontinuation and the investigator is unable to determine whether the event is related to both or 1 of the study treatments, the participant should discontinue both nivolumab or ipilimumab and BMS-986226 and should be taken off the treatment phase of the study.

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

All participants who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 5.1.3. The only exception to this requirement is when a participant withdraws consent for all study procedures, including posttreatment study follow-up, or loses the ability to consent freely (eg, imprisonment, involuntarily incarceration for the treatment of either a psychiatric or a 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 Criteria to Resume Treatment

Subsequent dosing with the study treatment may resume once drug-related DLT AEs resolve to Grade 1 or baseline.

In agreement with the Sponsor, after evaluation of the risk/benefit ratio, participants with selected drug-related AE that meet DLT criteria may resume treatment once the AE is resolved to Grade ≤ 1 or baseline value (see Section 7.3.5).

Participants who experience AEs and do not meet the criteria for permanent discontinuation as outlined in Section 8.1 may resume study treatment under the following criteria:

- Participants may resume treatment with study treatment when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:
  - Participants may resume treatment in the presence of Grade 2 fatigue.
  - Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
  - Participants with Grade 2 uveitis, episcleritis, iritis, eye pain, or blurred vision not meeting DLT criteria (Section 7.3.2) must resolve to baseline prior to resuming study treatment.
- For participants with Grade 2 AST, ALT, or total bilirubin elevations, dosing may resume when laboratory values return to baseline and management with corticosteroids (if needed) is complete.
  - Participants with combined Grade 2 AST/ALT and total bilirubin values meeting DLT criteria (Section 7.3.2) should have treatment permanently discontinued.
- 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, the BMS Medical Monitor/Study Director (or designee).
- Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

If the criteria to resume treatment are met, the participant should restart treatment at the next nominally scheduled time point per protocol.

Even if the criteria to resume treatment are met, the consideration to re-initiate study treatment under the following exception will be made on a case-by-case basis after considering the overall benefit/risk profile, and in consultation between the investigator and the Sponsor. Any AE with clinical risk will be assessed on a case-by-case basis with the investigator and the BMS Medical Monitor/Study Director (or designee) to determine the risks and benefits of continuing on the treatment following resolution versus discontinuing therapy permanently.

If study treatment is delayed > 6 weeks, the participant must be permanently discontinued from study treatment, except as specified in Section 7.3.5.

8.1.2 Treatment Beyond Disease Progression

As described in Section 5.4.3, accumulating evidence indicates that a minority of participants with solid tumors treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease. Participants will be permitted to continue on study treatment beyond initial

RECIST v1.1 defined progressive disease (see Appendix 5) or PCWG3 (prostate cancer only) (see Appendix 11) as long as they meet the following criteria:

- Investigator-assessed clinical benefit and no rapid disease progression
- Continue to meet all other study protocol eligibility criteria
- Tolerance of study treatment
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Participant provides written informed consent prior to receiving any additional BMS-986226, nivolumab, or ipilimumab treatment using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options

The assessment of clinical benefit should take into account whether the participant is clinically deteriorating and unlikely to receive further benefit from continued treatment. If the investigator feels that the participant continues to achieve clinical benefit by continuing treatment with the study treatment, the participant should remain on the study and continue to receive monitoring according to the Schedule of Activities (see Section 2). All decisions to continue treatment beyond initial progression must be discussed with the BMS Medical Monitor/Study Director (or designee), and an assessment of the risk/benefit of continuing with study treatment must be documented in the study records. Participants will be re-consented to explain the rationale for this ongoing treatment.

8.1.3 Discontinuation Due to Further Progression (Confirmed Progression)

Participants will continue to receive monitoring according to the on-treatment assessments in Section 2. Radiographic assessment by CT (preferred) or MRI (described in Section 9.1) is required when participants continue post-progression study treatment and should be performed at each scheduled tumor assessment 4 to 6 weeks following initial disease progression to determine whether there has been continued progressive disease or not. Participants should discontinue study treatment upon evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from the time of initial progression (including all target lesions and new measurable lesions).

The tumor burden volume from the time of initial progression should be used as the reference baseline for comparison with the post-progression assessment.

Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore must be included in the tumor burden measurement as follows:

- For solid tumors: 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).

For statistical analyses that include the investigator-assessed progression date, participants who continue treatment beyond initial investigator-assessed, RECIST v1.1 or PCWG3 (prostate cancer only) defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

For participants who discontinue post-progression study treatment, no additional radiographic assessments will be required.

8.1.4 Post-study Treatment Study Follow-up

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 up 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 -defined window (Section 2). At the time of this request, each participant will be contacted to determine his or her survival status unless the participant has withdrawn consent for all contacts or is lost to follow-up.

Participants who discontinue study treatment may continue to be followed 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 up for protocol-specified follow-up procedures, as indicated in Section 5.1.3. The only exception to this is when participants specifically withdraw consent for any further contact with them or persons previously authorized by participants to provide this information.

- Participants should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The investigator should explain the withdrawal of consent in detail in the medical records and enter on the appropriate CSR page 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; this explanation should be 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

Guidelines for participants lost to follow-up include the following:

- 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 for contact.

- Lost to follow-up is defined by the inability to reach the participant after a minimum of **3** documented phone calls, faxes, or emails as well as lack of response by participant to **1** registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a -retained third-party representative to assist site staff with obtaining the participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, 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 randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities (Section 2).

Additional measures, including non-study-required laboratory tests, should be performed 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 laboratories until all study treatment-related toxicities resolve, return to baseline, or are deemed irreversible.

If a participant shows pulmonary-related signs (hypoxia or fever) or symptoms (eg, dyspnea, cough, or fever) consistent with possible pulmonary AEs, the participant should be immediately

evaluated to rule out pulmonary toxicity according to the suspected pulmonary toxicity management algorithm in the ipilimumab IB.[18]

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.

9.1 Efficacy Assessments

Study evaluations will take place in accordance with the Schedule of Activities in Section 2.

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

9.1.1 Methods of Assessment

CT and MRI are essential parts of the work-up to establish recurrence. The following imaging assessments should be performed at prespecified intervals: CT of the chest and CT or MRI of the abdomen, pelvis, and other known/suspected sites of disease.

- CT scans should be acquired with a slice thickness of 5 mm or less with no intervening gap (continuous).
- Should a participant have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen and pelvis and other known/suspected sites of disease may be obtained. MRIs should be acquired with a slice thickness of 5 mm or less with no gap (continuous).
- Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging time points.
- PET alone will not be considered for the disease assessment. Complementary CT and/or MRI or biopsy must be performed in such cases.
  - Note: Use of CT component of a PET/CT scanner: Combined modality scanning, such as with fluorodeoxyglucose (FDG)-PET/CT, is increasingly used in clinical care and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low-dose or attenuation corrections of the CT portions of a combined FDG-PET/CT are of limited use in anatomically based efficacy assessments, and it is, therefore, suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based RECIST v1.1 (see Appendix 5) or PCWG3 (prostate cancer only) (see Appendix 11) measurements. However, if a site can document that the CT performed as part of an FDG-PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the FDG-PET/CT can be used for RECIST v1.1 measurements. Note, however, that the FDG-PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed.

- Histology or cytological evidence of recurrence should be attempted in all cases except for brain metastases. Cytology and/or histology are mandatory to confirm recurrence in solitary or in equivocal lesions, any new lesions occurring in the kidney, and lymph nodes unless the lesion is too small to biopsy or the risk of biopsy is substantial (eg, inter-aortal node with risk of bleed after biopsy because of close proximity to the aorta and inferior vena cava), in which case, the recurrence must be confirmed with a repeat scan 4 weeks later.

Disease assessment with CT and/or MRI, as appropriate, will be performed at baseline and approximately Q8W (± 1 week) during the treatment phase (prior to dosing at Cycles 3, 5 and 7) until progressive disease per RECIST v1.1 (see Appendix 5) or PCWG3 (prostate cancer only) (see Appendix 11), or until confirmed progressive disease for participants treated beyond progression (defined as an additional 10% or greater increase in tumor burden volume from time of initial progression [including all target lesions and new measurable lesions]), or withdrawal from study. Tumor assessments at other time points may be performed if the investigator is concerned about tumor progression. Tumor response will be assessed by the investigator according to RECIST v1.1 (see Appendix 5) or PCWG3 (prostate cancer only) (see Appendix 11) for participants with solid tumors.

For participants with prostate cancer, bone lesions should be assessed using Technetium-99m (Tc-99m) based radionuclide bone scans. Anterior and posterior whole body planar images should be acquired. Additional (including spot views and SPECT) images should be submitted if acquired. Assessments should be performed at baseline and at the time points described per PCWG3 criteria until disease progression per PCWG3 criteria (see Appendix 11), or discontinuation of study treatment, whichever occurs later. Tumor assessments at other time points may be performed if clinically indicated and should be confirmed at least 4 weeks after initial response. Changes in tumor measurements and tumor responses will be assessed by the investigator per study design using PCWG3 criteria. Investigators will also report the number and size of new lesions that appear while on study. For participants who are treated beyond PCWG3-defined progression, tumor assessments will continue to be performed until discontinuation of study treatment (typically upon evidence of further progression). Any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled time points and/or at an outside institution should be collected for PCWG3 tumor assessment and submitted to the BICR.

Images will be submitted to an imaging core laboratory. Sites should be trained prior to scanning the first study participant. Image acquisition guidelines and submission process will be outlined in the Imaging Manual to be provided by the core laboratory.

For Part A, images will be collected centrally and may be reviewed by BICR at a later date, or at any time during the study per BMS request. For Parts B, C, D and E, images will be collected centrally and reviewed by BICR.

9.1.2 Primary Efficacy Assessments

Not applicable.

9.1.3 Secondary Efficacy Assessments

The secondary efficacy assessments will include the objective response rate (ORR; eg, PR + CR), mDOR, and progression-free survival rate (PFSR) at 24 weeks based on assessment of tumor response using RECIST v1.1 or PCWG3 (prostate cancer only).

ORR is defined as the proportion of all treated participants whose best overall response (BOR) is either a CR or PR. BOR is defined as the best response designation over the study as a whole, recorded between the dates of first dose and the date of first objectively documented tumor progression per RECIST v1.1 (or PCWG3) or the date of subsequent therapy, whichever occurs first. CR or PR determinations included in the BOR assessment must be confirmed by a second scan performed no less than 4 weeks after the criteria for response are first met. A Best Overall Response of SD requires a minimum of 49 days on study from the date of first dose to the date of the first imaging assessment. For those participants who have surgical resection, only pre-surgical tumor assessments will be considered in the determination of BOR.

mDOR, computed for all treated participants with a BOR of CR or PR, is defined as the time between the date of first response and the date of the first objectively documented disease progression per RECIST v1.1 (or PCWG3) or death, whichever occurs first.

PFSR at 24 weeks is defined as the proportion of treated participants remaining progression free and surviving at 24 weeks. The proportion will be calculated by the Kaplan-Meier estimate, which takes into account censored data.

For prostate cancer, the consensus guidelines of the PCWG3 have been taken into consideration for the determination of radiographic disease progression assessment. All target and non-target sites of disease identified on the baseline assessment should be reassessed with the same imaging modality at subsequent assessments. Bone lesions should be assessed with Tc-99m based bone scans.

For prostate cancer disease progression, at each disease assessment, progressive disease will be determined using the criteria based on PCWG3.

Radiographic progression in soft tissue lesions (prostate only) is described in Table 9.1.3-1. See Appendix 11 (PCWG3) for additional information.

Table 9.1.3-1: Definition of Radiographic Progression

Parameter	Progression	Date of Progression
Soft tissue lesions (target, non-target lesions with CT or MRI)	Progression of soft tissue lesions (target, non-target, new lesions with CT or MRI)	Date of first unequivocal progression of soft tissue lesion (target, non-target, or new lesions) as per PCWG3[a]
Bone lesions on radionuclide bone scan per PCWG3	At least 2 new lesions on the first post-treatment bone scan, confirmed on the next scan (performed at least 6 weeks later) AND with at least 2 additional lesions as compared to the first post-treatment bone scan	Date of first post-treatment scan
	For scans after the first post-treatment scan, at least 2 new lesions relative to the first post-treatment scan AND confirmed on a subsequent scan (performed at least 6 weeks later)	Date of progression is the date of the scan that first documents at least 2 new lesions relative to the first post-treatment scan

[a] RECIST v1.1 criteria are modified for assessing soft tissue lesions per PCWG3. See Appendix 11.

[redacted]

9.2 Adverse Events

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

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

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, are considered related to the study treatment or the study, or caused the participant to discontinue before completing the study.

Contacts for SAE reporting are specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of non-serious AE information should begin at the initiation of study treatment until 100 days of the last dose of study treatment, at the time points specified in the Schedule of Activities (Section 2).

Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study treatment, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs that occur during the screening period and within 100 days of the last dose of study treatment must be collected. If applicable, SAEs that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy) must be collected. For participants assigned to treatment and never treated with study treatment, SAEs should be collected for 30 days from the date of treatment assignment.

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

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

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

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

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

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

9.2.2 Method of Detecting AEs and SAEs

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

9.2.3 Follow-up of AEs and SAEs

- Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified non-serious AEs must be recorded and described on the non-serious 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 will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

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

9.2.4 Regulatory Reporting Requirements for SAEs

All SAEs that occur during the screening period and within 100 days of the last dose of study treatment must be collected. For participants randomized/assigned to treatment and never treated with study treatment, SAEs should be collected for 30 days from the date of randomization/treatment assignment.

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities toward 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 IB and will notify the Institutional Review Board/EC, if appropriate according to local requirements.

Sponsor or designee will be reporting AEs to regulatory authorities and EC according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A suspected unexpected serious adverse reaction is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/Study Director (or 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.

In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the BMS Medical Monitor/Study Director (or designee) within 24 hours of awareness of the pregnancy.

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

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

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

9.2.6 Laboratory Test Result Abnormalities

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

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

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

9.2.7 Potential Drug-induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a p-DILI event. All occurrences of p-DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.2.4 and Appendix 3 for reporting details).

p-DILI is defined as:

1) Aminotransaminases (AT) (ALT or AST) elevation > 3× ULN
   AND
2) Total bilirubin > 2× ULN, without initial findings of cholestasis (elevated serum ALP),
   AND
3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, preexisting chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

The key responsibilities for investigators during p-DILI assessment include the following:

- Early detection, medical evaluation (including the exclusion of other potential causes), and rapid laboratory confirmation of liver-related abnormalities
- BMS notification of p-DILI cases via SAE forms

Following the gathering and assessment of relevant clinical information, BMS is responsible for:

- Timely evaluation and triaging of p-DILI cases
- Expedited reporting of p-DILI cases
- Expanded review of p-DILI cases, including a detailed assessment of all available clinical information, investigations, and biochemical data

Investigators are expected to monitor ongoing routine and ad hoc hepatic laboratory test results to rapidly determine whether a participant meets p-DILI criteria. They are expected to promptly notify BMS of all p-DILI cases. p-DILI cases may be identified by abnormal liver biochemistry values, whether or not they are accompanied by liver-related signs and/or symptoms. In both cases, expedited confirmation with repeat laboratory testing should occur within 3 business days using a hepatic laboratory panel (ALT, AST, total bilirubin, and ALP). Any participant with an abnormal hepatic laboratory panel that meets p-DILI criteria is a candidate for study treatment discontinuation. Any confirmed p-DILI event must be reported (along with a description of the clinical findings) to BMS as an SAE within 24 hours of confirmation.

An extensive clinical history examination and appropriate investigations should be obtained to exclude cholestatic and other apparent causes that may explain the observed abnormalities in liver function and/or hepatic signs and symptoms. Other apparent causes include, nonexhaustively and by way of example only, infectious diseases (such as active hepatitis A, B, and C), congenital diseases (such as Gilbert's syndrome), neoplastic diseases (such as hepatocellular carcinoma), autoimmune diseases (such as primary biliary cirrhosis), and the use of concomitant hepatotoxic medications (such as antibiotics, the oral contraceptive pill, and herbal medicines). All investigations to exclude potential causes of liver function abnormalities or hepatic signs and/or symptoms should be guided by relevant factors such as the participant's age, gender, clinical history, and signs and symptoms.

9.2.8 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, ECG, x-ray filming, and any other potential safety assessment required or not required by protocol should also be recorded as a non-serious AE or SAE, 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. For this study, any dose of BMS-986226, nivolumab and/or ipilimumab, that is greater than the assigned dose, and considered excessive and medically important by the investigator, will be considered an overdose.

In the event of an overdose, the investigator/treating physician should:

1) Contact the Medical Monitor/Study Director (or designee) immediately
2) Closely monitor the participant for AEs/SAEs and laboratory abnormalities until study treatment can no longer be detected systemically (at least 125 days)
3) Obtain a plasma sample for PK analysis within 125 days from the date of the last dose of study treatment if requested by the Medical Monitor/Study Director (or designee) (determined on a case-by-case basis)
4) Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor/Study Director (or designee) based on the clinical evaluation of the participant.

9.4 Safety

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

9.4.1 Physical Examinations

Refer to the Schedule of Activities for the timing of assessments (Section 2).

9.4.2 Vital Signs

Refer to the Schedule of Activities for the timing of assessments (Section 2).

9.4.3 Electrocardiograms

Refer to the Schedule of Activities for the timing of assessments (Section 2).

[redacted] For the purposes of monitoring participant safety, the investigators will review the 12lead ECGs using their site's standard ECG machines throughout the study. [redacted]

9.4.4 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- 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.
- The clinical tests that will be performed are shown in Table 9.4.4-1.
- Results of all laboratory tests required by this protocol must be provided to the Sponsor, recorded either on the laboratory pages of the CRF or by another mechanism as agreed upon between the investigator and BMS (eg, provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct

units. Any abnormal laboratory test result considered clinically significant by the investigator must be recorded on the appropriate AE page of the CRF (see Section 9.2.6).

Table 9.4.4-1: Clinical Laboratory Tests

Hematology	
Prothrombin time, activated partial thromboplastin time, and international normalized ratio (at screening only)	
Platelet count	Hemoglobin
Hematocrit	Total leukocyte count, including differential
Serum Chemistry	
Aspartate aminotransferase Alanine aminotransferase Total bilirubin Direct bilirubin (reflex only) Alkaline phosphatase Lactate dehydrogenase Creatinine Blood urea nitrogen Glucose (Fasting required at screening only) Gamma glutamyl transferase (reflex only) Lipase Testosterone (PRC only) C-reactive protein	Total protein Albumin Sodium Potassium Chloride Carbon Dioxide Calcium Phosphorus Magnesium Creatine kinase Creatinine clearance- screening only Thyroid stimulating hormone Free T3 and T4 (screening and reflex only) Amylase
Urinalysis	
Protein	Blood
Glucose	Leukocyte esterase
Specific gravity	pH
Microscopic examination of the sediment if positive for blood, protein, or leukocytes esterase on dipstick	
Serology	
Serum for hepatitis C antibody (If hepatitis C antibody is positive reflex to hepatitis C RNA) or hepatitis C RNA, hepatitis B surface antigen. Testing for HIV-1 and HIV-2 must be performed at sites only where mandated by local requirements. (Screening Only)	
Viral Status HNSCC and CC only: Sites should submit and document prior HPV status and subtype, particularly HPV16 and HPV18, within 28 days of dosing.	
Tetanus booster (administered 3-7 days prior to Cycle 1 Day 1 at screening; a tetanus booster does not have to be administered if the participant received a tetanus booster within 6 weeks of starting study drug)	

Table 9.4.4-1: Clinical Laboratory Tests

Other Analyses
Pregnancy test (women of childbearing potential only: screening, pre-dose, discharge).
Follicle-stimulating hormone (screening only for women only)

9.4.5 Imaging Safety Assessment

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

9.5 Pharmacokinetic and Immunogenicity Assessments

Samples for PK and immunogenicity assessments will be collected for all participants receiving BMS-986226, [redacted] as described in Table 9.5-1 through Table 9.5-4. Immunogenicity samples will be analyzed for anti-BMS-986226 antibodies, [redacted] by validated immunoassays.

All pre-dose samples should be taken within 30 minutes prior to the start of the infusion of first drug. End-of infusion (EOI) samples should be taken immediately prior to the stopping of the drug infusion (in monotherapy) or to the stopping of the second drug infusion (in combination therapy), preferably within 2 minutes prior to the end of infusion. 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. If it is known that a dose is going to be delayed, then the pre-dose sample should be collected just prior to the delayed dose. However, if a pre-dose sample is collected but the dose is subsequently delayed, an additional pre-dose sample should not be collected. Further details of sample collection, processing, and shipment will be provided in the Laboratory Manual.

Table 9.5-1: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986226 (Preliminary Safety Cohorts and Part A)

Study Day of Sample Collection (1 Cycle = 4 Weeks)	Event	Time (Relative to Start of BMS-986226 Infusion) Hour:Min	BMS-986226 Blood Sample	BMS-986226 Immunogenicity Sample
Treatment Cycles				
Cycle 1 Day 1 (C1D1)[a]	Pre-dose	0:00	X	X
	EOI[b]	0:30	X	
		4:00	X	
C1D2		24:00	X	
C1D4		72:00	X	
C1D8 (+/- 1 day)		168:00	X	
C1D15 (+/- 1 day)		336:00	X	X
C1D22 (+/- 1 day)		504:00	X	
C2D1	Pre-dose	0:00	X	X
	EOI[b]	0:30	X	
		4:00	X	
C2D2		24:00	X	
C2D8 (+/- 1 day)		168:00	X	
C2D15 (+/- 1 day)		336:00	X	
C2D22 (+/- 1 day)		504:00	X	
C3D1	Pre-dose	0:00	X	X
	EOI[b]	0:30	X	
C3D2		24:00	X	

Table 9.5-1: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986226 (Preliminary Safety Cohorts and Part A)

Study Day of Sample Collection (1 Cycle = 4 Weeks)	Event	Time (Relative to Start of BMS-986226 Infusion) Hour:Min	BMS-986226 Blood Sample	BMS-986226 Immunogenicity Sample
C3D8 (+/- 1 day)		168:00	X	
C3D15 (+/- 1 day)		336:00	X	
C3D22 (+/- 1 day)		504:00	X	
C4D1	Pre-dose	0:00	X	X
	EOI[b]	0:30	X	
C5D1	Pre-dose	0:00	X	X
C6D1	Pre-dose	0:00	X	X
Adverse Event				
Grade 3/4 Hypersensitivity Reaction[c]			X	X
End of Treatment and Follow-up Period				
EOT			X	X
30-Day FU			X	X
60-Day FU			X	X
100-Day FU			X	X

[a] Participants taking 2 or 8 mg of BMS-986226 in the Preliminary Safety Cohorts will follow the same sampling schedule as in Part A. In the event that participants taking 2 or 8 mg of BMS-986226 should be permitted to intra-dose escalate up to 8 and/or 25 mg, the sampling schedule should be restarted at Cycle 1 Day 1 at each dose escalation.

[b] This sample should be taken immediately prior to the stopping of the BMS-986226 drug infusion (in monotherapy), preferably within 2 minutes prior to the end of infusion. If the end of infusion is delayed beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. EOI samples may not be collected from the same IV access as the drug was administered.

[c] Samples will be taken as directed when drug-related adverse event, Grade 3/4 infusion reaction, or hypersensitivity reaction is confirmed.
Abbreviations: C = Cycle; D = Day; EOI = end of infusion; EOT = end of treatment; FU = follow-up.

Table 9.5-2: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986226 [redacted] (Parts B1 and C1)

Study Day of Sample Collection (Cycle = 4 weeks)	Event	Time (Relative to Start of Nivolumab or Ipilimumab Infusion) Hour:Min	BMS-986226 Blood Sample	BMS-986226 Immunogenicity Sample	[redacted]
Treatment Cycles					
Cycle 1 Day 1 (C1D1)	Pre-dose[a]	00:00	X	X	
	EOI[b]	00:30	X		
		04:00	X		
C1D2		24:00	X		
C1D4		72:00	X		
C1D8 (+/- 1 day)		168:00	X		
C1D15 (+/- 1 day)		336:00	X		
C1D22 (+/- 1 day)		504:00	X		
C2D1	Pre-dose	0:00:00	X	X	
C2D8 (+/- 1 day)		168:00	X		
C2D15 (+/- 1 day)		336:00	X		
C3D1	Pre-dose	0:00	X	X	
C4D1	Pre-dose	0:00	X	X	
	EOI[b]	0:30	X		
		4:00	X		
C4D2		24:00	X		
C4D8 (+/- 1 day)		168:00:00	X		
C4D15 (+/- 1 day)		336:00:00	X		

Table 9.5-2: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986226 [redacted] (Parts B1 and C1)

Study Day of Sample Collection (Cycle = 4 weeks)	Event	Time (Relative to Start of Nivolumab or Ipilimumab Infusion) Hour:Min	BMS-986226 Blood Sample	BMS-986226 Immunogenicity Sample	[redacted]
C4D22 (+/- 1 day)		504:00:00	X		
C5D1	Pre-dose	0:00	X		
C5D8 (+/- 1 day)		168:00	X		
C5D15 (+/- 1 day)		336:00	X		
C6D1	Pre-dose	0:00	X	X	
C7D1	Pre-dose	0:00	X	X	
C7D1	EOI[b]	0:30	X		
C8D1	Pre-dose	0:00	X		
C10D1	Pre-dose	0:00	X	X	
	EOI[b]	0:30	X		
Every 3 Cycles starting with C13D1 (example: C16D1, C19D1, etc)	Pre-dose	0:00	X	X	
Adverse Event					
Grade 3/4 Hypersensitivity Reaction[c]			X		
End of Treatment and Follow-up Period					
EOT			X	X	
30-Day FU			X	X	

Table 9.5-2: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986226 [redacted] (Parts B1 and C1)

Study Day of Sample Collection (Cycle = 4 weeks)	Event	Time (Relative to Start of Nivolumab or Ipilimumab Infusion) Hour:Min	BMS-986226 Blood Sample	BMS-986226 Immunogenicity Sample	[redacted]
60-Day FU			X	X	
100-Day FU			X	X	

[a] All pre-dose samples for BMS-986226 [redacted] should be taken prior to the start of nivolumab/ipilimumab infusion (preferably within 30 minutes).

[b] This sample should be taken immediately prior to the stopping of the second drug infusion (in combination therapy), preferably within 2 minutes prior to the end of infusion. If the end of infusion is delayed beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. EOI samples may not be collected from the same IV access as the drug was administered.

[c] Samples will be taken as directed when drug-related adverse event, Grade 3/4 infusion reaction, or hypersensitivity reaction is confirmed.

[redacted]

Abbreviations: C = Cycle; D = Day; EOI = end of infusion; EOT = end of treatment; FU = follow-up.

Table 9.5-3: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986226 [redacted] (Parts B2 and C2)

Study Day of Sample Collection (1 Cycle = 4 Weeks)	Event	Time (Relative to Start of BMS-986226 Infusion) Hour:Min	BMS-986226 Blood Sample	BMS-986226 Immunogenicity Sample	[redacted]
Treatment Cycles					
Cycle 1 Day 1 (C1D1)	Pre-dose[a]	00:00	X	X	
	EOI[b]	00:30	X		
		04:00	X		
C1D2		24:00	X		
C1D4		72:00	X		
C1D8 (+/- 1 day)		168:00	X		
C1D15 (+/- 1 day)		336:00	X		
C1D22 (+/- 1 day)		504:00	X		
C2D1	Pre-dose	00:00	X	X	
	EOI[b,]	00:30	X		
		4:00	X		
C2D2		24:00	X		
C2D8 (+/- 1 day)		168:00	X		
C2D15 (+/- 1 day)		336:00	X		
C2D22 (+/- 1 day)		504:00	X		
C3D1	Pre-dose	00:00	X	X	
	EOI[b]	00:30	X		
		4:00	X		

Table 9.5-3: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986226 [redacted] (Parts B2 and C2)

Study Day of Sample Collection (1 Cycle = 4 Weeks)	Event	Time (Relative to Start of BMS-986226 Infusion) Hour:Min	BMS-986226 Blood Sample	BMS-986226 Immunogenicity Sample	[redacted]
C3D2		24:00	X		
C3D8 (+/- 1 day)		168:00	X		
C3D15 (+/- 1 day)		336:00	X		
C3D22 (+/- 1 day)		504:00	X		
C4D1	Pre-dose	00:00	X	X	
C5D1	Pre-dose	00:00	X	X	
C7D1	Pre-dose	00:00	X	X	
Every 3 Cycles starting with C10D1 (example: C13D1, C16D1, etc)	Pre-dose	00:00	X	X	
Adverse Event					
Grade 3/4 Hypersensitivity Reaction[c]			X	X	
End of Treatment and Follow-up Period					
EOT			X	X	
30-Day FU			X	X	
60-Day FU			X	X	
100-Day FU			X	X	

[a] All pre-dose samples for BMS-986226 [redacted] should be taken prior to the start of nivolumab/ipilimumab infusion (preferably within 30 minutes).

[b] This sample should be taken immediately prior to the stopping of the second drug infusion (in combination therapy), preferably within 2 minutes prior to the end of infusion. If the end of infusion is delayed beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. EOI samples may not be collected from the same IV access as the drug was administered.

[c] Samples will be taken as directed when drug-related adverse event, Grade 3/4 infusion reaction, or hypersensitivity reaction is confirmed.

[redacted]

Abbreviations: C = Cycle; D = Day; EOI = end of infusion; EOT = end of treatment; FU = follow-up.

Table 9.5-4: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986226 [redacted] (Parts D and E)

Study Day of Sample Collection (Cycle = 4 weeks)	Event	Time (Relative to Start of BMS-986226 Infusion) Hour:Min	BMS-986226 Blood Sample	BMS-986226 Immunogenicity Sample	[redacted]
Treatment Cycles					
Cycle 1 Day 1 (C1D1)	Pre-dose[a]	00:00	X	X	
	EOI[b]	00:30	X		
C2D1	Pre-dose	00:00	X	X	
C3D1	Pre-dose	00:00	X	X	
C4D1	Pre-dose	00:00	X	X	
C7D1	Pre-dose	00:00	X	X	
Every 3 Cycles starting with C10D1 (example: C13D1, C16D1, etc)	Pre-dose	0:00	X	X	
Adverse Event					
Grade 3/4 Hypersensitivity Reaction[c]			X		
End of Treatment and Follow-up Period					
EOT			X	X	
30-Day FU			X	X	
60-Day FU			X	X	
100-Day FU			X	X	

[a] All pre-dose samples for BMS-986226 [redacted] should be taken prior to the start of nivolumab/ipilimumab infusion (preferably within 30 minutes).

[b] This sample should be taken immediately prior to the stopping of the second drug infusion (in combination therapy), preferably within 2 minutes prior to the end of infusion. If the end of infusion is delayed beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. EOI samples may not be collected from the same IV access as the drug was administered.

[c] Samples will be taken as directed when drug-related adverse event, Grade 3/4 infusion reaction, or hypersensitivity reaction is confirmed.

[redacted]

Abbreviations: C = Cycle; D = Day; EOI = end of infusion; EOT = end of treatment; FU = follow-up

The serum samples will be analyzed for drug (BMS-986226 [redacted]) and ADA (BMS-986226 antibodies and/or anti-nivolumab or anti-ipilimumab antibodies) by validated immunoassays. [redacted] Serum samples designated for PK [redacted] assessments may also be used for immunogenicity analysis if required (eg, insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity related AEs).

[redacted]

Labeling and Shipping of Biological Samples: Detailed instructions for the PK and PD blood collection, labeling, processing, storage, and shipping will be provided to the site in the procedure manual.

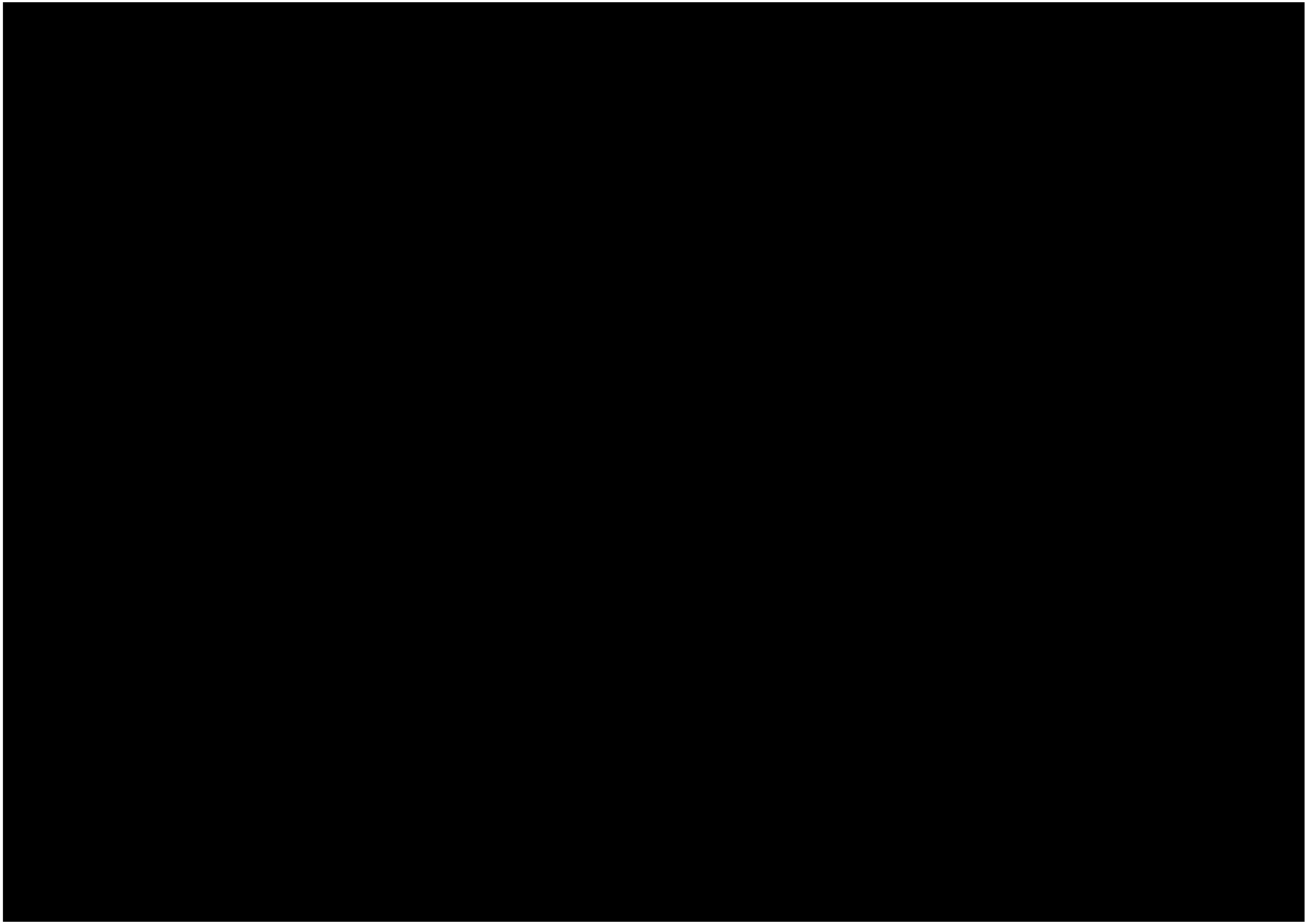
9.6 Pharmacodynamics

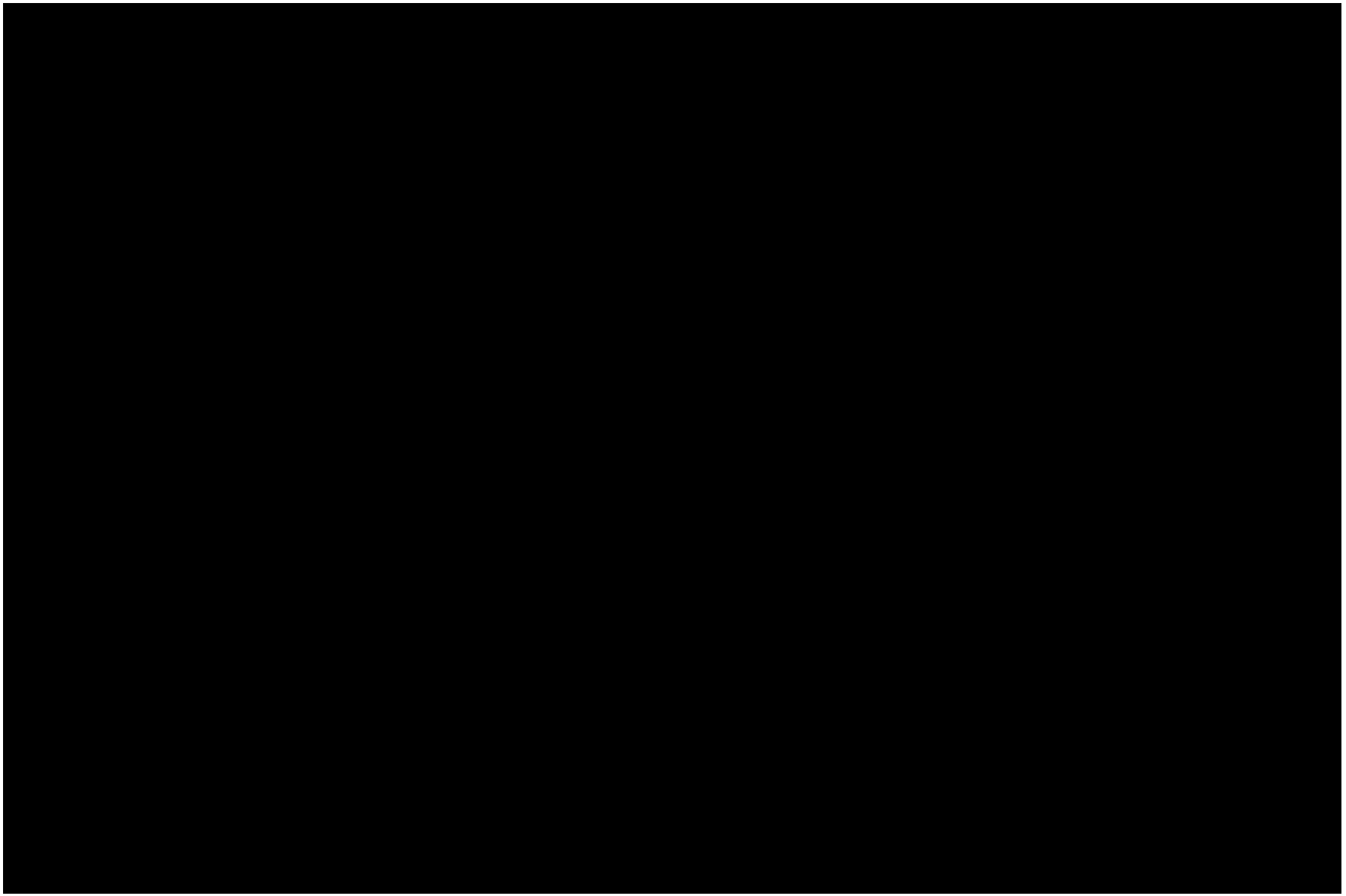
Details on the PD biomarker assessments are included [redacted].

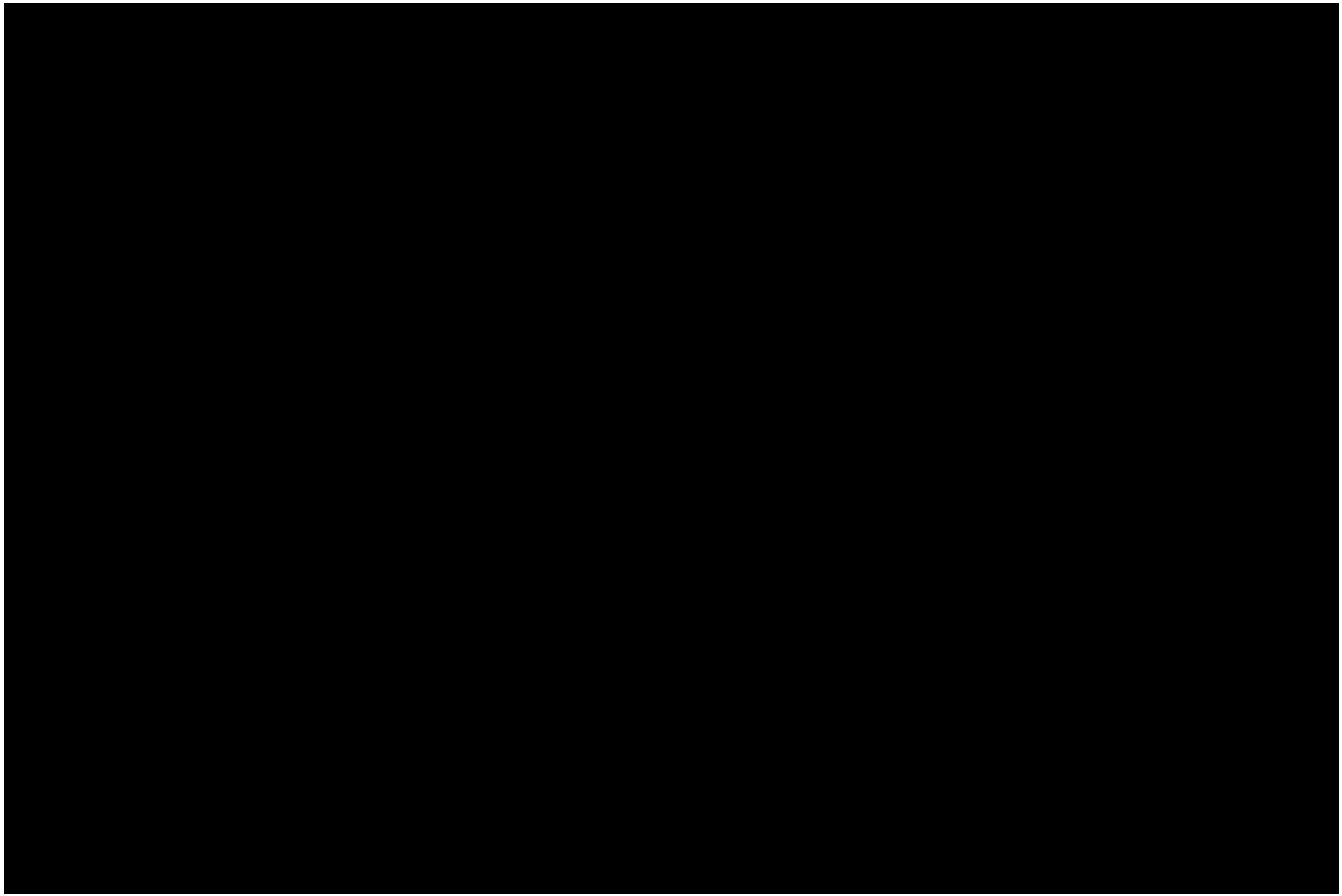
9.7 Pharmacogenomics

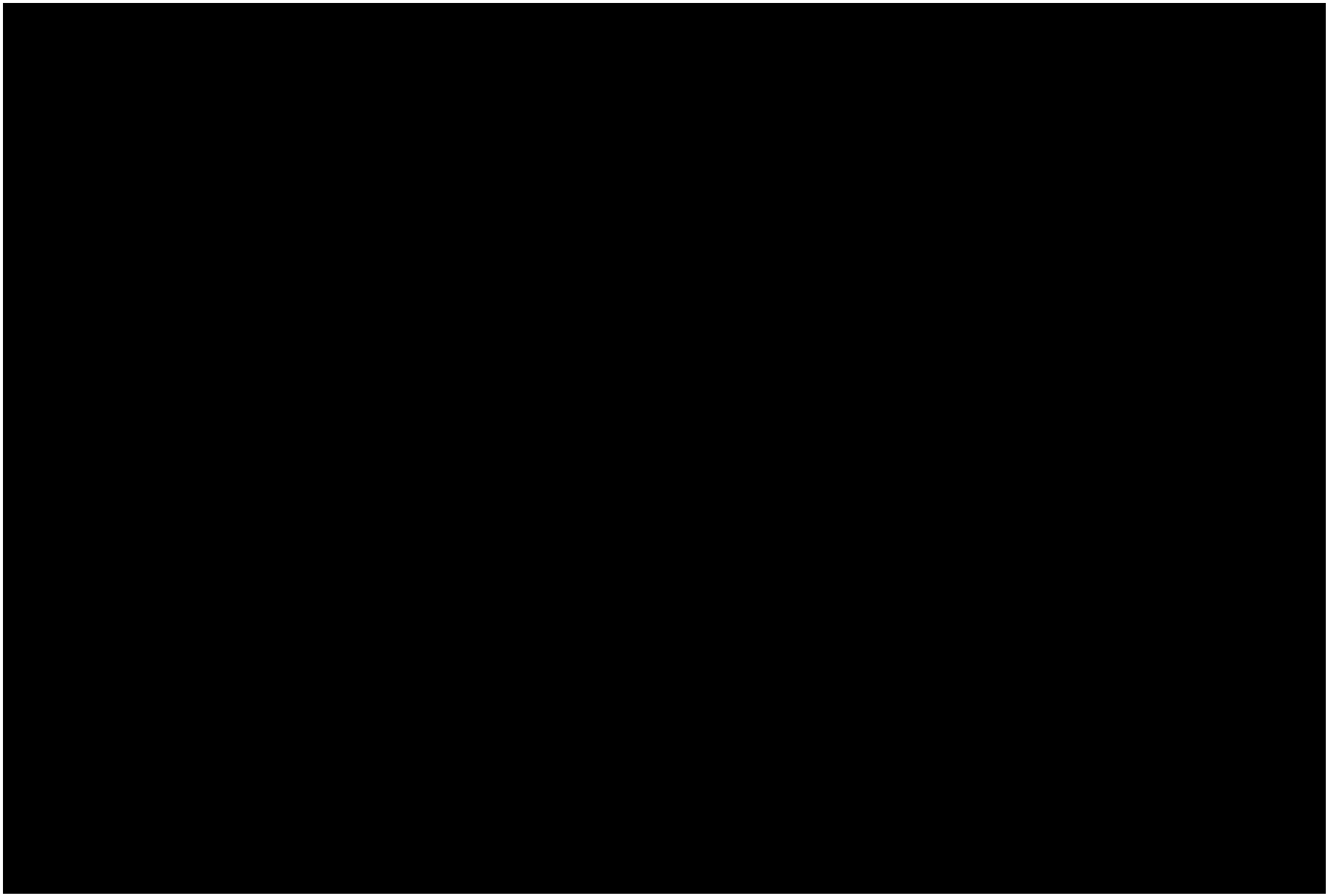
Not applicable.

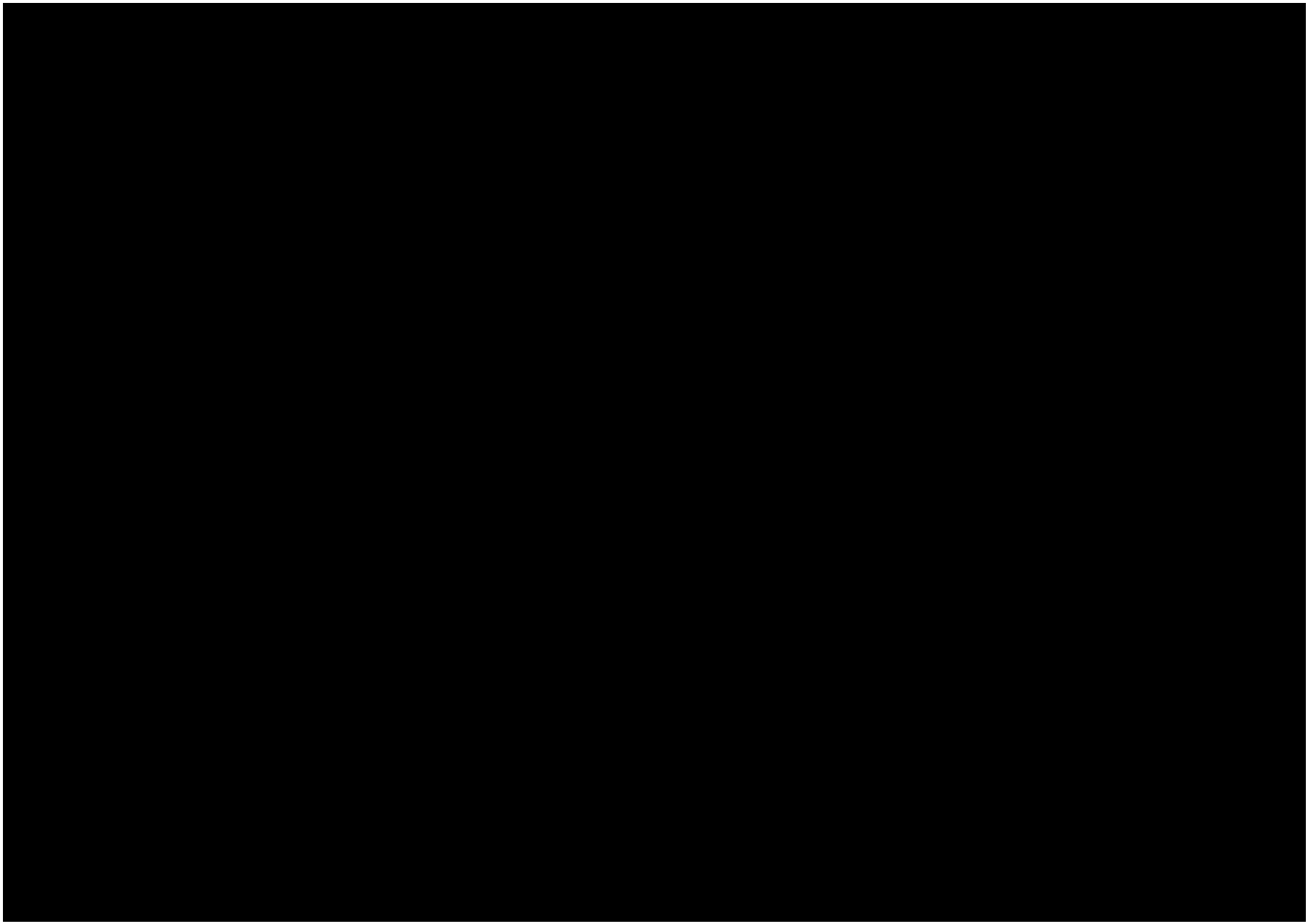
[redacted]

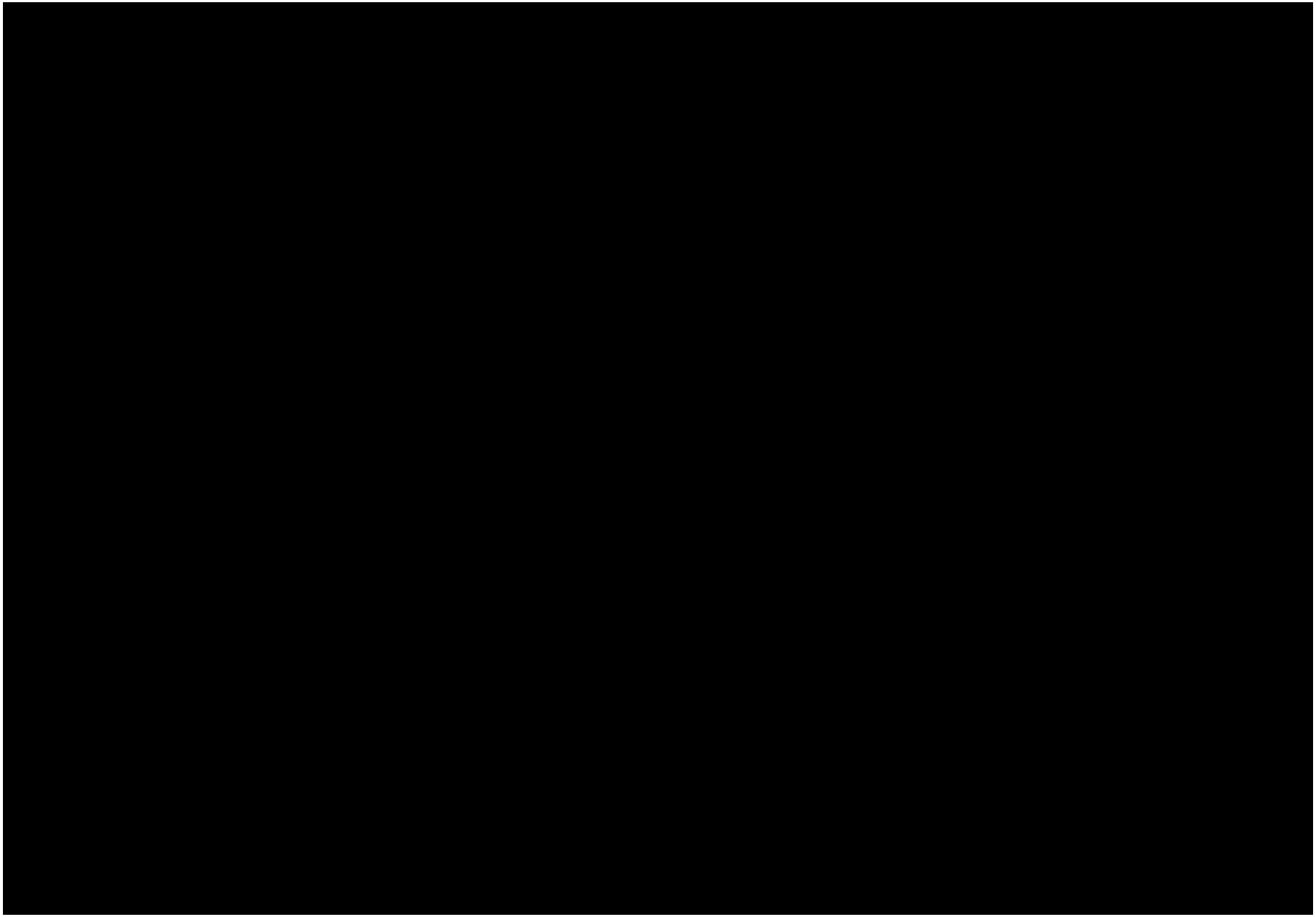


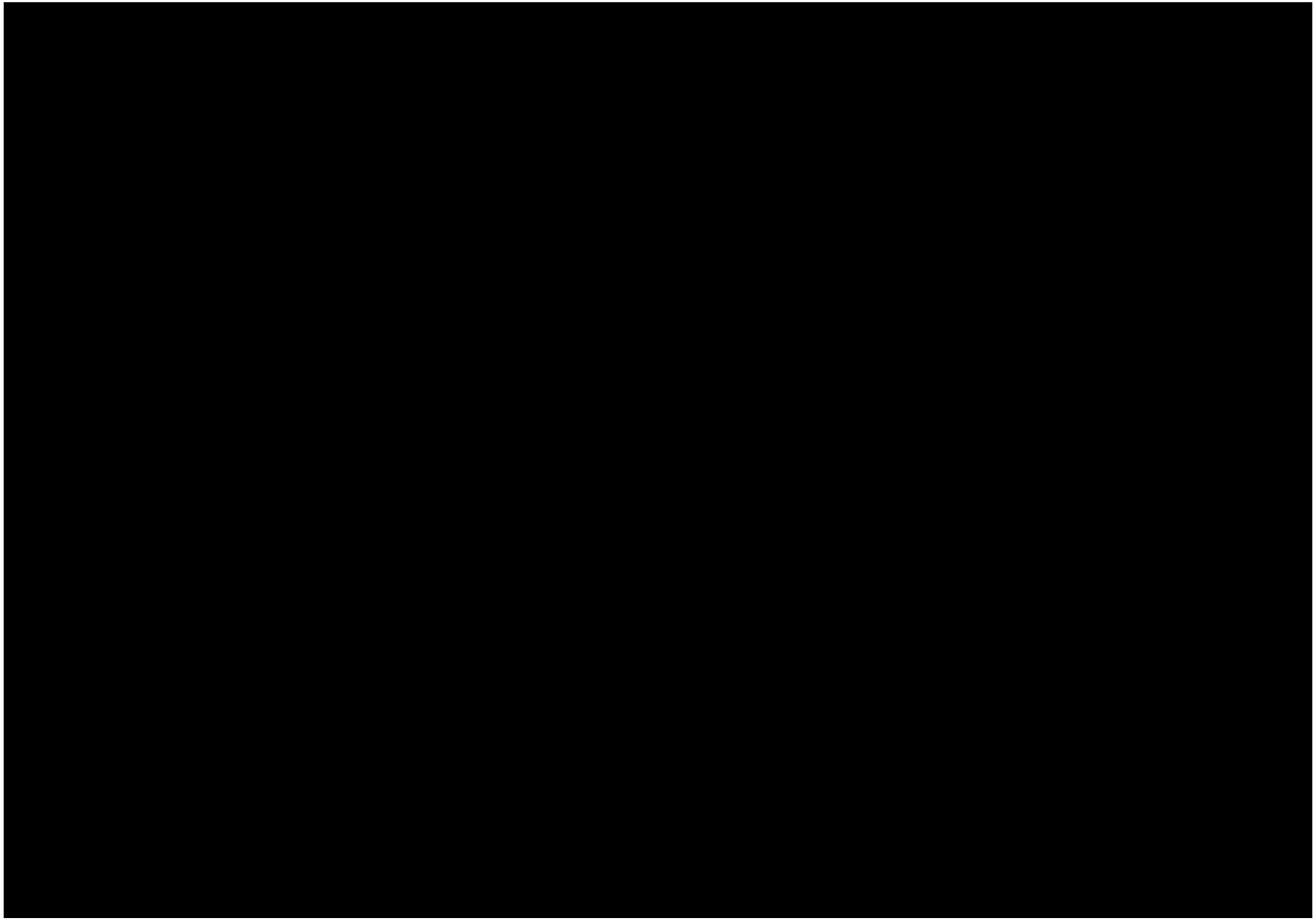












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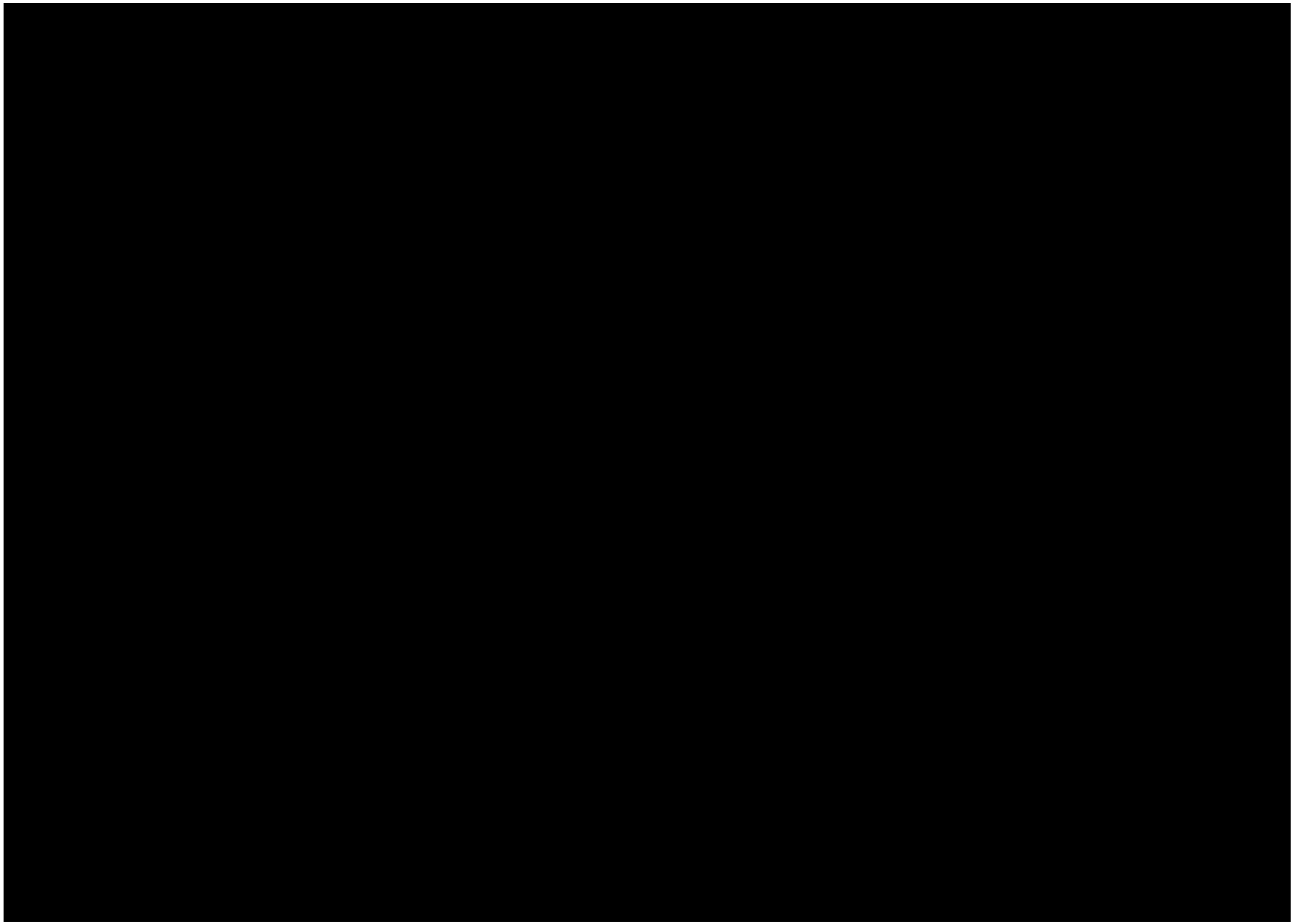

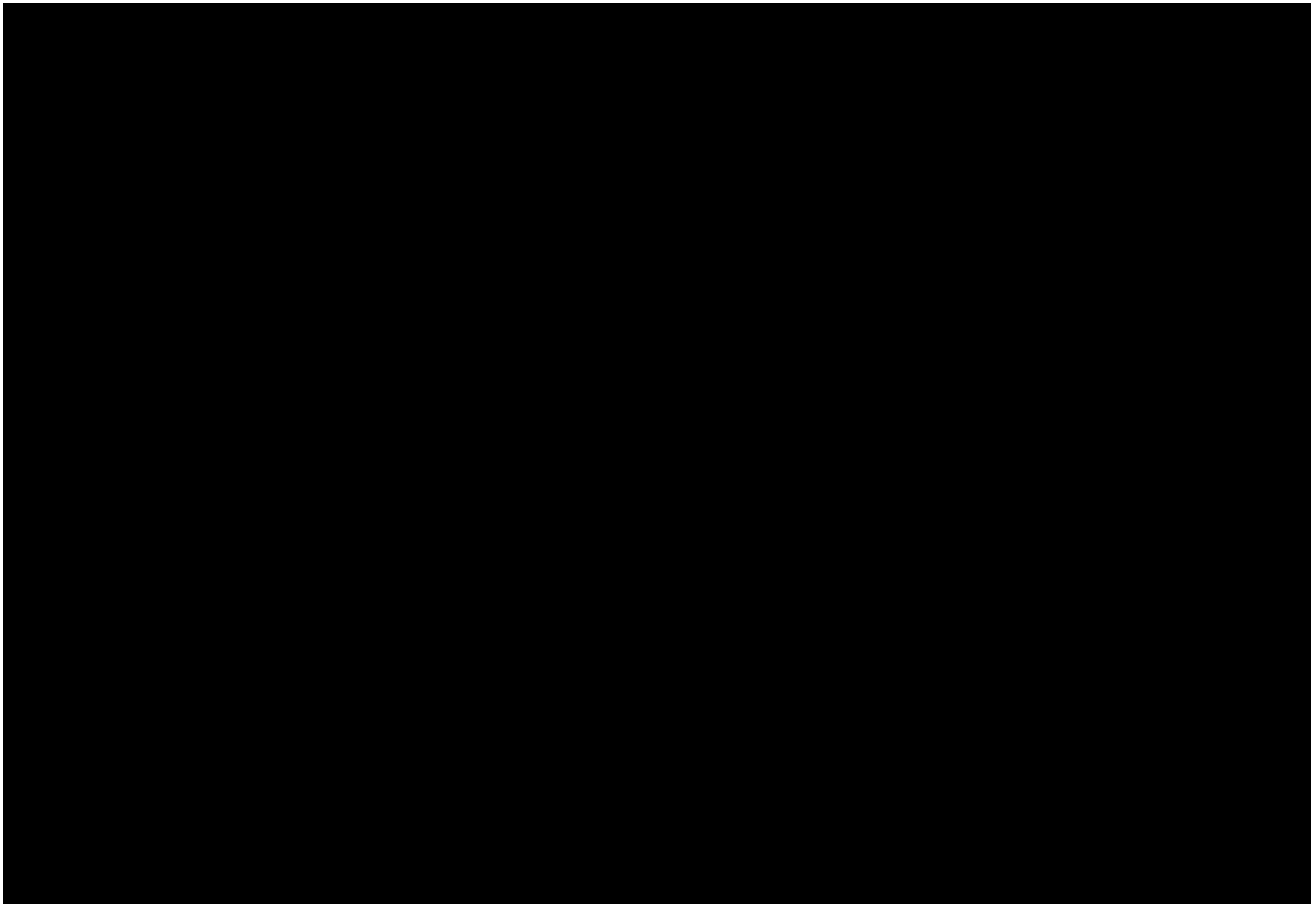

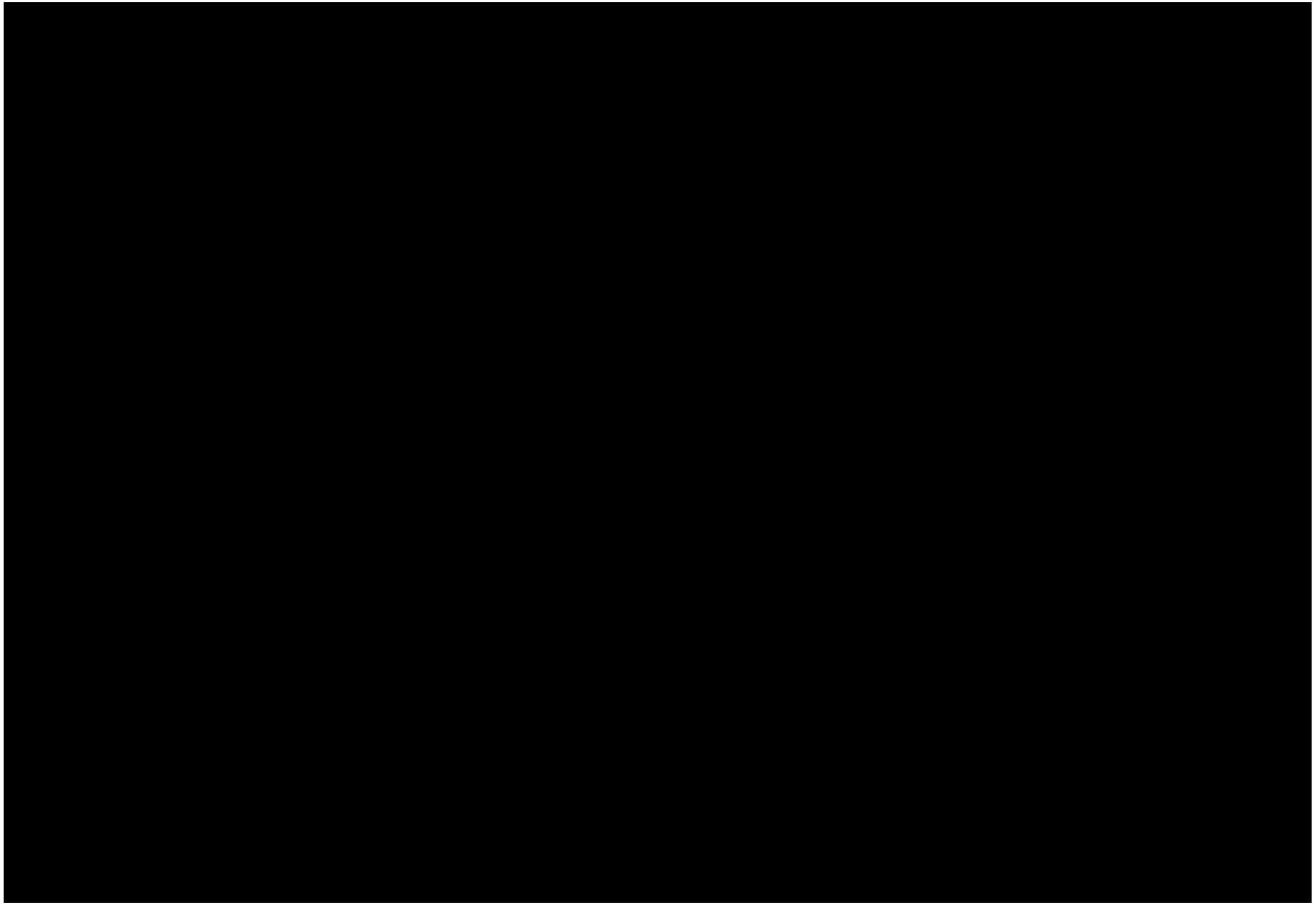

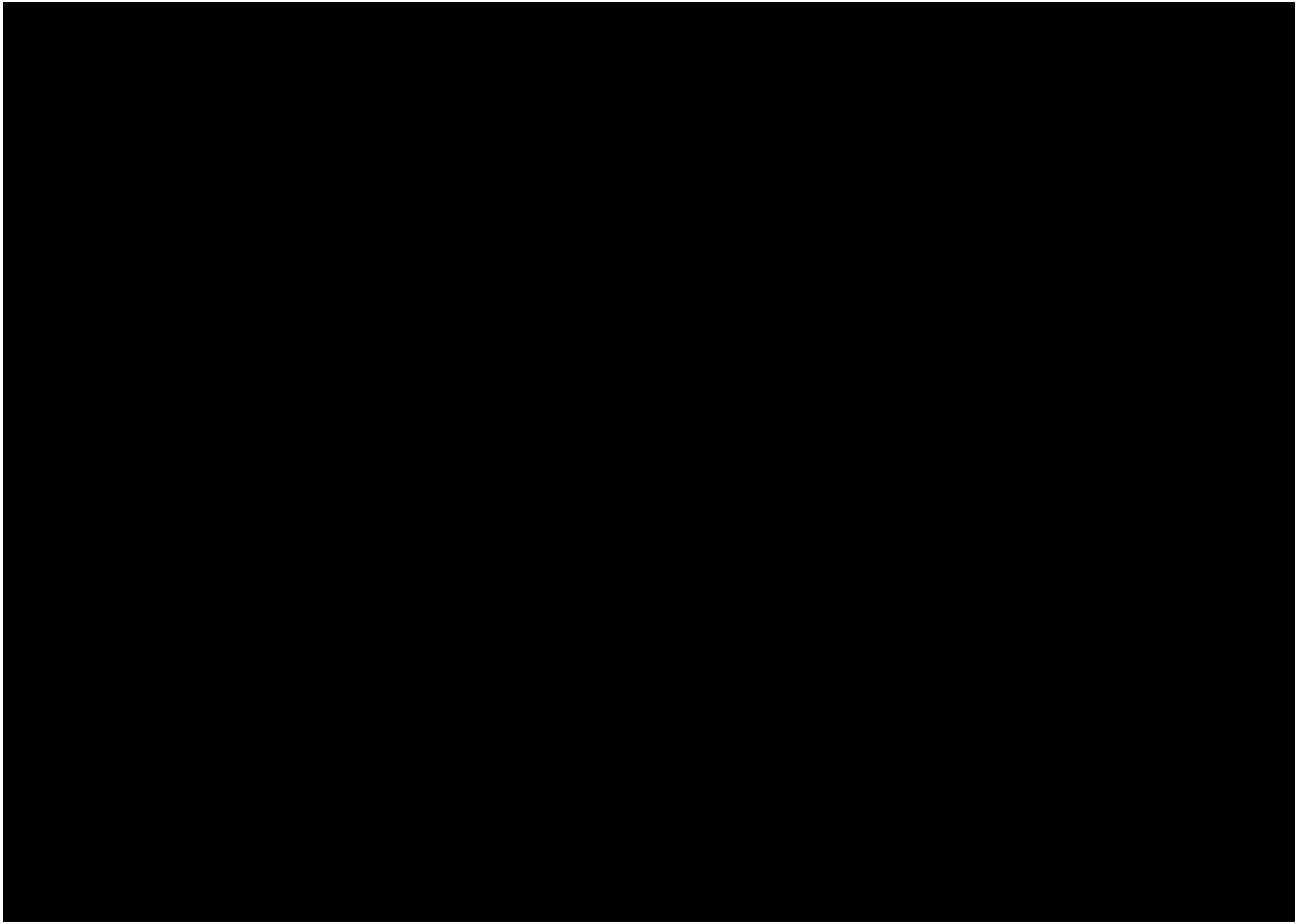

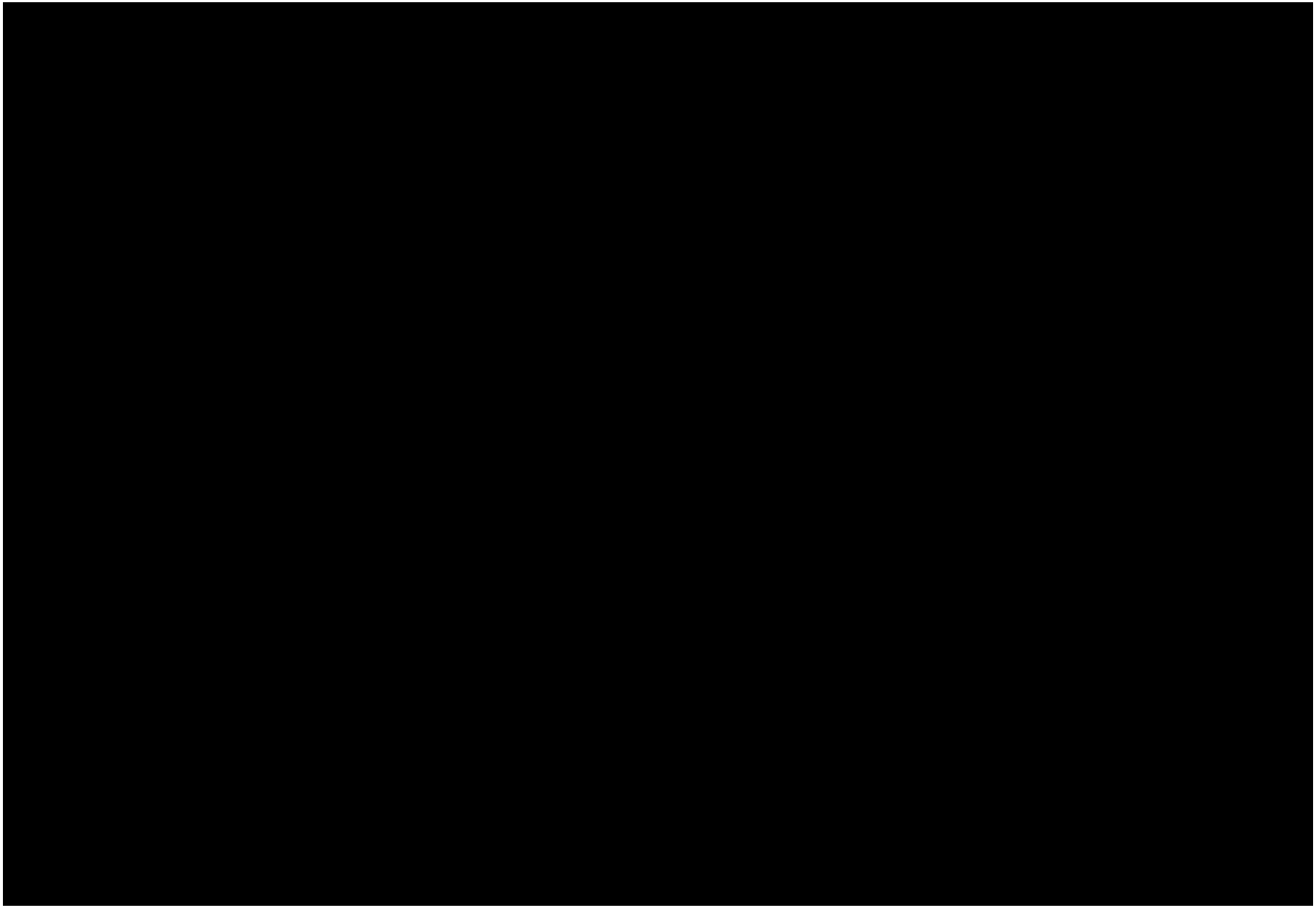

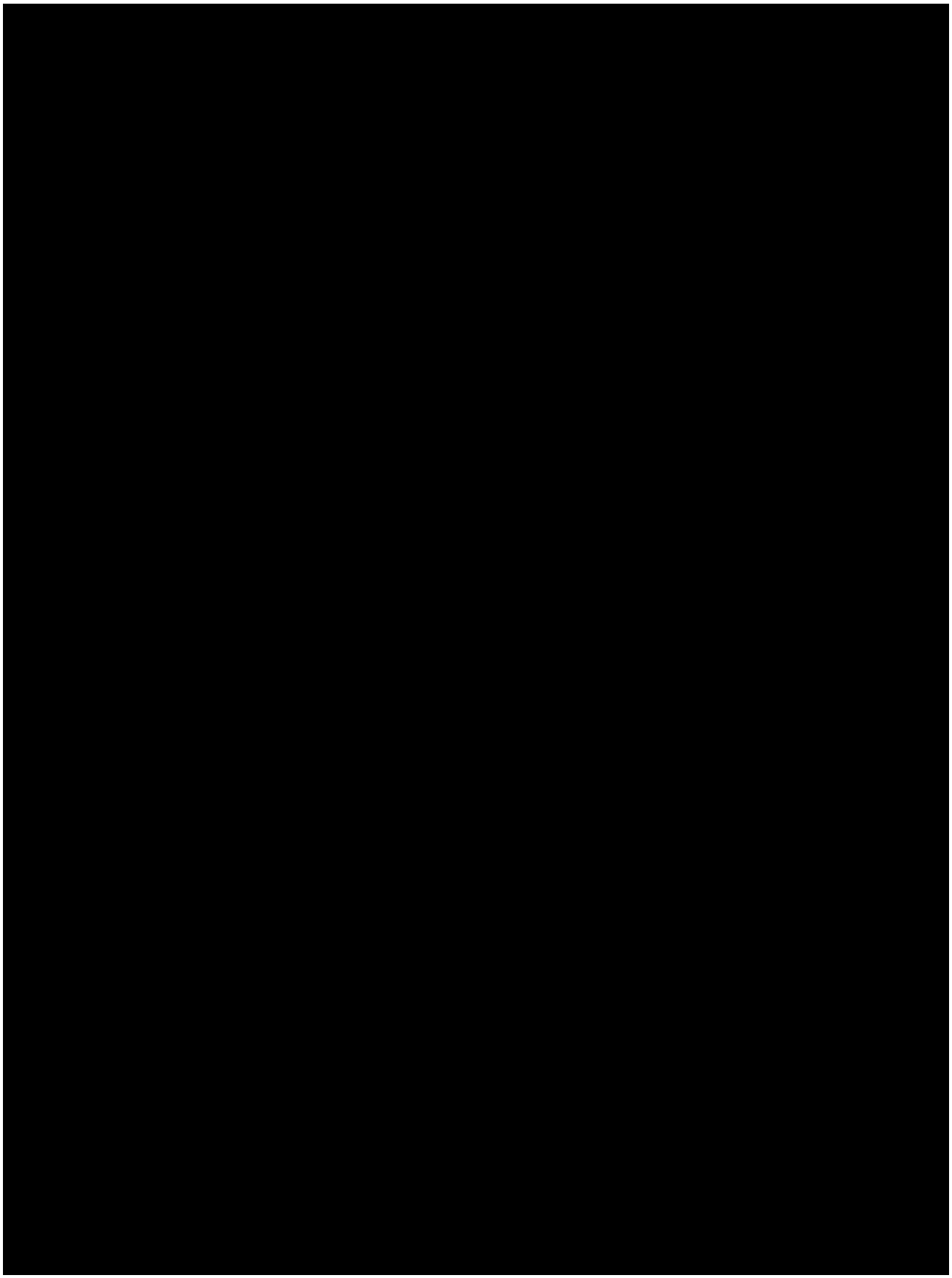

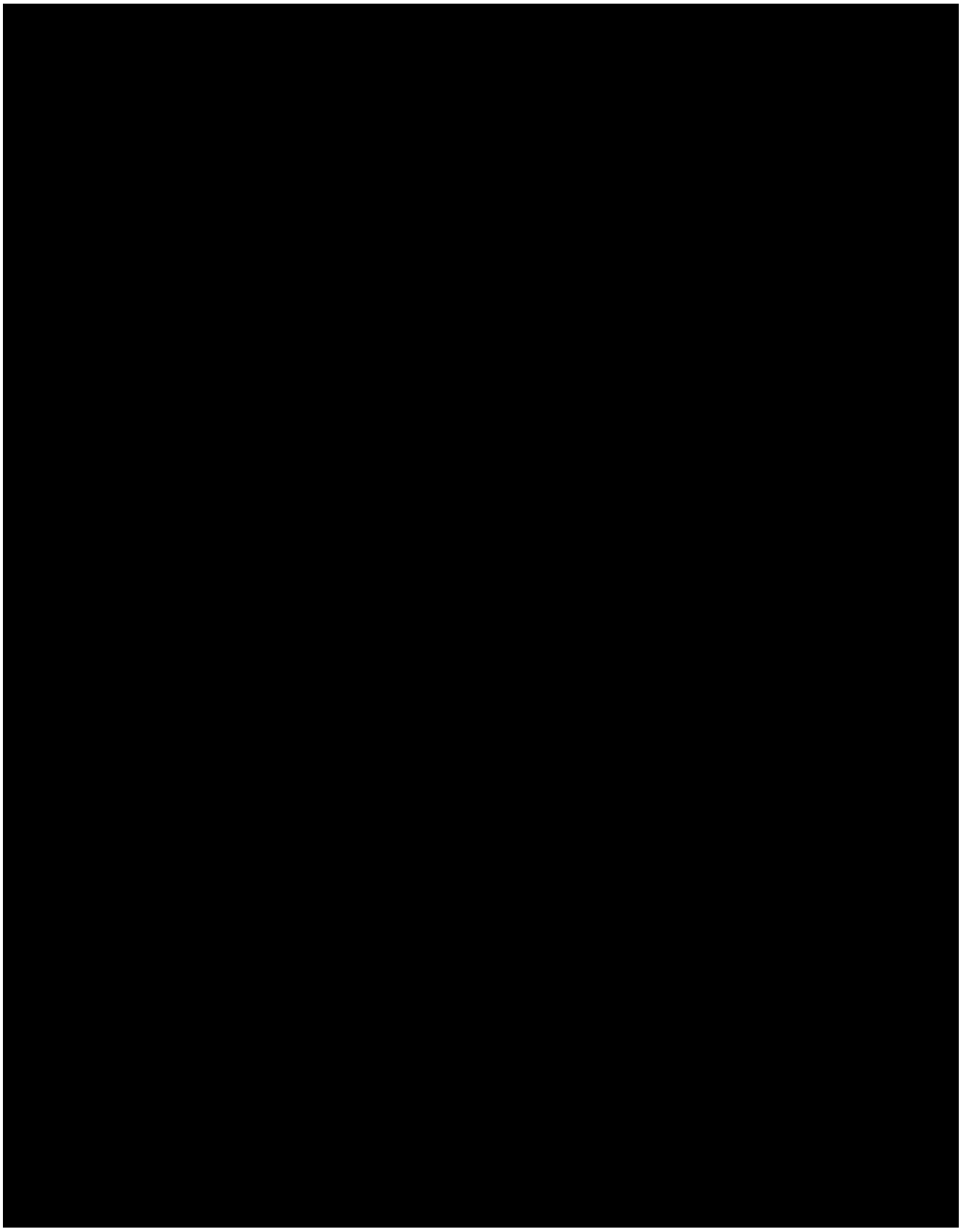

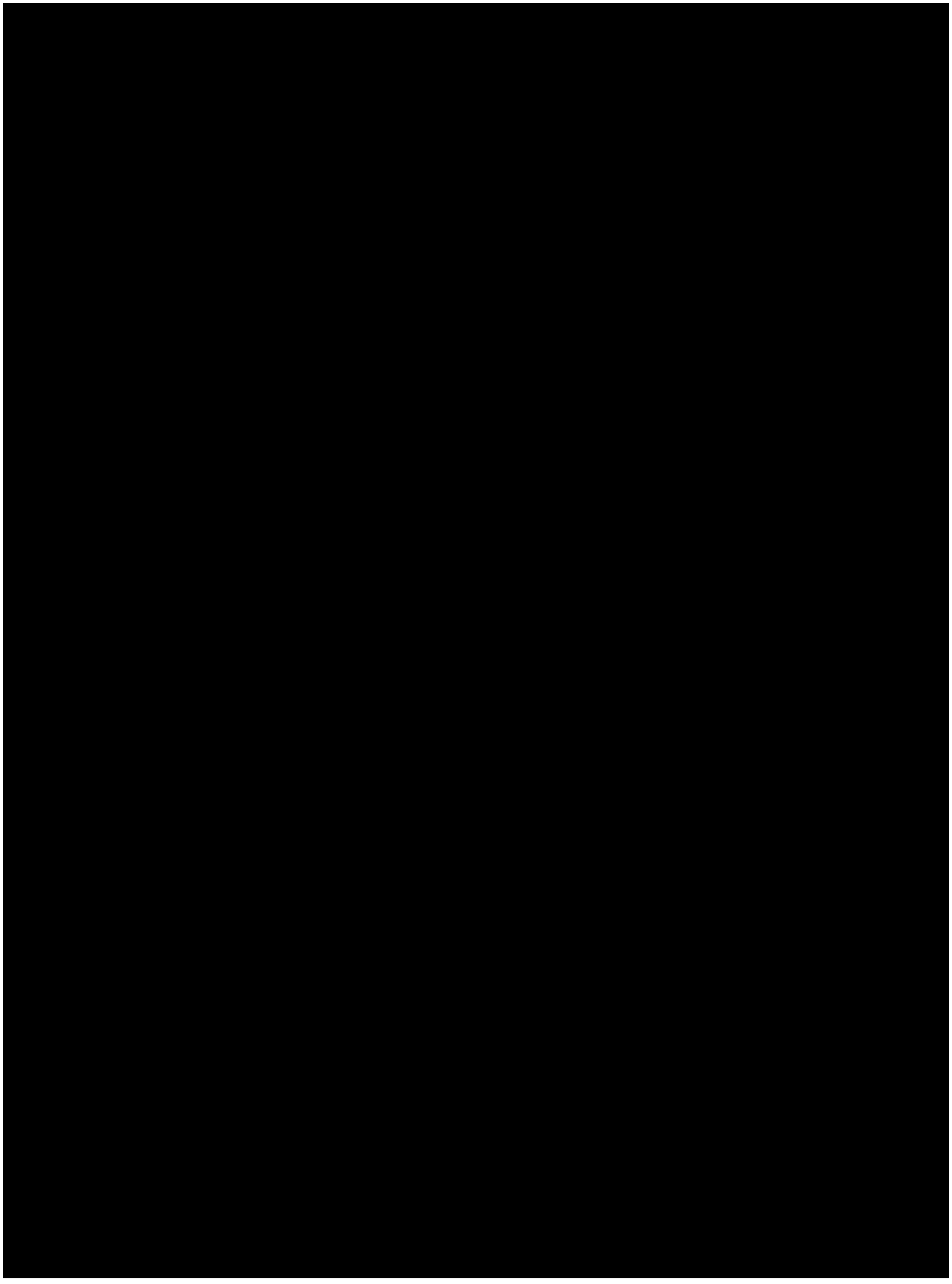

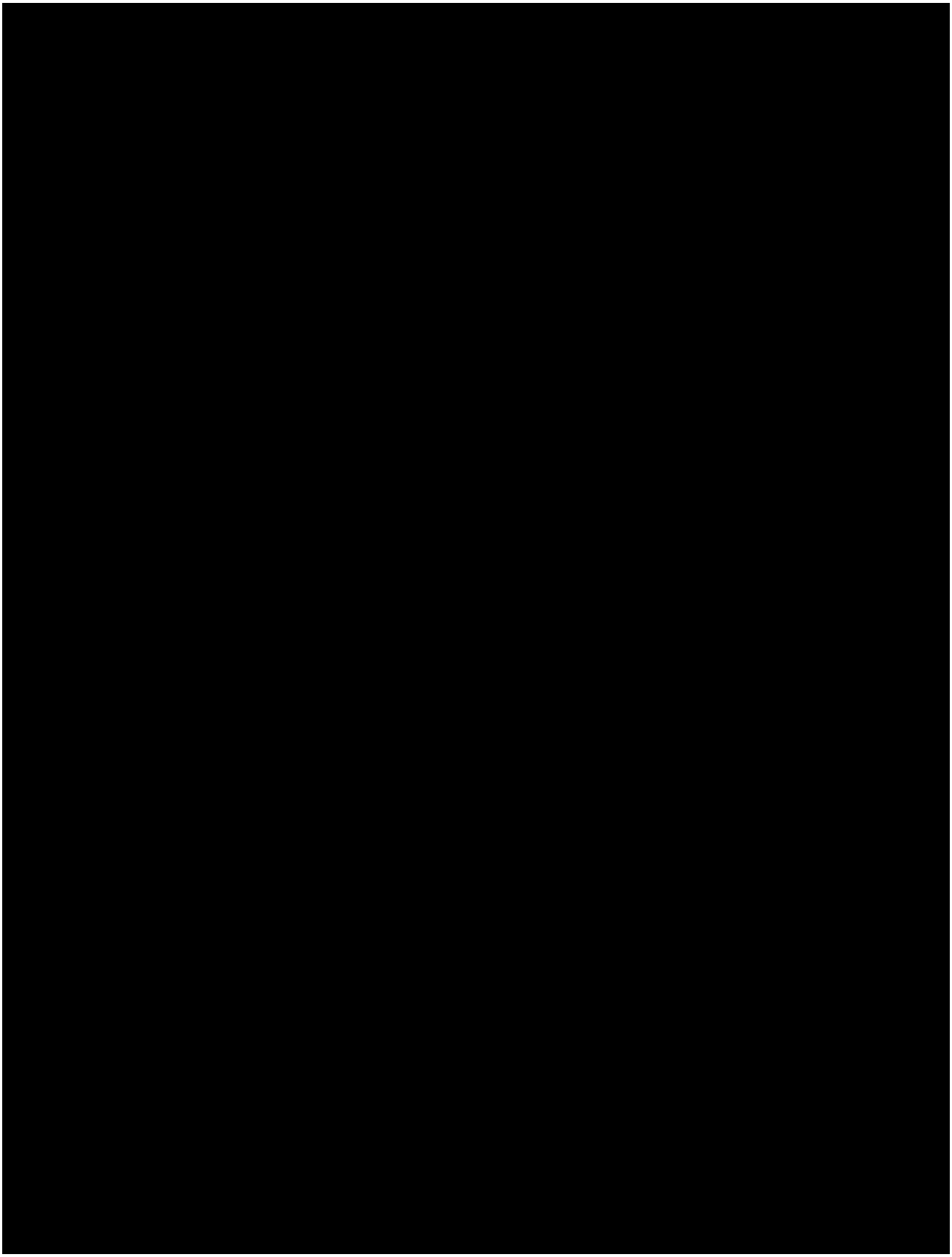

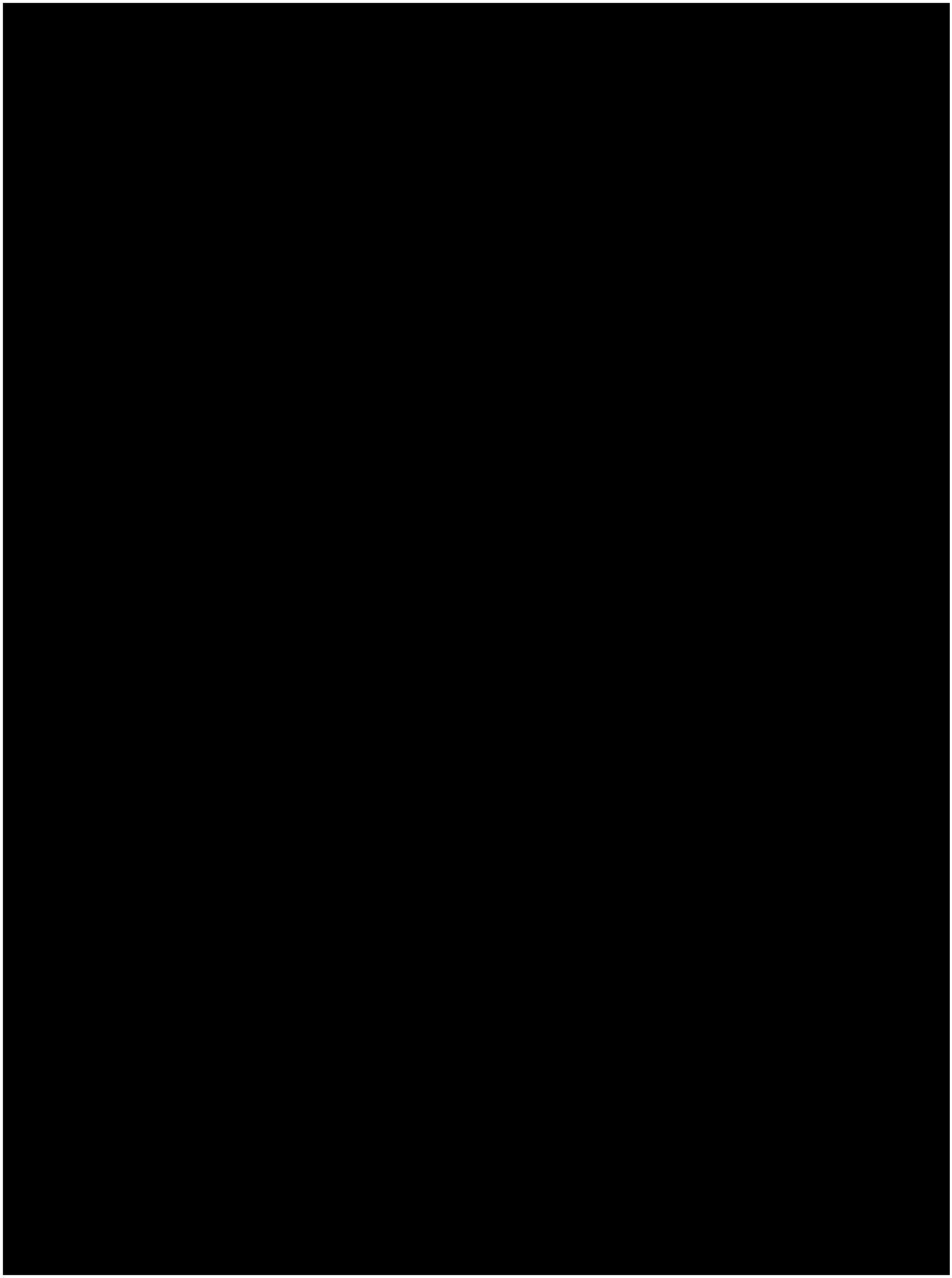

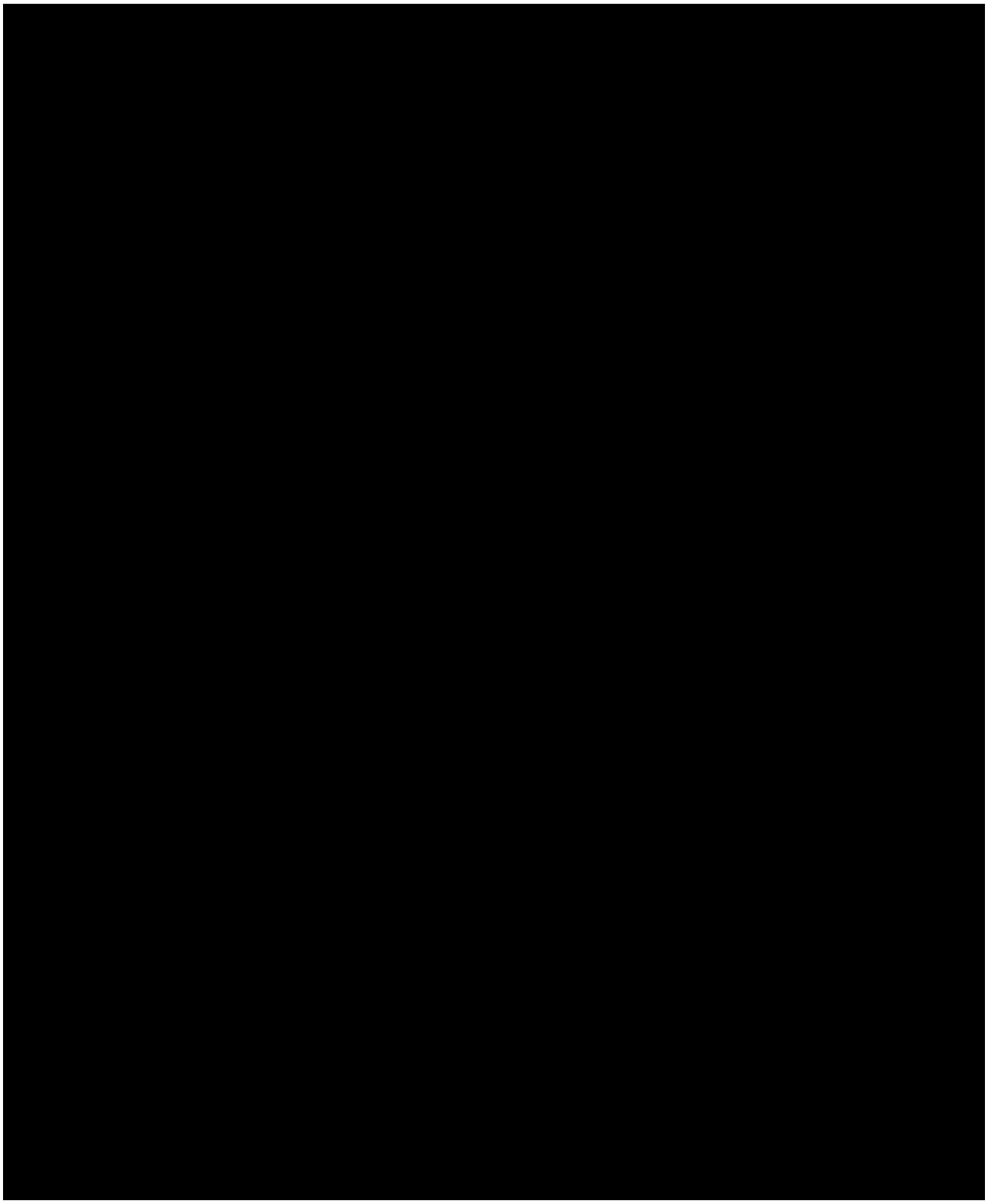

9.9 Health Economics or Medical Resource Utilization and Health Economics

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

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

10.1.1 Preliminary Safety Cohorts and Dose Escalation (Part A)

Two single participants will be treated at BMS-986226 2 mg and 8 mg, respectively, in the Preliminary Safety Cohorts. Additional participants may be enrolled in the Preliminary Safety Cohorts at each dose level to gather additional information on the safety, PK, and PD profile. Approximately 3 participants will be treated at the starting dose levels of BMS-986226 in Part A. During the dose-escalation phase, an adaptive dose-escalation scheme (BLRM for monotherapy and BLRM-Copula for combination therapy) employing the escalation with overdose control (EWOC) principle will be used. The method is fully adaptive, makes use of all the information available at the time of each dose assignment, not just data from the current dose level, and directly addresses the ethical need to control the probability of overdosing. The targeted toxicity rate in this study is in the range of 16% to 33%. The boundary is similar to the toxicity boundary used by a rule-based design (ie, 3 + 3 design) in that a minimum is set at 16% (approximately 1 in 6) DLT rate and at a maximum at 33% (approximately 2 in 6) DLT rate. The use of the EWOC principle limits the risk of exposing participants in the next cohort to an unsafe dose by ensuring the posterior probability of the DLT rate exceeding 33% at any dose is capped at 30%.

Due to the nature of the dose escalation process, the exact number of participants to be treated at each dose level cannot be precisely determined. The maximum number of participants to be treated in Part A will be approximately 30 for dose escalation. However, simulation studies with various scenarios show that the expected number of DLT-evaluable participants is approximately 20 participants or less (Appendix 10).

While the BLRM/BLRM-Copula will use DLT information from the DLT period only, clinical assessment will take into consideration the totality of available data, including PK/PD from all treated participants encompassing monotherapy and combination therapy, in assigning a dose level for the next cohort of 3 participants. At most, 12 DLT-evaluable participants will be treated at each dose level. Additional participants (up to a total of 12) may be treated at or any dose level below the estimated MTD for further evaluation of safety, PK, or PD parameters as required.

The model-recommended MTD is the dose that satisfies the following 3 conditions:

1) The empirical posterior probability that the "DLT rate of 16% to < 33%" is greater than a prespecified value (ie, 50%);
2) This probability needs to be the largest among the dose levels that satisfy the EWOC condition (ie, the probability that the "DLT rate > 33%" must be less than 30%);
3) The minimum number of participants (ie, 6 participants) was treated at this dose level.

The final recommended MTD/RP2D will be based on the recommendation from the BLRM/BLRM-Copula and the overall assessment of all available safety, PK/PD, and efficacy data. Lower doses of BMS-986226 may be tested if none of the planned doses are found to be tolerable as monotherapy or in combination with either nivolumab or ipilimumab. Such decisions will be made after discussion and agreement between the investigators and the BMS Medical Monitor/Study Director (or designee).

10.1.2 BMS-986226 and Nivolumab or Ipilimumab Combination Therapy Cohorts (Parts B and C)

The purpose of the combination cohort phase of the study is to gather safety, tolerability, preliminary efficacy, PK, and PD information regarding BMS-986226 in combination with either nivolumab (Parts B) or ipilimumab (Parts C). For each dose level of the Parts B1 and C1, approximately 6 evaluable participants will be treated. This sample size also provides each dose level in Parts B1 and C1 with about 80% probability to detect any AE with an event rate of 24%. Approximately 6-12 evaluable participants may be treated at each dose level for Parts B2 (BMS-986226 + nivolumab) and C2 (BMS-986226 + ipilimumab) if additional safety, PD, or PD data is required to optimize dose and/or schedule selection. With up to 12 evaluable participant in each of Parts B2 and C2, it provides each dose level with up to 96% probability to detect any AE with an event rate of 24%.

Once the safety (during the DLT evaluation) of a combination of BMS-986226 and nivolumab (ipilimumab) has been established and a recommended BMS-986226 dose regimen has been selected for Part D (E), additional participants (up to 6 additional evaluable participants for each of nivolumab and ipilimumab in combination with BMS-986226) may be treated at the recommended dose to better characterize the safety, PK, and PD profile.

During this part of the study, the BLRM-Copula model, incorporating single-agent toxicity profiles of both BMS-986226 (Part A) and nivolumab or ipilimumab, as well as any available information from the combination cohorts, will be used to guide any potential dose recommendation. Details regarding the BLRM-Copula model are given in Appendix 10.

10.1.3 Combination Expansion Arms (Parts D and E)

Approximately 40 evaluable participants will be treated in each of Parts D and E. This sample size provides each cohort with about 87% probability to detect any AE with an event rate of 5%.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have signed an ICF and are registered into the IRT
Treated	All participants who received any dose of study treatment
Response-evaluable	All treated participants with measurable disease at baseline and 1 of the following: (1) at least 1 postbaseline tumor assessment, (2) clinical progression, or (3) death.
Pharmacokinetic	All treated participants who have evaluable concentration-time data.

Population	Description
Immunogenicity	All treated participants who have a baseline and at least 1 postbaseline immunogenicity measurement.
[redacted]	

Abbreviations: ICF = informed consent form; IRT = Interactive Response Technology.

Analyses of safety, extent of exposure, [redacted] PK, efficacy, and immunogenicity will be based on all treated participants.

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of planned statistical analyses of the primary and secondary endpoints. In general, summaries will be performed by cohort. If sufficient data are not available such that adequate interpretation of the result is not warranted, some summaries may not be performed and only listings will be presented. Efficacy analyses will be performed using the RECIST v1.1 (all indications except prostate) or PCWG3 criteria (prostate). Details on censoring scheme on time-to-event endpoints such as DOR, PFS, and OS will be described in the SAP. A description of the participant population will be included in the statistical output reported, including subgroup of age, gender, and race.

10.3.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
ORR is defined as the proportion of all treated participants whose BOR is either CR or PR. BOR for a participant will be assessed per RECIST v1.1 or PCWG3 (for prostate cancer) by investigator	Estimate of ORR and corresponding 2-sided exact 95% CI using the Clopper-Pearson method
mDOR DOR for a participant with a BOR of CR or PR is defined as the time between the date of first response and the date of the first objectively documented tumor progression per RECIST v1.1 / PCWG3 or death, whichever occurs first.	mDOR using the Kaplan-Meier method and corresponding two 2-sided 95% CI using Brookmeyer and Crowley methodology (using log-log transformation), if appropriate
PFSR at 24 weeks PFS for a participant is defined as the time from the first dosing date to the date of first objectively documented disease progression or death due to any cause, whichever occurs first.	Estimate by the Kaplan-Meier method and corresponding 95% CI will be derived based on Greenwood formula

Abbreviations: BOR = best overall response; CI = confidence interval; CR = complete response; DOR = duration of response; mDOR = median duration of response; ORR = objective response rate; PCWG = Prostate Cancer Working Group; PFS = progression free survival; PFSR = progression free survival rate; PR = partial response; RECIST = Response Evaluation Criteria In Solid Tumors.

10.3.2 Safety Analyses

All safety analyses for will be performed on the treated population.

Endpoint	Statistical Analysis Methods
Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, deaths AEs will be graded according to CTCAE v4.03[27].	DLT rate by dose level; frequency distribution of treated participants with AE using the worst CTC grade. Participants will only be counted (1) once at the preferred term (PT) level, (2) once at the system organ class (SOC) level, and (3) once in the 'Total participant' row at their worst CTC grade, regardless of SOC or PT.
Laboratory abnormalities Laboratory values will be graded according to CTCAE v4.03[27].	Laboratory shift table using the worst CTC grade on treatment per participant

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

10.3.3 Pharmacokinetic Analyses

The PK parameters to be assessed, if data permit, include:

Cmax	Maximum observed plasma concentration
Tmax	Time of maximum observed plasma concentration
AUC(0-T)	Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
AUC(TAU)	Area under the concentration-time curve in 1 dosing interval

The PK parameters that may be assessed, if data permit and if deemed necessary, include:

Cmin	The minimum observed concentration within a dosing interval (eg, occurring no matter when over the dosing interval)
CLT	Total body clearance
Css-avg	Average concentration over a dosing interval (AUC[TAU]/tau)
AI	Accumulation index; ratio of an exposure measure at steady-state to that after the first dose (exposure measure includes AUC[TAU], Cmax, and concentrations at the end of dosing interval (Ctau).
T-HALF	Apparent terminal half-life in serum
T-HALFeff	Effective elimination half-life that explains the degree of accumulation observed for a specific exposure measure (exposure measure includes AUC[TAU], Cmax, and Ctau)

The following PK parameter will be reported as a separate listing, summary, and plot:

- Ctrough: Trough observed plasma concentrations (this includes pre-dose concentrations and Ctau)

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

Endpoint	**Statistical Analysis Methods**
Cmax, AUC(0-T), AUC(TAU), Ctau, CLT, Css-avg, AI_AUC, AI_Cmax, AI-Ctau, THALFeff_AUC, THALFeff_Cmax	Summary statistics: geometric means and coefficients of variation
[redacted]	
Tmax	Summary statistics: medians and ranges
Ctrough	Summary statistics to assess attainment of steady state: geometric means and coefficients of variation; plots vs time by dose

[redacted]

10.3.4 Immunogenicity Analyses

Endpoint	Statistical Analysis Methods
Incidence of ADA to BMS-986226 Baseline ADA-positive participant is defined as a participant who has an ADA-detected sample at baseline[a]. ADA-positive participant is a participant with at least 1 ADA-positive sample relative to baseline after initiation of the treatment	Frequency distribution of baseline ADA-positive participants and ADA-positive participants after initiation of the treatment
[redacted]	

[a] Baseline sample is the last sample before initiation of the treatment.
Abbreviations: ADA = anti-drug antibody.

[redacted]

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
5-FU	5-fluorouracil
AE	adverse event
ADA	anti-drug antibody
ADT	androgen deprivation therapy
AI	accumulation index
AIDS	acquired immunodeficiency syndrome
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANC	absolute neutrophil count
APC	antigen presenting cell
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
AUC(0-xh)	area under the concentration-time curve from time zero to x hours
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 in one dosing interval
BICR	blinded independent central review
β-HCG	beta-human chorionic gonadotrophin
BID	bis in die, twice daily
BLRM	Bayesian Logistic Regression Model
BLRM-RD	Bayesian Logistic Regression Model-Recommended Dose
BMS	Bristol-Myers Squibb
BOR	best overall response
BSC	best supportive care
BTLA	B- and T-lymphocyte attenuator
BUN	blood urea nitrogen
C	Cycle

Term	Definition
CA19-9	cancer antigen 19-9
Css-avg	average concentration over a dosing interval (AUC[TAU]/tau)
CBC	complete blood count
CC	cervical cancer
CD	cluster of differentiation
CEA	cancer embryonic antigen
Cexpected-tau	expected concentration in a dosing interval
CFR	Code of Federal Regulations
CI	confidence interval
CL	total plasma clearance
CLT	total body clearance
Cmax	maximum observed plasma concentration
Cmaxss	steady state peak concentration
Cmin	minimum observed plasma concentration
CMV	cytomegalovirus
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CRF	Case Report Form, paper or electronic
CRP	C-reactive protein
CT	computerized tomography
Ctau	concentrations at the end of dosing interval
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte-associated antigen-4
Ctrough	trough observed plasma concentration
CV	coefficient of variation
D	day

Term	Definition
DLT	dose-limiting toxicity
DMC	Data monitoring committee
DNA	deoxyribonucleic acid
DOR	duration of response
DTIC	dacarbazine
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
GFR	glomerular filtration rate
EGFR	epidermal growth factor receptor
[redacted]	
EOI	end of infusion
EOT	end of treatment
eSAE	electronic serious adverse event
EU	European Union
EWOC	escalation with overdose control
F	bioavailability
FcγRs	Fc gamma receptors
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose-positron emission tomography
FFPE	formalin-fixed paraffin embedded
FIH	first-in-human
FITC	fluorescein isothiocyanate
FNR	false-negative rate
FPR	false-positive rate
FSH	follicle-stimulating hormone
FU	Follow-up
GGT	gamma-glutamyl transferase
GI	gastrointestinal

Term	Definition
GLP	Good Laboratory Practice
GPVE	Global Pharmacovigilance and Epidemiology
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HLA-DR	human leukocyte antigen - antigen D related
HNSCC	head and neck squamous cell carcinoma
HNSTD	highest non-severely toxic dose
HPV	human papillomavirus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICOS	Inducible T-cell COStimulator
ICOS-L	Inducible T-cell COStimulator ligand
IFN-γ	interferon gamma
Ig	immunoglobulin
IHC	immunohistochemistry
IL	interleukin
IMAE	immune-mediated adverse event
IMP	investigational medicinal product
I-O	immuno-oncology
Ipi	ipilimumab
IP	investigational product
irAE	Immune-related adverse event
irPR	immune-related partial response
irSD	immune-related stable disease
IRT	Interactive Response Technology
IV	intravenous
IVRS	Interactive Voice Response System

Term	Definition
KLH	keyhole limpet hemocyanin
KRAS	Kirsten rat sarcoma
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MAD	maximum administered dose
MAD-1	one dose level below the maximum administered dose
mCRPC	metastatic castration-resistant prostate cancer
mDOR	median duration of response
MEL	melanoma
[redacted]	
MMR	mismatch repair
mOS	median overall survival
MRI	magnetic resonance imaging
MRSD	maximum recommended starting dose
MSI	microsatellite instability
MTD	maximum tolerated dose
mWHO	modified World Health Organization
N	number of participants or observations
N1 + I3	nivolumab 1 mg/kg + ipilimumab 3 mg/kg
N3 + I1	nivolumab 3 mg/kg + ipilimumab 1 mg/kg
N/A	not applicable
NaF	sodium fluoride
NCI	National Cancer Institute
NK	natural killer
NOAEL	no-observed-adverse-effect level
NSCLC	non-small cell lung cancer
NCSLC-AD	non-small cell lung carcinoma-adenocarcinoma cell type
NSCLC-SQC	non-small cell lung carcinoma, squamous cell type
ORR	objective response rate
OS	overall survival

Term	Definition
[redacted]	
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	pharmacodynamics
PD-1	programmed death-1
p-DILI	potential drug-induced liver injury
PD-L1	programmed death ligand-1
PE	physical examination
PET	positron emission tomography
PFS	progression-free survival
PFSR	progression-free survival rate
PID	participant identification number
PK	pharmacokinetic(s)
PPK	population pharmacokinetics
PR	partial response
PRC	adenocarcinoma of the prostate
PSA	prostate-specific antigen
PT	preferred term
Q1W	once every week
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks
Q12W	every 12 weeks
[redacted]	
R&D	Research and Development
RCC	renal cell carcinoma
RD	recommended dose
RE	receptor expression

Term	Definition
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid
RO	receptor occupancy
RP2D	Recommended Phase II dose
R/R	resistant/recurrent
RT-qPCR	quantitative real-time polymerase chain reaction
SAE	serious adverse event
SD	stable disease
[redacted]	
SOC	system organ class
SPECT	single photon emission computed tomography
Std. Dev.	standard deviation
T3	triiodothyronine
T4	thyroxine
TBD	to be determined
T-cell	T lymphocyte cell
Teff	T-effector cell
TGI	tumor growth inhibition
T-HALF	apparent terminal half-life in serum
T-HALFeff	effective elimination half-life that explains the degree of accumulation observed for a specific exposure measure (exposure measure includes AUC[TAU], Cmax, and Ctau)
TIL	tumor-infiltrating lymphocytes
TKI	tyrosine kinase inhibitor
Tmax	time of maximum observed plasma concentration
TNBC	triple-negative breast cancer
Treg	T-regulatory
TSH	thyroid-stimulating hormone
T-VEC	talimogene laherparepvec
UCC	urothelial carcinoma
ULN	upper limit of normal

Term	Definition
US	United States
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Good Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

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

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

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

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

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

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

SOURCE DOCUMENTS

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs),

adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

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

STUDY TREATMENT RECORDS

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

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (e.g., lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence/biocomparability, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include:

If	Then
	• label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

CASE REPORT FORMS

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

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

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

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

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

Each individual electronically signing electronic CRFs must meet Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user

account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals

MONITORING

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

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

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 (e.g., cytotoxics or biologics).

	If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

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

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, i.e., 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

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

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

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

SCIENTIFIC PUBLICATIONS

The data collected during this study are confidential and proprietary to Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) 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 CTA.

Scientific Publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any principal investigator, sub-investigator, or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

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

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

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

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

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

ADVERSE EVENTS

Adverse Event Definition:

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

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

Events Meeting the AE Definition

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

Events NOT Meeting the AE Definition

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

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

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

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

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

EVALUATING AES AND SAES

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

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

If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment.*

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable

Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Hormonal methods of contraception including vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Unacceptable Methods of Contraception*
• Male condoms (except in setting of azoospermic male participants) 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
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus).
- Spermicide only
- Lactation amenorrhea method (LAM)

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

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

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

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 7 months after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.

COLLECTION OF PREGNANCY INFORMATION

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

APPENDIX 5 RECIST 1.1 CRITERIA

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least 1 measurable tumor lesion. When computed tomographic (CT) scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable.

1.1 Measurable Lesions

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

- 10 mm by computed tomography (CT)/magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable)
- 20 mm by chest X-ray
- *Malignant lymph nodes*: To be considered pathologically enlarged *and* measurable, a lymph node must be ≥ 15 mm in the ***short*** axis when assessed by CT scan (CT scan slice thickness is recommended to be no greater than 5 mm). At baseline and in follow-up, only the ***short*** axis will be measured and followed.

1.2 Non-measurable Lesions

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

1.3 Special Considerations Regarding Lesion Measurability

1.3.1 Bone Lesions

- Bone scan, positron emission tomography (PET) scan, or 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 nonmeasurable.

1.3.2 Cystic Lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above in Section 1.1. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

1.3.3 Lesions with Prior Local Treatment

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

1.4 Specifications by Methods of Measurements

1.4.1 Measurement of Lesions

All measurements should be recorded in metric notation (mm). All baseline evaluations should be performed as close as possible to the treatment start and never more than 30 days before the beginning of the treatment.

1.4.2 Method of Assessment

The **same method of assessment and the same technique should be used** to characterize each identified and reported lesion at baseline and during follow-up. Unless the lesions being followed cannot be imaged, and are assessable only by clinical examination, imaging-based evaluation should always be done.

1.4.2.1 CT/MRI Scan

CT/MRI is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT/MRI scan is based on the assumption that CT/MRI slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

1.4.2.2 Chest X-ray

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

1.4.2.3 Clinical Examination

Lesions identified by clinical examination will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested. As previously noted, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

1.4.2.4 Ultrasound

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

1.4.2.5 Endoscopy, Laparoscopy

The utilization of these techniques for objective tumor evaluation is ***not*** advised.

2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

2.1 Target Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to **a maximum of 5 lesions total (and a maximum of 2 lesions per organ) that are representative of all involved organs should be identified as *target lesions*** and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their **size** (lesions with the longest diameter), should be representative of all involved organs, and should lend themselves to ***reproducible repeated measurements***.

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

2.1.1 Lymph Nodes

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. Pathological nodes that are defined as measurable, and may be identified as target lesions, must meet the criterion of a **short axis of ≥ 15 mm by CT scan**. Only the *short* axis of these nodes will contribute to the baseline sum diameters. Nodes that have a short axis < 10 mm are considered nonpathological and should not be recorded or followed.

2.2 Non-target Lesions

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'**. 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').

3 TUMOR RESPONSE EVALUATION

3.1 Evaluation of Target Lesions

Complete Response (CR): **Disappearance of all target lesions.** Any pathological lymph nodes (whether target or non-target) must also have reduction in the short axis to < 10 mm.

Partial Response (PR): At least a **30% decrease in the sum of the diameters of target lesions**, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a **20% increase in the sum of the 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 1 or more new lesions is also considered progression.)

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

3.1.1 Special Notes on the Assessment of Target Lesions

3.1.1.1 Lymph Nodes

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. Pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a **short axis of ≥ 15 mm by CT scan**. Only the *short* axis of these nodes will contribute to the baseline sum. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

3.1.1.2 Target Lesions That Become 'Too Small to Measure'

All lesions (nodal and nonnodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation. If the radiologist is able to provide an actual measurement, even if it is below 5 mm it should be recorded.

However, when such a lesion becomes difficult to assign an exact measurement to then:

- 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 or 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 =. This default value is derived from the 5-mm CT-slice thickness (but should not be changed with varying CT-slice thickness).

3.1.1.3 Target 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.
- 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'.

3.2 Evaluation 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 timepoints specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must also be nonpathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) above the normal limits.

Progressive Disease (PD): *Unequivocal progression* of existing non-target lesions. (*Note:* The appearance of 1 or more new lesions is also considered progression.)

3.2.1 Special Notes on Assessment of Non-Target Lesions

The concept of progression of non-target disease requires additional explanation.

3.2.1.1 When the Subject Also Has Measurable Disease

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest 'increase' in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

3.2.1.2 When the Subject Has Only Non-Measurable Disease

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest 'increase' in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

- Because worsening in non-target disease cannot be easily quantified as the lesions are nonmeasurable, a useful test that can be applied when assessing subjects 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 target disease: that is, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large' or an increase in lymphangitic disease from localized to widespread or may be described in protocols as 'sufficient to require a change in therapy'.
- If 'unequivocal progression' is seen, the subject should be considered to have had overall PD at that point.

3.2.1.3 Tumor Markers

Tumor markers *alone* cannot be used to assess objective tumor responses. If markers are initially above the upper normal limit, however, they must normalize in order for a subject to be considered as having attained a CR.

3.3 New Lesions

The appearance of new malignant lesions denotes PD. The finding of a new lesion should be unequivocal: that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (eg, some 'new' bone lesions may be simply healing or a flare of pre-existing lesions). This distinction is particularly important when the subject'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.

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 PD. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI brain scan that reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. *If repeat scans confirm there is definitely a new lesion, then PD should be declared using the date of the initial scan.*

3.3.1 FDG-PET Evaluation

While [^{18}F] fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of the qualitative assessment of FDG-PET scanning to complement CT scanning in assessment of PD (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up, is a sign of PD based on a new lesion.
- 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 by CT, additional follow-up CT scans are needed to determine if there is truly PD occurring at that site (if so, the date of PD will be the date of the initial positive 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.

4 RESPONSE CRITERIA

4.1 Timepoint Response

A response assessment should occur at each timepoint specified in the protocol.

For subjects who have **measurable disease** at baseline Table 4.1-1 provides a summary of the overall response status calculation at each timepoint.

Table 4.1-1: Timepoint Response: Subjects with Target (+/– Non-Target) Disease

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

Abbreviation: NE =not evaluable

Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the subject is **not evaluable** at that timepoint. If only a subset of lesion measurements are made at an assessment, the subject is also considered NE at that timepoint, unless a convincing argument can be made that the

contribution of the individual missing lesion(s) would not have changed the assigned timepoint response.

4.1.1 Confirmation Scans

- **Verification of Response:** *Confirmation of PR and CR is required at least 4 weeks following initial assessment to ensure responses identified are not the result of measurement error.*

4.2 Best Overall Response: All Timepoints

The *best overall response* is determined once all the data for the subject are known. It is the best response recorded from the start of the study treatment until the date of objectively documented PD based on RECIST v1.1, taking into account any requirement for confirmation or the date of subsequent anti-cancer therapy, whichever occurs first in the study. The subject'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.

The best overall response is defined as the best response across all timepoints with subsequent confirmation. CR or PR may be claimed only if the criteria for each are met at a subsequent timepoint as specified in the protocol (generally 4 weeks later).

In this circumstance, the best overall response can be interpreted as specified in Table 4.2-1. When SD is believed to be best response, it must meet the protocol specified minimum time from baseline. Measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6 to 8 weeks) that is defined in the study protocol.

Table 4.2-1: Best Overall Response When Confirmation of CR and PR Is Required

Overall Response First Timepoint	Overall Response Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR

Table 4.2-1: Best Overall Response When Confirmation of CR and PR Is Required

Overall Response First Timepoint	Overall Response Subsequent Timepoint	Best Overall Response
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

.

[a] If a CR is truly met at the first timepoint, then any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since the disease must have reappeared after CR). The 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 subject had PR, not CR at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

4.3 Duration of Response

4.3.1 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

4.3.2 Duration of Stable Disease

SD is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

CR (Complete Remission)

The designation of CR requires all of the following:

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms, if present before therapy.

a) Typically FDG-avid lymphoma: in patients without a pre-treatment PET scan or if the pre-treatment PET scan was positive, a post-treatment residual mass of any size is permitted as long as it is PET negative.
b) Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pre-treatment PET scan, or if a pre-treatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT scan to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and > 1.0 cm in their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment.

2. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.
3. If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry, but demonstrates a small population of clonal lymphocytes by flow cytometry, will be considered a CR until data become available demonstrating a clear difference in patient outcome.

PR (Partial Remission)

The designation of PR requires all of the following:

1. At least a 50% decrease in the sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. These nodes or nodal masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible, they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase should be observed in the size of other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.
4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable, and no measurable disease should be present.
5. Bone marrow assessment is irrelevant for determination of a PR, if the sample was positive before treatment. However, if positive, the cell type should be specified (eg, large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria but have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved but with no bone marrow assessment after treatment, patients should be considered partial responders.
6. No new sites of disease should be observed.

7. FDG:
   a) Typically FDG-avid lymphoma: for patients without a pre-treatment PET scan or if the pre-treatment PET scan was positive, the post-treatment PET scan should be positive in at least 1 previously involved site.
   b) Variably FDG-avid lymphomas/FDG avidity unknown: for patients without a pre-treatment PET scan, or if a pre-treatment PET scan was negative, CT criteria should be used. In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with 1 or at most 2 residual masses that have regressed by > 50% on CT; those with more than 2 residual lesions are unlikely to be PET negative and should be considered partial responders.

SD (Stable Disease)

1. The designation of SD requires all of the following: A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR but does not fulfill those for PD (see Relapsed Disease [after CR]/PD [after PR, SD]).
2. Typically FDG-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET scan.
3. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pre-treatment PET scan or if the pre-treatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

PD: Relapsed Disease (after CR)/PD (after PR, SD)

Lymph nodes should be considered abnormal if the long axis is > 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is > 1.0. Lymph nodes ≤ 1.0 × ≤ 1.0 cm will not be considered abnormal for relapse or progressive disease.

1. Appearance of any new lesion > 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or PD after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET scan without histologic confirmation.
2. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules). To be considered PD, a lymph node with a diameter of the short axis of < 1.0 cm must increase by ≥ 50% and to a size of 1.5 × 1.5 cm or > 1.5 cm in the long axis.
3. At least a 50% increase in the longest diameter of any single previously identified node > 1 cm in its short axis.
4. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy, unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these assessments, the spleen is considered nodal disease. Disease that is only assessable by physical examination (eg, pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use (eg, a trial in patients with mucosa-associated lymphoid tissue lymphoma), response should be assessed as above, but only using CT scans. However, residual masses should not be assigned CRu status but should be considered a PR.

Reference: Cheson BD, Pfisner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579-86.

APPENDIX 6 MANAGEMENT ALGORITHMS FOR IMMUNO-ONCOLOGY AGENTS

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 (I-O) agents and regimens.

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

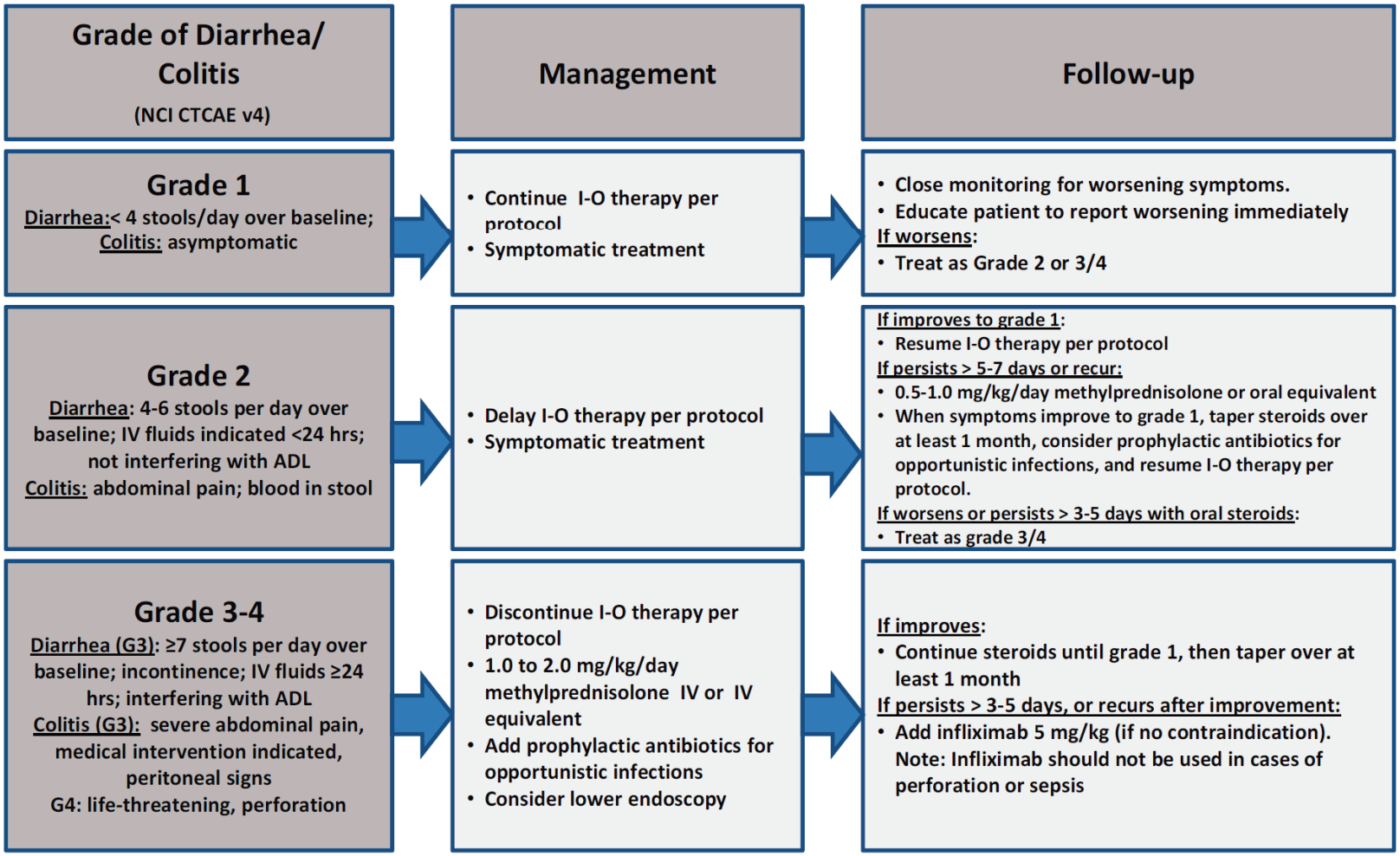
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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

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

GI Adverse Event Management Algorithm

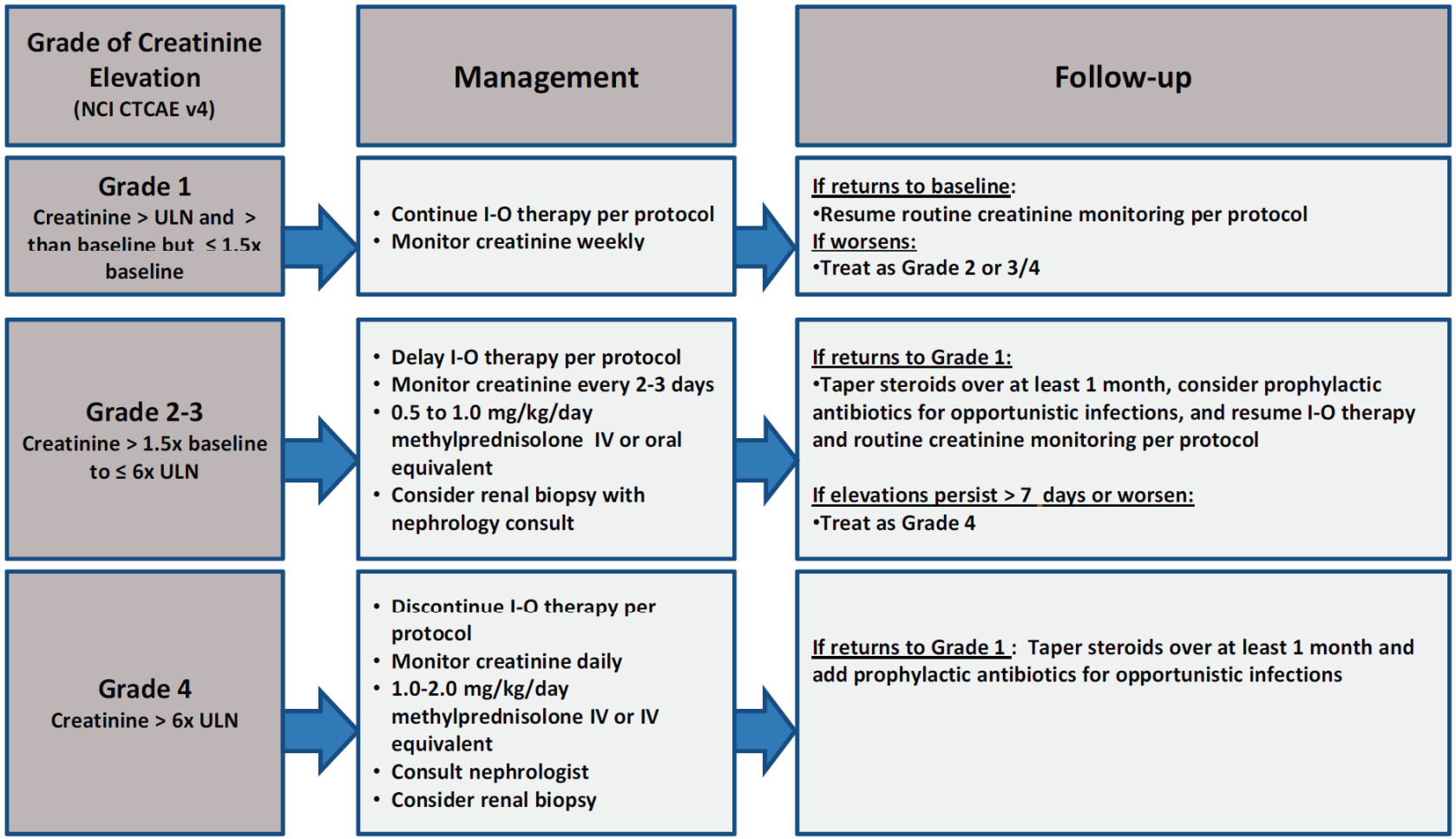
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

Renal Adverse Event Management Algorithm

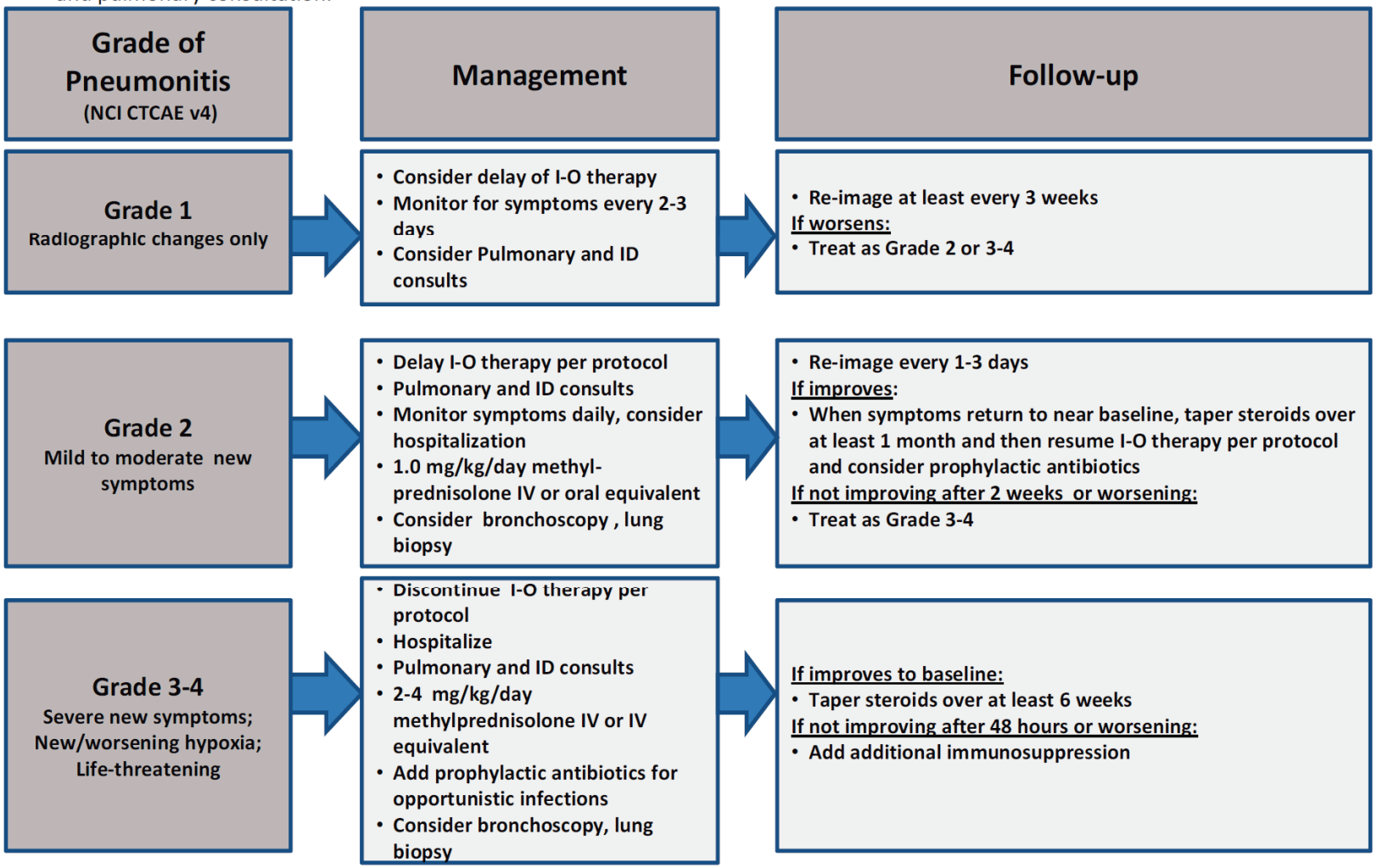
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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

Pulmonary Adverse Event Management Algorithm

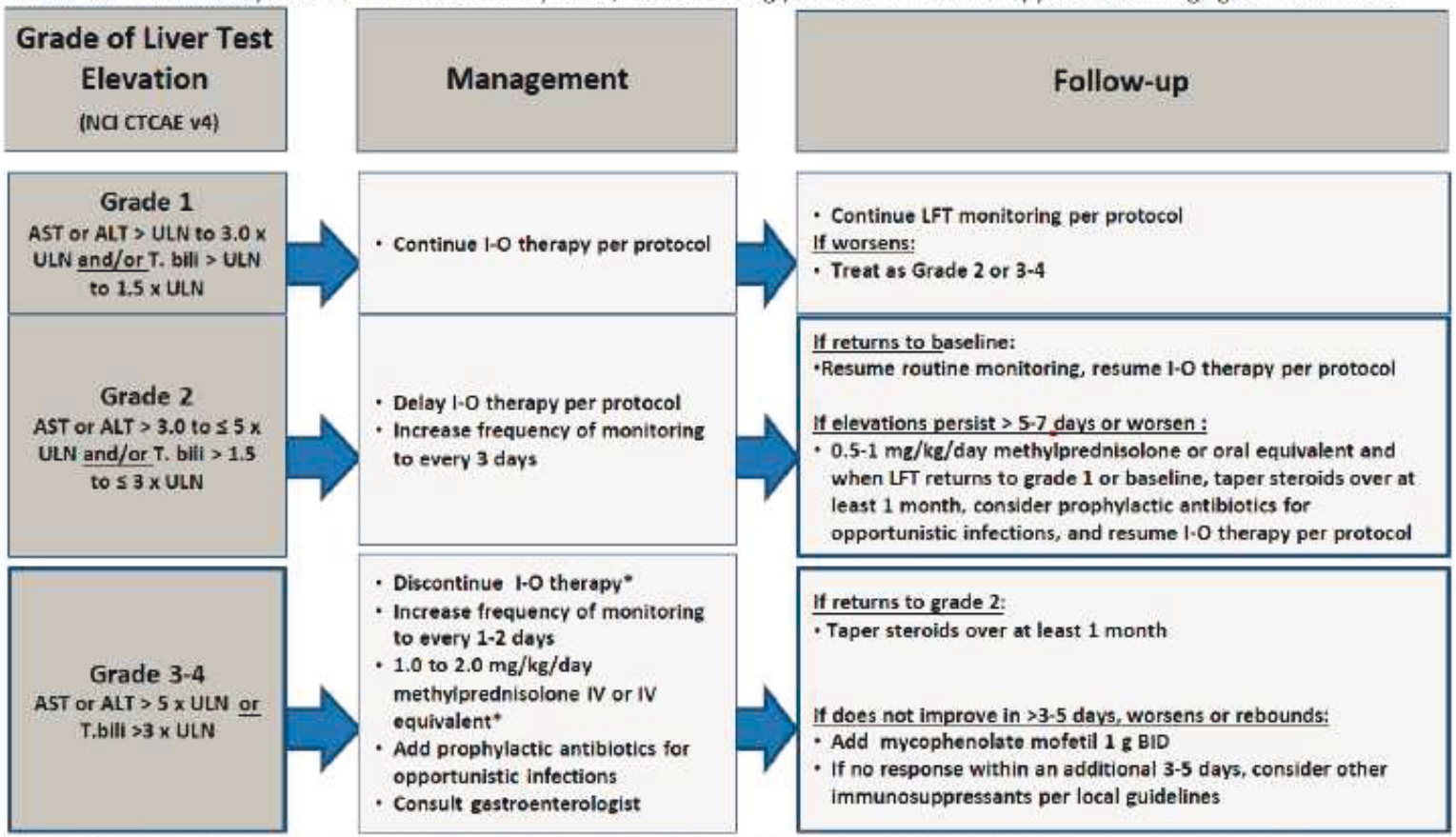
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

Hepatic Adverse Event Management Algorithm

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



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

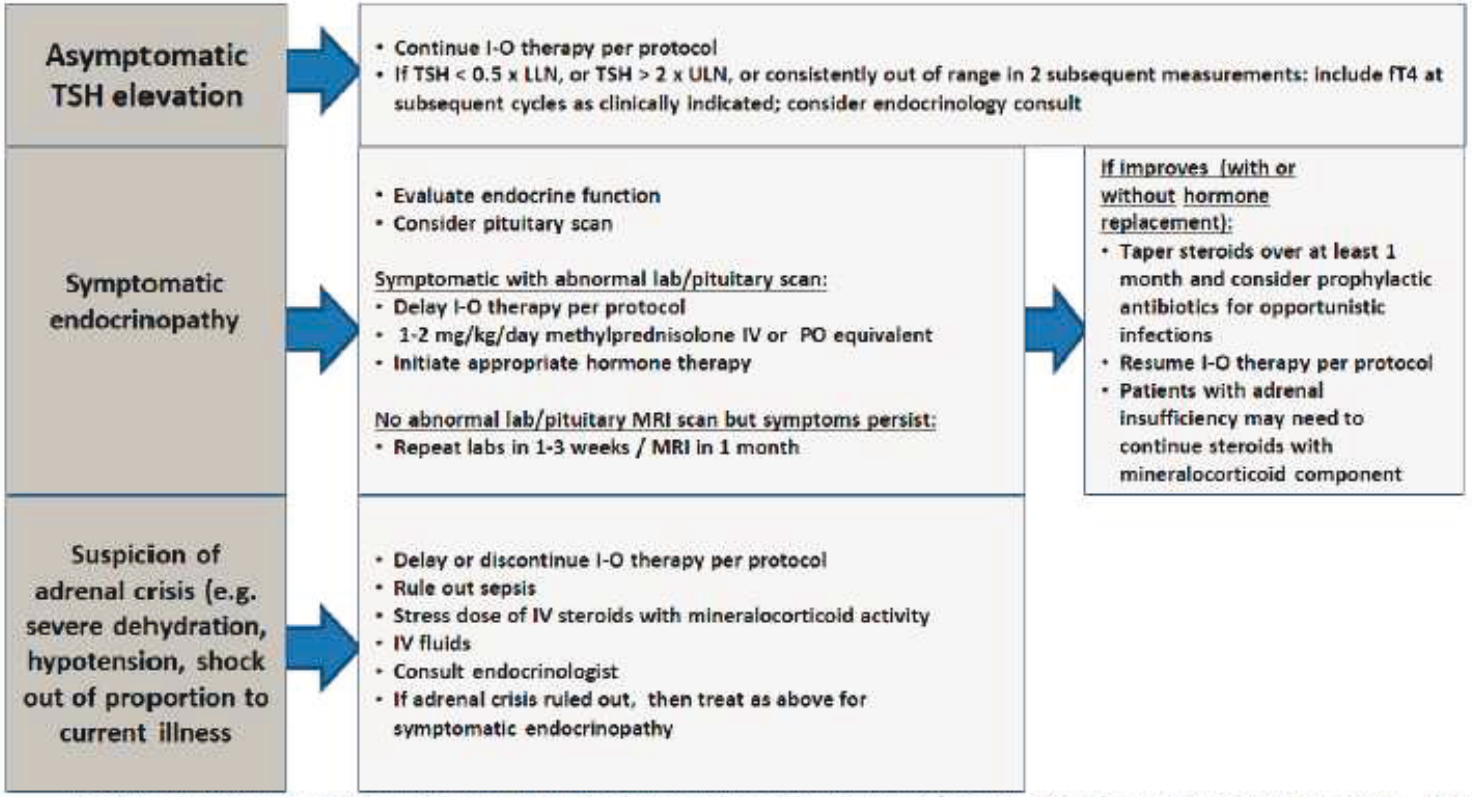
*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

27-Jun-2018

Refer to http://livertox.nih.gov/ for a compendium of agents that may cause liver injury

Endocrinopathy Adverse Event Management Algorithm

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

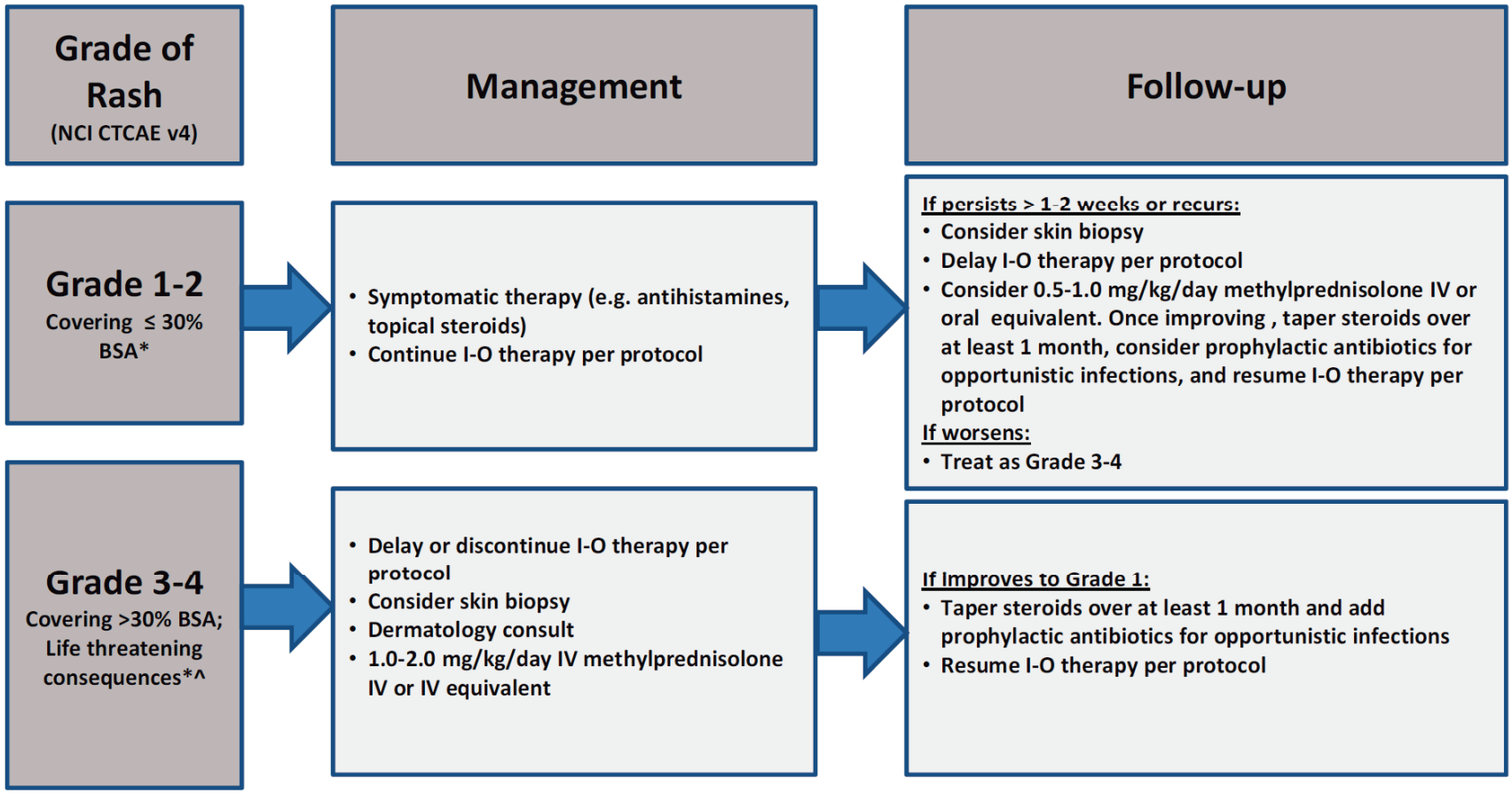


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2018

Skin Adverse Event Management Algorithm

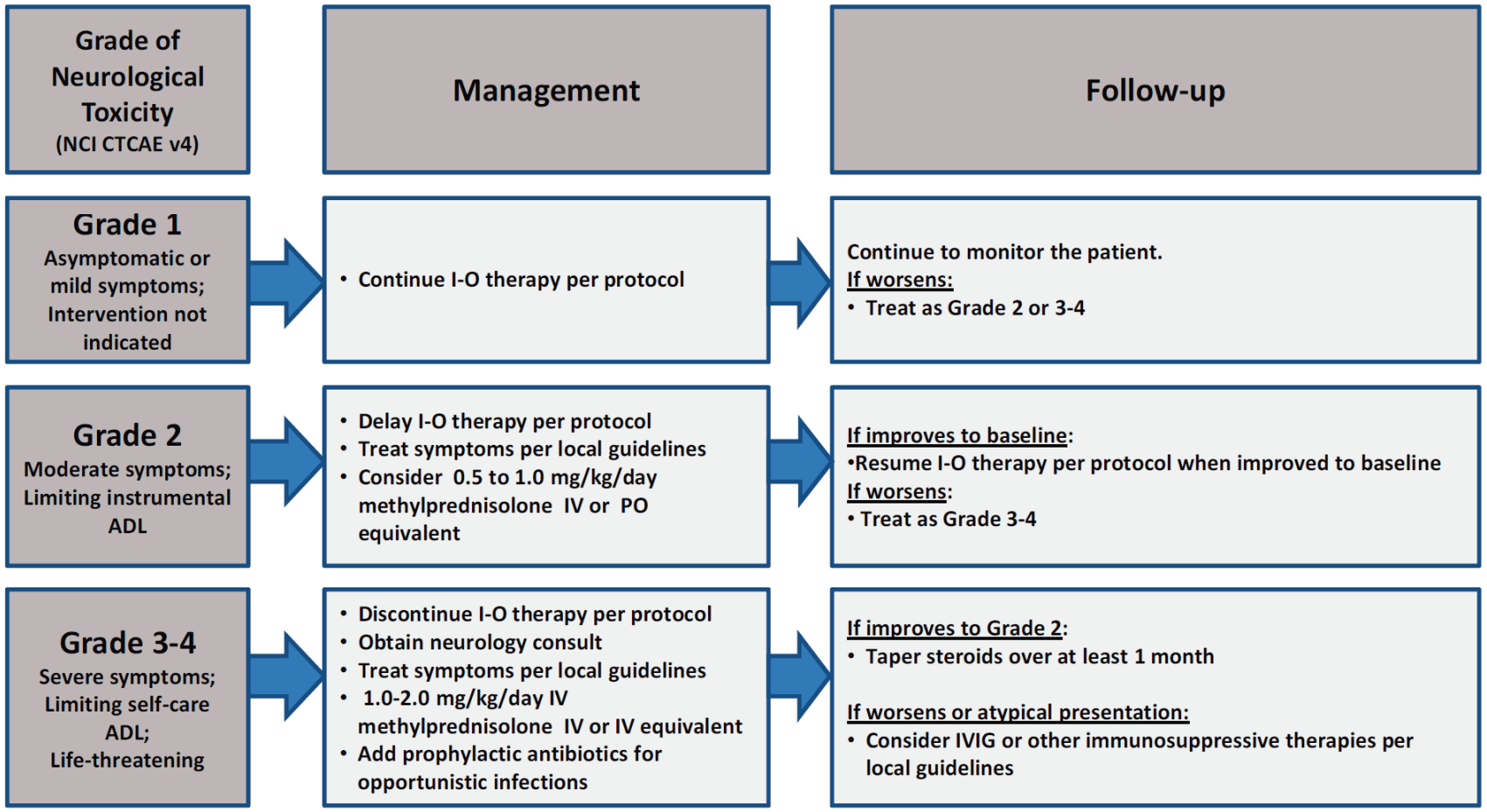
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Neurological Adverse Event Management Algorithm

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



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

APPENDIX 7 EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

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

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

APPENDIX 8 CONSORT PUBLISHING REQUIREMENTS

The Consolidated Standards of Reporting Trials (CONSORT) encompasses various initiatives developed by the CONSORT Group to alleviate the problems arising from inadequate reporting of randomized controlled trials.

The CONSORT Statement

The main product of CONSORT is the CONSORT Statement, which is an evidence-based, minimum set of recommendations for reporting randomized trials. It offers a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, and aiding their critical appraisal and interpretation. CONSORT 2010 is the current version of the statement and supersedes the 2001 and 1996 versions.

The CONSORT Statement comprises a 25-item checklist and a flow diagram. The checklist items focus on reporting how the trial was designed, analyzed, and interpreted. The flow diagram displays the progress of all participants through the trial. The checklist and flow diagram are freely available for viewing and downloading at the CONSORT website (http://www.consort-statement.org/consort-2010). The CONSORT Statement is endorsed by general medical journals, specialty medical journals, and leading editorial organizations. CONSORT is part of a broader effort, to improve the reporting of different types of health research, and indeed, to improve the quality of research used in decision-making in healthcare.

CONSORT 2010 Guideline

The CONSORT (CONsolidated Standards of Reporting Trials) 2010 guideline is intended to improve the reporting of parallel-group randomized controlled trial (RCT), enabling readers to understand a trial's design, conduct, analysis and interpretation, and to assess the validity of its results. This can only be achieved through complete adherence and transparency by authors. CONSORT 2010 was developed through collaboration and consensus between clinical trial methodologists, guideline developers, knowledge translation specialists, and journal editors (see CONSORT group). CONSORT 2010 is the current version of the guideline and supersedes the 2001 and 1996 versions.

CONSORT “Explanation and Elaboration” Document

The CONSORT “Explanation and Elaboration” document explains and illustrates the principles underlying the CONSORT Statement, and should preferably be used in conjunction with the CONSORT Statement. In addition, extensions of the CONSORT Statement have been developed to give additional guidance for RCTs with specific designs, data and interventions. The CONSORT website (http://www.consort-statement.org/consort-2010) contains the current definitive version of the CONSORT 2010 Statement and up-to-date information on extensions.

APPENDIX 9 NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION

Heart failure is usually classified according to the severity of their symptoms. The table below describes the most commonly used classification system, the New York Heart Association (NYHA) Functional Classification. It places patients in one of four categories based on how much they are limited during physical activity.

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Class	Objective Assessment
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

APPENDIX 10 STATISTICAL METHODOLOGY

STATISTICAL DETAILS FOR BAYESIAN LOGISTIC REGRESSION MODEL AND PRIORS FOR DOSE ESCALATION AND SAFETY MONITORING

1 MODEL SETUP FOR BMS-986226 MONOTHERAPY

1.1 Monotherapy Methodology Description

An adaptive 2-parameter Bayesian Logistic Regression Model (BLRM) guided by the escalation with overdose control (EWOC) principle[1,2,3] will be used to guide the dose escalation of BMS-986226 monotherapy in the monotherapy phase, providing dose recommendation during dose escalation.

The BLRM will be fitted on the dose-limiting toxicity (DLT) data during the first 5 weeks of treatment accumulated throughout the dose escalation to model the dose-toxicity relationship of BMS-986226 in the monotherapy dose escalation phase.

The dose-toxicity relationships for BMS-986226 monotherapy is assumed to follow a logistic model:

$$logit(p_i) = log(\alpha_1) + \beta_1 log(^{d_{1i}}/_{d_1^*}),$$

where p_i is the probability of toxicity at dose level d_{1i}. Note that the α_1 and β_1 parameters are assumed positive, and d_1^* is the reference dose for BMS-986226 (please refer to the meaning of α_1 and β_1 in Section 1.2 for detailed implementation).

1.2 Prior Specification for BMS-986226 Monotherapy

The Bayesian approach requires the specification of prior distributions for model parameters, which include parameters (α_1, β_1) for BMS-986226. The prior distributions for BMS-986226 single agent activity were derived using a weakly informative prior, as well as discussion with the Bristol-Myers Squibb (BMS) clinical team. Details are provided below.

Weakly Informative Prior

- The median DLT rate at the reference dose (BMS-986226 at 800 mg every 4 weeks) was assumed to be 30%, that is, mean (log(α_1)) = logit (0.3) = log(0.3/(1-0.3)) = -0.847.
- A doubling in dose was assumed to double the odds of DLT, that is, mean (log(β_1)) = 0.

The standard deviation (sd) of log(α_1) was set to 1.53 using the following steps:

- If the toxicity probability range was set to be [1%, 99%], then the toxicity interval would be logit (0.99)-logit (0.01) = 9.19.
- To cover 99.7% of the variance, the toxicity interval will cover 6×sd (log(α_1)), which gives us sd (log(α_1)) = 9.19/6 = 1.53.

Correspondingly, the standard deviation of $\log(\beta_1)$ was set to 1, which allows for considerably larger prior uncertainty for the dose toxicity.

1) The correlation between $\log(\alpha_1)$ and $\log(\beta_1)$ was set to 0.
2) $\text{Log}(\alpha_1)$ and $\log(\beta_1)$ follow a bivariate normal distribution.

Through those steps, the prior obtained is given in Table 1.2-1.

Table 1.2-1: Prior Distribution for Model Parameters for BMS-986226

Parameter	Means	Standard Deviations	Correlation
$\log(\alpha_1)$, $\log(\beta_1)$	(-0.847, 0)	(1.53, 1)	0

This prior will be fitted into EAST® v6.3.1 Dose Escalation Module by Cytel for the Monotherapy Escalation of BMS-986226 as stated in model setup section.

2 DECISION RULE FOR DOSE ESCALATION AND SIMULATION

Dose escalation recommendations for BMS-986226 monotherapy will be based on the inference from the Bayesian posterior and the probability that the true DLT rate for each dose lies in 1 of the following categories:

- [0%, 16%) under-dosing
- [16%, 33%) targeted toxicity
- [33%, 100%] excessive toxicity

Note: "[" or "]" is inclusive of the respective endpoint, and "(" or ")"exclusive of the respective endpoint.

These boundaries are similar to the toxicity boundaries used by a rule-based design (ie, 3 + 3 design) in that a minimum is set at 16% (~ 1 in 6) DLT rate and a maximum at 33% (~ 2 in 6) DLT rate. Following the principle of EWOC, dose recommendations for the next cohort will be based on the Bayesian model after DLT information becomes available during the DLT period, accounting for all of the available data from the administered doses, and the candidate doses are the ones fulfilling the overdose criterion that there is less than 30% chance of excessive toxicity. Only the candidate doses will be considered for the next cohort. While the Bayesian model will use DLT information from the DLT period only, clinical assessment will take into consideration of the totality of available data including pharmacokinetics (PK)/pharmacodynamics from all treated participants.

Stopping Rules:

The following is the general stopping rules of BLRM (-Copula) during Dose Escalation:

- If all of 30 DLT evaluable participants are treated.

- If all of the current pre-specified doses are considered intolerable according to the pre-specified cutoff (ie, EWOC criteria), then the model will recommend stopping the current dose level and a new dose level lower than the current lowest dose level will need to be identified.
- The maximum number of DLT-evaluable participants in a dose level will be 12. This limit is set to avoid instances in which the model could recommend adding subjects indefinitely to a specific dose level due to uncertainty in the tolerability profile.
- If, for a specific dose level, 6 subjects have been treated and the chance of determining that the dose level to be the "target" dose is > 50%, then the model will suggest to stop and declare the current dose level to be the maximum tolerated dose (MTD).

Model-recommended MTD:

The MTD is the dose that satisfies the following 3 conditions:

1) The empirical posterior probability that the 'DLT rate of 16% -< 33%' is greater than 50%.
2) This probability needs to be the largest among the dose levels that satisfy the EWOC condition (ie, the probability that 'DLT rate ≥ 33%' must be less than 30%).
3) Minimum number of participants (ie, 6) were treated at this dose level.

Final MTD:

The final recommended MTD in Part A will be based on the recommendation from the BLRM and overall clinical assessment of all available safety, PK/pharmacodynamics, and efficacy data. Lower doses of BMS-986226 may be tested if none of the planned doses are found to be tolerable. Such decisions will be made after discussion and agreement between the investigators and the BMS Medical Monitor.

2.1 Simulation Parameters

One thousand trial simulations will be used for each scenario. All simulations will be run using EAST v6.3.1 software for BLRM model for the BMS-986226 monotherapy. The number of subjects to be treated in each cohort in a specific dose level and the stopping rules used to declare MTD are defined as:

- Fixed cohort size: 3
- Probability of overdosing: < 30%
- Probability of achieving the target toxicity: > 50%
- Maximum number of participants treated: 30
- Minimum number of participants treated at a given dose level in order to declare MTD: 6
- Maximum number of participants at a dose:12

The provisional dose levels for BMS-986226 monotherapy are 25 mg, 80 mg, 200 mg, 400 mg, and 800 mg.

2.2 Operating Characteristics

Section 2.2.1 demonstrates operating characteristics of BLRM for monotherapy.

2.2.1 Operating Characteristics of BLRM for Monotherapy

Five scenarios were investigated by selecting (1) dose-DLT relationship derived by prior, (2) dose-DLT curve flatter than the one by the prior; (3) narrow safety window in order to explore how EWOC limits the risk of exposing participants from a toxic dose level, (4) all doses below the target toxicity, and (5) all doses above the target toxicity. Simulations were performed using EAST v6 BLRM which allows dose skipping.

For scenario (1), the % DLT by prior was derived using the model solving for the probability, p_i at the ith dose.

$$\text{logit}(p_i) = \log(\alpha_1) + \beta_1 \log(^{d_{1i}}/_{d_1^*})$$

The model can be re-written as follows.

$$p_i = \frac{1}{1 + \exp\left(-\log(\alpha_1) - \beta_1 \log(^{d_{1i}}/_{d_1^*})\right)}$$

Using the estimates in Section 1.2, ie, $\log(\alpha_1) = -0.847$ and $\beta_1 = 1, d_1^* = 800$ mg, the prior probability of DLTs at dose 25, 80, 200, 400, and 800 mg is 0.01, 0.04, 0.1, 0.18, and 0.30, respectively.

Table 2.2.1-1: Simulation Results of BLRM for Monotherapy

Scenario	BMS-986226 Dose (mg)	25	80	200	400	800	MTD Not Selected (%)	Fitted Median MTD	Toxicity Observed (%)	Avg No. of Patients
By prior	% DLT	*1*	*4*	*10*	***18***	***30***	0	698.7	17.3	18.2
	% MTD	0	0.9	9.9	61	28.2				
	# Pts	3.1	0.5	2.0	8.2	4.4				
	# DLTs	0	0	0.2	1.5	1.4				
Flatter than the one by the prior	% DLT	*10*	*15*	***20***	***25***	***30***	6.6	510.4	22.4	17.4
	% MTD	3.9	11.9	22.2	38.5	16.9				
	# Pts	4.1	2.0	2.7	5.8	2.7				
	# DLTs	0.4	0.3	0.6	1.4	0.8				
Narrow safety window	% DLT	*3*	*7*	***18***	***31***	*80*	1	443.4	23.2	18.3
	% MTD	0.4	7.9	40.7	49.8	0.2				
	# Pts	3.4	1.9	4.9	7.1	1.1				

Table 2.2.1-1: Simulation Results of BLRM for Monotherapy

Scenario	BMS-986226 Dose (mg)	25	80	200	400	800	MTD Not Selected (%)	Fitted Median MTD	Toxicity Observed (%)	Avg No. of Patients
	# DLTs	0.1	0.1	0.9	2.2	0.9				
All low	% DLT	*1*	*5*	*10*	*15*	***20***				
	% MTD	0.1	0.8	5.4	39.2	54.3	0.2	925.1	13.9	18.4
	# Pts	3.1	0.3	1.3	7.0	6.8				
	# DLTs	0	0	0.1	1.0	1.3				
All high	% DLT	*45*	*50*	*60*	*75*	*80*				
	% MTD	11.6	2.6	0.7	0.1	0	85	10.7	57.8	7.0
	# Pts	5.2	1	0.26	0.6	0				
	# DLTs	2.3	0.5	0.1	0.5	0				

% DLT, true DLT rate; % MTD, proportion of the dose selected as the MTD; # Pts, average number of participants by assuming 3 participants for skipped dose level where the true toxicity rate is below the target rate; # DLTs, average number of DLTs by assuming no DLT for skipped dose level where the true toxicity rate is below the target rate; Fitted MTD: fitted MTD at 30% as the target toxicity rate; % toxicity observed, average proportion of DLTs given the doses were tried

The average sample size in this simulation was observed to be no more than 20 participants. The results for the scenarios of narrow safety window and all high show how the EWOC principle limits the risk of exposing participants from a toxic dose level. Overall, the scenarios illustrated above demonstrate that the model performs well in the hypothetical scenarios investigated.

3 INTERIM MONITORING CASE STUDY TO ILLUSTRATE PROVISION OF DOSE RECOMMENDATIONS DURING DOSE-ESCALATION

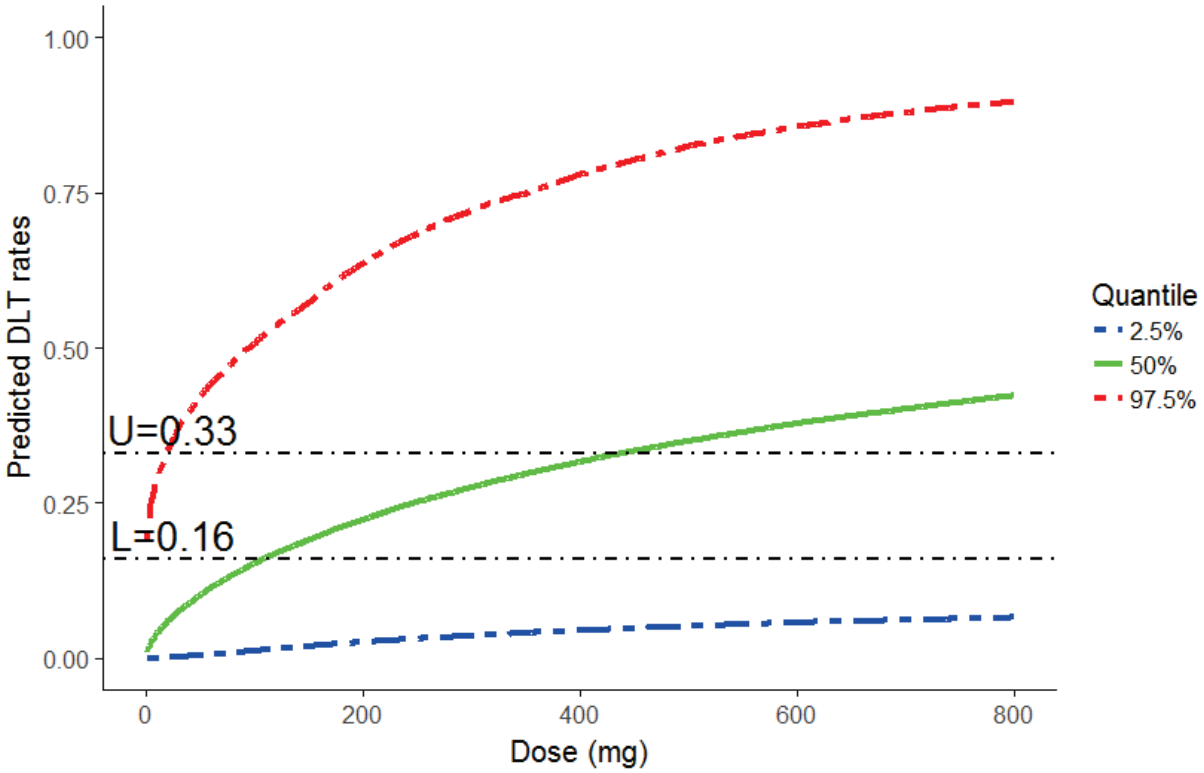
In order to provide a comprehensive view of the dynamics of the models, different hypothetical scenarios exploring all possibilities are examined. For the simplicity of illustration purposes, a static cohort size of 3 subjects is applied for dose levels 25 mg, 80 mg, 200 mg, 400 mg, and 800 mg in the BMS-986226 monotherapy. This cohort size could vary during the actual clinical trial, and the BLRM models are designed to fit various different cohort sizes, adaptively. In general, there are 4 possible scenarios for a specific dose level, which are 0 DLT observed in 3 total subjects in that cohort (denoted as 0/3), 1 DLT observed in 3 subjects (1/3), 2 DLTs observed in 3 subjects (2/3), and 3 DLTs observed in 3 subjects (3/3).

During interim monitoring, posterior probabilities will be updated when there is new DLT information available. The following three visualization plots will be produced to reflect the real time dose-DLT relationship, to quantify benefit (in the form of target dosing) and risk (in the form of overdosing and underdosing) during model's recommendation process, and to facilitate clinical team's interpretation of the model recommendations for the final decision making:

- Dose-DLT profile for the doses ranging between 0 mg and 800 mg (Figure 3-1).
- Stacking histograms displaying predictive probabilities on DLT rates classified into 3 different categories (Underdosing, Target dosing, and Overdosing) (Figure 3-2).
- Box plots summarizing the Markov Chain Monte Carlo samples of predicted DLT rates for the 5 pre-specified dose levels (Figure 3-3).

In the following illustrations, Figure 3-1 to Figure 3-3 are produced using a hypothetical example assuming 0/3 DLTs observed in the 25-mg cohort and 1/3 DLTs observed in the 80-mg cohort.

Figure 3-1: Updated Dose-DLT Profile After Incorporating Prior Information and All Previous DLT Information up to 80 mg



Abbreviations: DLT = dose-limiting toxicity; L = low boundary; U = upper boundary.

Interpretation and usage of Figure 3-1:

Figure 3-1 is a snapshot of an updated dose-DLT profile with DLT information available at dose level 80 mg. The dose-DLT profile is captured with a continuous dose spectrum ranging from 0 mg to 800 mg. For each dose within the range, there is a corresponding distribution of the predicted DLT rates calculated from the posterior samples of the model parameters. This figure will be updated each time when new DLT information becomes available.

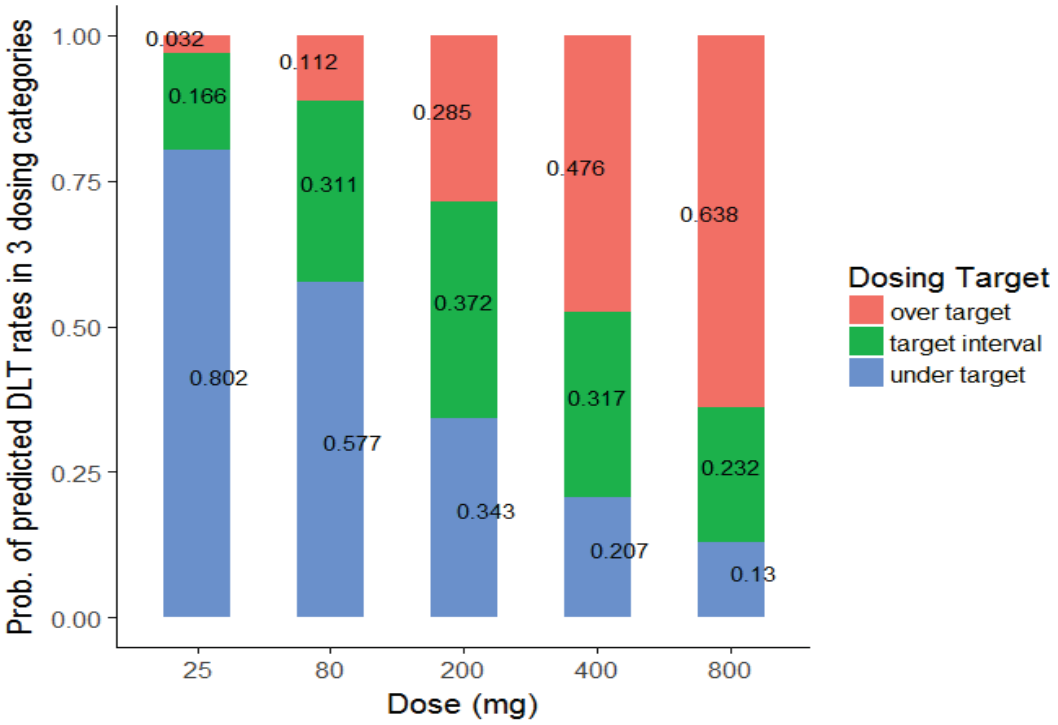
In Figure 3-1, there are 3 different quantiles (2.5%, 50%, and 97.5%) plotted to characterize the current trend of the toxicity profile (as shown by the 50% quantile), as well as the variation of the

dose-DLT profile (as shown by the 2.5% percentile and the 97.5% percentile), according to the accumulation of DLT data from all previous and current dose levels. The toxicity boundaries (low boundary 0.16 and high boundary 0.33) are illustrated in two dotted horizontal lines to benchmark the way, in which the dose-DLT profile is trending.

Intermediate dose levels can be identified using different boundary cutoffs. For example, using the 50% percentile curve (green highlight), which represents the nearly average DLT distribution for each dose level, the 100 mg could be a potential intermediate dose level corresponding to the lower pre-specified DLT rate boundary of 0.16, and the 450 mg could be a fitted MTD dose level associated with the upper boundary of 0.33.

Moreover, if all of the current pre-specified doses are considered intolerable (overdosing probabilities > 0.3, a case not shown on the current Figure 3-1), the model will recommend to stop the current dose level, and the clinical team can leverage the current updated dose-DLT curve to pinpoint a new dose, which is lower than pre-specified lowest dose (25 mg) by using the DLT rate boundaries.

Figure 3-2: Updated Stacking Histogram after Incorporating Prior Information and All Previous DLT Information up to 80 mg Monotherapy Data to Classify Predicted DLT Rates Into 3 Categories (Under Target, Target Interval and Over Target)



Interpretation and usage of Figure 3-2:

Figure 3-2 is a snapshot of stacking histogram with DLT information available at dose level 80 mg for the combination studies. This figure will be updated each time when new DLT information

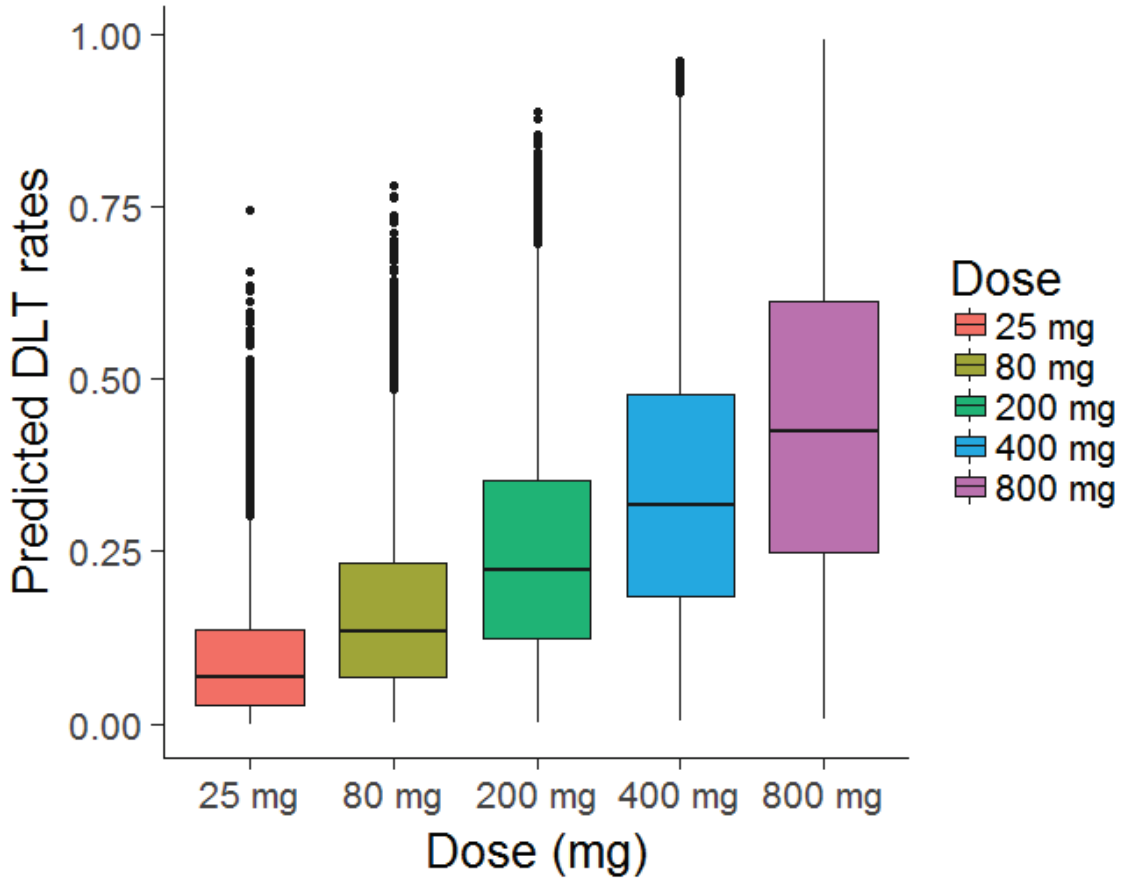
becomes available in the combination setting. Similar graphs will also be produced for the BMS-986226 monotherapy.

When recommending the next dose level, the model will first exclude doses that are intolerable (with overdosing probabilities > 30%, the rate that has been specified for BMS-986226 in combination with ipilimumab). Among those qualified candidate doses that are considered "tolerable", the model will select the dose that maximizes the probability of being within the target toxicity range (DLT rate of 16% up to 33%).

As illustrated in Figure 3-2, when there is 0 DLT observed out of 3 subjects for the dose level 25 mg and 1 DLT out of 3 subjects for the dose level 80 mg, the distribution of predicted DLT rates will be characterized into possibilities falling into 3 different categories. First, dose levels of 400 mg and 800 mg for BMS-986226 are excluded according to the higher-than-cutoff (0.3 for mono therapy) overdosing probabilities. Among the remainder of tolerable dose levels (25, 80, and 200 mg), the BLRM-Copula model recommends the dose that maximizes the probability of being within the target dosing interval. Therefore, the model's recommendation would be to escalate to 200 mg, which is associated with the highest target dosing probability of 0.372 compared with that of 80 mg (0.311).

Similarly (although not shown on Figure 3-2), according to the rules specified above, the model could possibly recommend to de-escalate to a lower dose level than current treated dose level, extend the current dose level, or even recommend to stop and identify a new dose level lower than 80 mg, the lowest pre-specified dose level. Please refer to description of Figure 3-1 for details on how to specify the new dose levels.

Figure 3-3: Updated Box Plot after Incorporating Prior Information and All Previous DLT Information up to BMS-986226 80 mg for Pre-specified Dose Levels



Interpretation and usage of Figure 3-3:

Figure 3-3 is a snapshot with DLT information available at dose level 80 mg for the combination setting. The dose-DLT distributions calculated from the posterior samples of the model parameters are characterized in the format of boxplots for the pre-specified dose levels. This figure will be updated each time when there is new DLT information available. Similar graphs will also be produced for the BMS-986226 monotherapy.

This plot supplements the information provided in Figure 3-1. It allows for a more in-depth and focused visualization of general trend of dose-DLT relationship, as well as the magnitude and variability in the DLT rates for each pre-specified dose level.

3.1 Example of the BLRM using BMS-986226 Monotherapy Dose Escalation

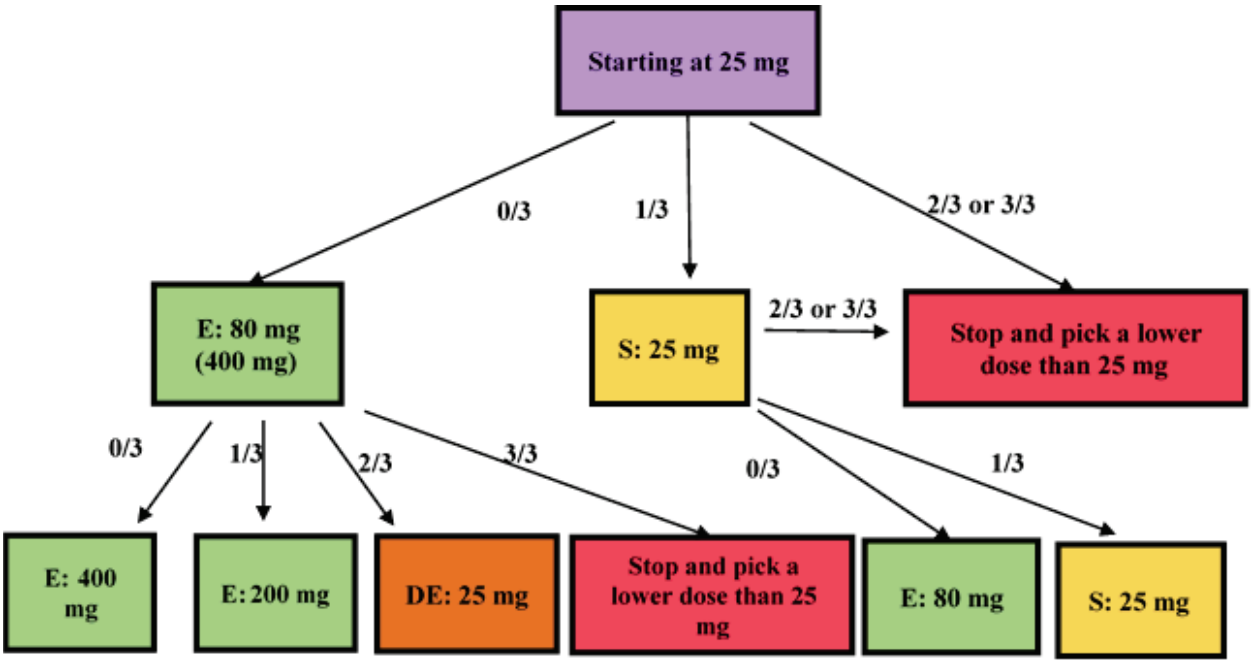
According to safety consideration and clinical judgement, the dose level 25 mg is recommended as the starting dose for BMS-986226 monotherapy. With the current BMS-986226 prior specified

in the Section 1.2 and all available DLT information up to 80 mg, a corresponding decision tree illustrating various models' recommendations under all possible scenarios (for dose levels of 200 mg and 400 mg) is provided in Figure 3.1-1.

Tracing a branch of the decision tree in Figure 3.1-1 illustrates the decision making process. Taking the left-most branch of the tree as an example, starting at 25 mg, there were 0 DLT observed at 25 mg in the real clinical trial, the model recommended to escalate to 80 mg (The BLRM actually recommends escalating to dose level 400 mg, but since this is a 16-fold increase of dose and this type of dose skipping is not allowed, the dose level 80 mg is selected), one level above the current treated dose level according escalation rules per protocol. Additionally, if there was 0 DLT observed at 80 mg in real data, the model recommended to escalate further one dose level to 400 mg.

As illustrated in Figure 3.1-1, there are 6 potential decision paths for dose levels 80 mg and moving onwards up to 200 mg. During the actual clinical study, the tree would be narrowed or deepened based on actual DLT. The clinical team will be able to leverage this decision tree to preview decisions at each interim monitoring step and to plan proactively.

Figure 3.1-1: The BLRM Model Hypothetical Decision Tree for BMS-986226 Monotherapy during Dose Escalation (up to 400 mg)



Abbreviations: DE = de-escalation; E = escalation; S = stay.

4 BLRM-COPULA MODEL SETUP FOR BMS-986226 AND NIVOLUMAB OR IPILIMUMAB COMBINATION

For Parts B and C of this study, the BLRM-Copula model will be used to evaluate the starting dose and to guide the subsequent doses of BMS-986226 in combination with nivolumab or ipilimumab.

The BLRM-Copula model incorporates the latest information, including monotherapy information from Part A and any available toxicity information in completed portion of Parts B and C, available at the time of dose recommendation. In other words, the model concept covers both the starting doses and any subsequent doses of BMS-986226 in combination with nivolumab or ipilimumab in Parts B and C. Specifically, the starting dose of BMS-986226 in Parts B and C will be guided using the BLRM-Copula model, incorporating available single-agent toxicity profiles of BMS-986226 from the preliminary safety cohorts and Part A and nivolumab or ipilimumab. Any subsequent dose of BMS-986226 in Parts B and C will be evaluated using the BLRM-Copula model, incorporating single-agent toxicity profiles of BMS-986226, nivolumab or ipilimumab and any available combination toxicity profiles from on-going Parts B and C.

In any case, the dose of BMS-986226 in combination with nivolumab or ipilimumab in Parts B and C will not exceed the maximum administered dose for BMS-986226 monotherapy in Part A. In summary, the doses of BMS-986226 in Parts B and C (combination with nivolumab or ipilimumab) will be determined using all available safety (clinical and laboratory), PK, and target engagement [redacted] data, and the modelling recommendation using the BLRM-Copula model. The toxicity profiles of both BMS-986226 monotherapy and nivolumab or ipilimumab monotherapy, to be incorporated in the BLRM-Copula model, will be discussed in upcoming subsections. We introduce briefly the technical background of the BLRM-Copula model in the following paragraph.

A copula-type model can be used to cover all general combination cases, including additive and synergistic effects. The combination of the 2 treatments will be explored using a Bayesian hierarchical model by utilizing the toxicity profiles of the single agents as prior marginal profiles for the combination. The following copula-type model[4] will be used to describe the probability p_{ij} of toxicity when dose level i of agent A and dose level j of agent B are administered in combination:

$$p_{ij} = 1 - exp(-\left[\{-log(1-{p_i}^m)\}^{1/\gamma_1} + \{-log(1-{q_j}^n)\}^{1/\gamma_1}\right]^{\gamma_1}),$$

where p_i is the prespecified best guess toxicity probability for agent A, q_j is the prespecified best guess toxicity probability for agent B, m and n characterize the individual drug effect, and γ_1 characterizes the drug-drug interactive effect.

The joint toxicity framework models the toxicity rates of both agents as well as their interaction effects in a 7-parameter hierarchical model, where each monotherapy dose-toxicity relationship will be characterized by a 2-parameter BLRM model (see Section 1.1). There are 3 additional parameters for the copula-type model, 1 for each agent (m and n) as well as 1 for the interaction term (γ_1). A dose-toxicity surface will be characterized for different dose combinations of these 2 agents.

As there are currently no historical data or prior knowledge to indicate how much information is to be borrowed for each of the single agents, parameters m and n are both set to be 1, meaning borrowing 100% of the information from the 2 agents. The above formula is then simplified into a 5-parameter model as follows:

$$p_{ij} = 1 - exp(-\left[\{-log(1-p_i)\}^{1/\gamma_1} + \{-log(1-q_j)\}^{1/\gamma_1}\right]^{\gamma_1}.$$

In each cohort of the study, since only a fixed nivolumab dose (in Part B1) or ipilimumab dose (1 mg/kg in Part B2, 3mg/kg in Part B3) will be used in the combination with BMS-986226, this surface will be simplified into a 2-dimensional dose-toxicity curve. Posteriors for the corresponding 5 parameters (2 logistic regression parameters $[\alpha_1, \beta_1]$ for BMS-986226 and 2 logistic regression parameters $[\alpha_2, \beta_2]$ for nivolumab or ipilimumab, as well as 1 interaction parameter for the copula-type model [γ_1, which will be discussed in detail in the following section]) will be fitted into the in-house developed model. It implements the above-described theoretical setup.

4.1 Prior Specification for Combination Therapy

In this section, we illustrate the prior specification of parameters in the BLRM-copula model for combination therapies. While we give prior examples for illustration purposes, all of those specifications may be subject to change when new data of monotherapies are available.

4.1.1 Marginal Prior for BMS-986226

Posterior information on $\log(\alpha_1)$ and $\log(\beta_1)$ from the monotherapy part of the study will be used as marginal BMS-986226 prior for combination with ipilimumab. This prior information is not prespecified and will be continuously updated when additional DLT information from the monotherapy is available. In the simulation (see Section 3, the prior of BMS-986226 as described in Section 1.2 (Table 1.2-1) is used for illustration purposes because no real-time DLT data are available at this time.

4.1.2 Marginal Prior for Nivolumab Parameters (log(α₂),log(β₂))

Similar to BMS-986226 monotherapy in the lead-in phase, the logistic model for nivolumab is as follows:

$$logit(q_j) = log(\alpha_2) + \beta_2 log(^{d_{2j}}/_{d_2^*}) \text{ , where } a_2,\ \beta_2 > 0.$$

Note that the α_2 and β_2 parameters are assumed positive, and d_2^* is the reference dose for nivolumab.

The toxicity profile of nivolumab has been studied in several studies. A bivariate normal prior for the nivolumab model parameters ($\log(\alpha_2)$, $\log(\beta_2)$) was obtained by extracting a posterior of nivolumab using incidence of treatment-related Grade 3 to 4 AEs from a Phase 1 dose-escalation study and several Phase 3 nivolumab studies, which are used later as the MAP prior for nivolumab. These include a Phase 1 dose-escalation study of nivolumab (Study CA209003, N=306 in doses of 0.1, 0.3, 1, 3, and 10 mg/kg across multiple tumor types), a randomized Phase 3 study in advanced melanoma participants progressing post anti-CTLA-4 therapy (Study CA209037, N=268 in a dose of 3 mg/kg), a Phase 3 study in previously treated participants with squamous cell NSCLC (Study CA209017, N=131 in a dose of 3 mg/kg), a Phase 3 study in previously treated participants with non-squamous cell NSCLC (Study CA209057, N=287 in a dose of 3 mg/kg), and a Phase 3

study in previously treated participants with clear-cell RCC (Study CA209025, N=406 in a dose of 3 mg/kg). The results from the simulation of nivolumab flat dose exposures, the corresponding exposure-response analyses, and review of nivolumab safety support nivolumab flat dose and the overall distributions of nivolumab exposures are comparable after treatment with either 3 mg/kg Q2W or 240 mg Q2W nivolumab. [redacted]

The MAP prior for the model parameters ($\log(\alpha_2)$, $\log(\beta_2)$) was obtained in the following steps.

First, a prior distribution for nivolumab was developed:

- The median DLT rate at the reference dose (3 mg/kg every 2 weeks) was assumed to be 10%, that is, mean ($\log(\alpha_2)$) = logit(0.10) = log(0.1/0.9) = -2.197.
- A doubling in dose was assumed to double odds of DLT, that is, mean($\log(\beta_2)$) = 0.
- The standard deviation of $\log(\alpha_2)$ was set to 2, and the standard deviation of $\log(\beta_2)$ to 1, which allows for considerable prior uncertainty for the dose-toxicity profile.
- The correlation between $\log(\alpha_2)$,and $\log(\beta_2)$ is assumed to be 0 (assuming independence of $\log(\alpha_2)$ and $\log(\beta_2)$).
- In addition, heterogeneity between the historical study and current study was incorporated using a MAP by defining between-trial standard deviations τ_1 and τ_2 for $\log(\alpha_2)$ and $\log(\beta_2)$, respectively. The between-trial variability is assumed to be moderate. Therefore, τ_1 and τ_2 were set to follow a log-normal distribution with mean log(0.25) and log(0.125), respectively, with a common standard deviation log(2)/1.96.

With this prior, the clinical trial data below were used to generate the posterior for nivolumab, which is then used as the MAP prior for this study.

Table 4.1.2-1: Data from Nivolumab Studies

Nivolumab Flat Dose (mg), Q4W	Dose of Nivolumab (mg/kg) Q2W	Toxicity[a]
	0.1	29% (5/17)
	0.3	17% (3/18)
160	1	14% (12/86)
480	3	13% (150/1146)
	10	16% (21/131)

[a] % of participants with treatment-related Grade 3-4 AEs

Abbreviation: Q2W = every 2 weeks; Q4W - every 4 weeks.

Table 4.1.2-2: Marginal Prior Distribution for Model Parameters for Nivolumab (ie, Posterior from MAP Method)

Parameter	Means	Standard Deviations	Correlation
$\log(\alpha_2)$, $\log(\beta_2)$	(-1.856, -2.131)	(0.404, 0.546)	-0.009

Note: Nivolumab prior information was based on mg/kg dosing instead of flat dosing. If real pharmacokinetic (PK) data from this study show difference from mg/kg assumption, the nivolumab prior will be revisited and modified accordingly.

4.1.3 Marginal Prior Derivation for Ipilimumab Parameters ($\log(\alpha_3)$, $\log(\beta_3)$)

Similar to BMS-986226 monotherapy in the monotherapy phase, the logistic model for ipilimumab is as follows:

$$logit(q_j) = log(\alpha_3) + \beta_3 log(^{d_{3j}}/_{d_3^*}),$$

where q_j is the probability of toxicity at dose level d_{3j}. Note that the α_3 and β_3 parameters are assumed positive, and d_3^* is the reference dose for ipilimumab.

Since DLT information from ipilimumab studies was not available, incidence of treatment-related Grade 3 to 4 adverse events (AEs) from various Phase 2 to 3 ipilimumab studies at Bristol-Myers Squibb (BMS) in participants with previously treated or untreated advanced melanoma was used in lieu of DLT rate in order to derive the prior for the BLRM parameters corresponding to the effect of ipilimumab, ($\log(\alpha_3)$, $\log(\beta_3)$). Specifically, a bivariate normal MAP prior for the ipilimumab model parameters ($\log(\alpha_3)$, $\log(\beta_3)$) was obtained by extracting a posterior of ipilimumab using DLT and safety data from Phase 2 and 3 ipilimumab studies in BMS and the meta-analytical-predictive approach. Finally, a mixture prior with both MAP and weakly informative components will be generated for BLRM parameters of ipilimumab.

The MAP prior for the model parameters ($\log(\alpha_3)$, $\log(\beta_3)$) was obtained in the following steps.

First, a weakly informative prior for ipilimumab was developed:

- The median toxicity rate at the ipilimumab reference dose (10 mg/kg every 3 weeks) was assumed to be 30%, ie, mean ($\log(\alpha_3)$) = logit(0.30)= -0.847.
- A doubling in dose was assumed to double the odds of DLT, ie, mean ($\log(\beta_3)$) = 0.
- The standard deviation of $\log(\alpha_3)$ was set to 2, and the standard deviation of $\log(\beta_3)$ was set to 1, which allows for considerable prior uncertainty for the dose-toxicity profile.
- The correlation between $\log(\alpha_3)$ and $\log(\beta_3)$ was assumed to be 0 (assuming independence of $\log(\alpha_3)$ and $\log(\beta_3)$).

With this prior, the clinical trial data below (Table 4.1.3-1), including:

- Phase 3 study of ipilimumab administered at 3 mg/kg vs 10 mg/kg (Study CA184169, N=360 per arm)

- Phase 2 study of multiple doses of ipilimumab monotherapy (Study CA184022, N=71 per arm)
- Phase 3 study in HLA-A*0201 positive participants (Study MDX010-20, ipilimumab 3 mg/kg monotherapy arm with N=131)
- Data from other various Phase 2 studies (N=111 for pooled 3 mg/kg; N=325 for pooled 10 mg/kg, from Clinical Overview of a Common Technical Document for ipilimumab)

were used to generate the posterior for ipilimumab. The generation of the posterior uses the meta-analytic predictive approach, such that heterogeneity between the historical study and the current study was incorporated, by defining between-trial standard deviations $\tau 1$ and $\tau 2$ for $\log(\alpha_3)$ and $\log(\beta_3)$, respectively. The between-trial variability is assumed to be moderate. Therefore, $\tau 1$ and $\tau 2$ were set to follow a log-normal distribution with mean log(0.25) and log(0.125) respectively with a common standard deviation log(2)/1.96. This leads to the MAP prior in Table 4.1.3-2.

To obtain the mixture prior, 50% weight is assigned to the MAP component, and 50% weight is assigned to the weakly informative component. The mixture prior is also presented in Table 4.1.3-2. Note that the prior of Ipilimumab is derived using mg/kg-based Q3W historical data, and the reference dose was selected to be 10 mg/kg Q3W. Since the DLT-evaluation period is 5 weeks and to be conservative, we will keep the reference dose as is when evaluating Ipilimumab as Q4W in our current study. In other words, we conservatively assume that the DLT toxicity profile in the DLT-evaluation period from Ipilimumab Q4W is similar to that for the Ipilimumab Q3W from historical studies.

Table 4.1.3-1: Data from Phase 2 and 3 Ipilimumab Studies at BMS in Participants with Previously Treated or Untreated Advanced Melanoma

Source	Dose of Ipilimumab (mg/kg*)	Toxicity (percentage [number of participants/total participants])[a]
Phase 3 study MDX010-20	3	20.6% (27/131)
Phase 2 Studies Pooled	3	14.4% (16/111)
	10	30.5% (99/325)
CA184169	3	18.2% (66/362)
	10	34.1% (124/364)
CA184022	0.3	9.7% (7/72)
	3	14.1% (10/71)
	10	26.8% (19/71)

[a] % of participants with treatment-related Grade 3-4 AEs

Table 4.1.3-2: Prior Distribution for Model Parameters of Ipilimumab

Parameter: (log(α_3), log(β_3))	Means	Standard Deviations	Correlation
Prior for Ipilimumab	(-0.827, -0.289)	(1.444, 0.787)	0.009
MAP component	(-0.805, -0.578)	(0.276, 0.232)	0.263
Weakly Informative Prior	(-0.847, 0)	(2, 1)	0

Note: Ipilimumab prior information was based on mg/kg Q3W dosing.

4.1.4 Prior for Interaction Parameters for Joint Toxicity of BMS-986226 and Nivolumab or Ipilimumab Combination

A gamma prior distribution for the interaction parameter γ_1 is derived to reflect the current uncertainty about the toxicity profile of the combination of BMS-986226 and nivolumab or ipilimumab. Although no PK drug-drug interaction is expected, the possibility of a significant positive interaction between BMS-986226 and nivolumab or ipilimumab cannot be totally excluded. The interaction parameter γ_1 was chosen accordingly but with a degree of uncertainty to allow for the possibility that the interaction may be positive or negative. Therefore, the following assumptions are made for the interaction parameter:

- γ_1 follows a gamma distribution and with a mean centered at 1.2, which means the combination of 2 agents is likely to have only a small synergistic effect.
- The standard deviation of γ is 0.5 such that there is a 61% prior probability that γ is larger than 1.

This model assigns the highest probability to there being small synergistic interaction and also allows for the potential of larger synergism of the toxic profiles. It also does not completely ignore the possibility of antagonism because there is a 39% prior probability that γ_1 is less than 1.

5 DOSE RECOMMENDATION BY BLRM-COPULA FOR BMS-986226 IN COMBINATION COHORTS

Similar to the dose escalation recommendation for BMS-986226 monotherapy, any recommended dose by BLRM Copula (for Parts B and C, and not to exceed the maximum administrated dose of the BMS-986226 monotherapy in Part A) and any potential dose recommendation for the combination cohorts will be based on the inference from the Bayesian posterior and the probability (obtained from the BLRM-Copula model) that the true DLT rate for each dose lies in 1 of the following categories:

- [0%, 16%) under-dosing
- [16%, 33%) targeted toxicity
- [33%, 100%] excessive toxicity

While the Bayesian model will use DLT information of all available data from the DLT period only, clinical assessment will take into consideration of the totality of available data including PK/PD from all treated participants.

BLRM-Copula Model-Recommended Dose:

At any time a dose recommended by BLRM-Copula model for BMS-986226, using all available data to date and time, is the dose that satisfies the following conditions:

1) Not to exceed the maximum administrated dose of BMS-986226 in Part A, ie., the BMS-986226 monotherapy phase
2) This probability of the true DLT rate falling into the targeted toxicity interval, i.e., [16%, 33%), needs to be the largest (or be comparable to numerically the largest with negligible practical difference) among the dose levels that satisfy the EWOC condition (ie, the probability that 'DLT rate ≥ 33%') must be less than 30%;

Final BLRM-Copula Recommended Dose:

Any final recommended BLRM-Copula recommended dose will be based on the recommendation from the BLRM-copula and overall clinical assessment of all available safety, PK/PD, and efficacy data. Also, note that the dose recommendation by BLRM-Copula is a real-time on-going process, and can be done whenever new DLT information is available.

6 REFERENCES

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APPENDIX 11 PROSTATE CANCER WORKING GROUP 3 (PCWG3) GUIDELINES (WITH MODIFIED RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) CRITERIA FOR SOFT TISSUE LESION ASSESSMENT)

1 EVALUATION OF LESIONS

Bone lesions should be evaluated with Technecium-99m based radionuclide bone scan as per PCWG3[1].

At baseline, soft tissue 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 soft tissue 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 bone lesions

Bone lesions will be assessed with Technecium-99m based radionuclide bone scans as per PCWG3.

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 20 lesions total (and a maximum of 5 lesions per organ system) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Note: A maximum of 5 lesions can be selected per organ system. For example, a maximum of 5 lung lesions can be selected. A maximum of 5 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. Pelvic lymph nodes and extrapelvic lymph nodes (retroperitoneal, mediastinal, thoracic and other) may be reported separately, per PCWG3. 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 (e.g., '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 (e.g., 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 (see below) 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 (see examples in Appendix 2 and further details below). 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: i.e., 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

New bone lesions

New bone lesions should be evaluated as per PCWG3 criteria. Bone lesions will be assessed by radionuclide bone scan only. Radiographic progression on bone scan is defined by the following criteria:

- At least 2 new lesions on the first posttreatment bone scan, with at least 2 additional lesions on the next scan (performed at least 6 weeks later) as compared to first posttreatment bone scan. Date of progression is then the date of first post-treatment scan,
- For scans after the first post-treatment scan, at least 2 new lesions relative to the first post-treatment scan AND confirmed on a subsequent scan (performed at least 6 weeks later). Date of progression is the date of the scan that first documents at least 2 new lesions relative to the first post-treatment scan.

New soft tissue lesions

The appearance of new malignant soft tissue 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. 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.

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 per PCWG3 criteria, 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&PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**BEST Overall Response**
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD

Table 2.3.3-1: Best Overall Response (Confirmation of CR&PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**BEST Overall Response**
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] Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. Scher et al. J Clin Oncol 2016, 34(12):1402-1418

APPENDIX 12 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 03, 02-Dec-2018

This protocol has been revised in several ways to improve access to study treatment for participants with incurable cancer, while enhancing the scientific knowledge gained from each enrolled participant. The inclusion criteria in the protocol was modified in order to expand the study population that could potentially benefit from BMS-986226 by adding additional tumor types, as well as increasing the number of prior therapies allowed for participants enrolled on study. The requirement for confirmation of ICOS expression by IHC on pre-treatment biopsy samples was removed, in order to expedite the treatment of participants on the study. The integrity of the biopsy sample will be ensured through a new requirement for the provision of the FFPE block obtained from the core-needle pre-treatment and on-treatment biopsies. The exact timing of tetanus booster administration, to be used as a surrogate measure of antigen-specific immune activation, was defined, in order to synchronize the post-booster immune response in the treatment cohorts. Additionally, changes were made in the content and timing of clinical, PK, PD [redacted] analysis, including stool collection for pre-treatment microbiota content analysis, in order to enhance the robustness and interpretability of the scientific data gathered from every participant enrolled on the study.

Sections in the synopsis have been updated to align with the protocol section changes listed below.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3 Introduction Section 3.2.1: Indication Background Table 5.1-1: Study Cohorts per Part Section 5.1.2.4: Combination Expansion Arms (Parts D and E) Section 6.1: Inclusion Criteria Appendix 1: Abbreviations and Trademarks	New tumor types were added and discussed: cervical cancer (CC), melanoma (MEL), renal cell carcinoma (RCC), and triple negative breast cancer (TNBC). Up to three courses of prior systemic therapy are permitted in HNSCC, NSCLC, PRC and UCC tumor types, which has been changed from two prior courses.	Modifications were made to expand the study population to include additional disease types and patient cohorts that could potentially derive benefit from ICOS agonist therapy, based on recently published literature.
Table 2.1: Screening Procedural Outline. Section 6.1 Inclusion Criteria [redacted]	Fresh Pretreatment Tumor Biopsy procedures were modified as follows: The requirement for central assessment of tumor content and ICOS expression prior to Day 1 of study treatment administration (Cycle 1 Day 1) was removed. A requirement for pretreatment biopsy collection and shipment for analysis has been added. [redacted]	Modification was made to expedite the time-between enrollment and first treatment, as well as to reduce the potential risk of re-biopsy for participants who had recently undergone the procedure for confirmation of disease progression. [redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2.1: Screening Procedural Outline Section 5.1.1: Screening	Timing for tetanus booster administration between Days -7 to -3, prior to dosing was added.	The timing of tetanus booster administration was narrowed in order to synchronize the antigen specific immune response within each treatment cohort.
Section 2.2: On-treatment Procedural Outline	Chemistry and CBC with Differential and Platelets were added to list of laboratory tests performed on Cycle 2 Day 2 and Cycle 2 Day 8. Additionally, all laboratory tests were specified to be performed on Day 1 of each cycle.	Modification was made to improve clinical monitoring of hematologic and metabolic effects of BMS-986226 therapy.
Pharmacokinetic and Immunogenicity Tables 9.5-1 through Table 9.5-4	Sampling time points were adjusted and/or tables removed	The tables in this section were modified to support more robust assessment for PK and immunogenicity while aligning with clinical [redacted] assessment.
[redacted]		
Table 2-4: Additional Treatment Procedural Outline (Former Table 2-4: Retreatment Day 0 Procedural Outline) Table 2-5: Additional Treatment Follow-up Procedural Outline (Former Table 2-5: Retreatment and Extended Treatment Procedural Outline) Former Table 2-6: Retreatment and Extended Treatment Follow-up Procedural Outline Section 5.1.5.1: Retreatment During Response Follow-up	Retreatment was removed as an option for patients who have relapsed after experiencing CR/PR or SD after completing study treatment. All tables and text referring to retreatment were removed from the protocol.	The option for retreatment of participants on the study was removed from the protocol as there is minimal evidence to support retreatment of participants who have progressed after completing a course of experimental therapy.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 3: Adverse Events and Serious Adverse Events: definitions and procedures for recording, evaluating, follow up and reporting	The previous version of Appendix 3 was replaced.	The Appendix was replaced to align with latest BMS standards.
Section 1 Synopsis Section 5.1 Section 10.1.1 Appendix 10	Clarifications made to the language describing the application of BLRM/BLRM-Copula. Reference to BLRM-RD removed from protocol.	Language referencing the BLRM model was adjusted in order to clarify starting dose decision algorithms for the combination cohorts as well as more precisely defining the application of BLRM/BLRM-Copula in dose escalation assessments.
Section 3.2.2.4: Clinical Pharmacology and Safety. Section 3.2.2.5: Pharmacokinetics of BMS-986226	Sections were updated to describe results from dosing of 12 participants to date.	Information was updated to provide latest data available on the safety of BMS-986226 in human subjects.
All	Minor formatting and typographical corrections.	Made corrections for clarity and consistency within the document.

Overall Rationale for the Revised Protocol 02, 03-Apr-2018

This protocol has been revised to modify the combination escalation of BMS-986226 with either nivolumab (Part B) or ipilimumab (Part C) to include and prioritize a Q12W dosing schedule that will provide pharmacodynamic data to inform dose and schedule. To rapidly inform a combination dose and schedule, the protocol was modified to allow Parts B and C to accrue while Part A is still open. In addition, on-treatment biopsy collections were changed to the 2W and 12W timepoints to more accurately capture pharmacodynamic activity and a tetanus booster will be administered to capture pharmacodynamic activity in an antigen-specific context. Finally, treatment duration of BMS-986226 in combination with nivolumab or ipilimumab will be 2 years, rather than 24 weeks, to align with published data on the efficacy of treatment with nivolumab monotherapy for 2 years.

Sections in the synopsis have been updated to align with the protocol section changes listed below.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-1: Screening Procedural Outline (CA021002); [redacted] Table 9.4.4-1; Clinical	New information about a tetanus booster to be administered for all participants in Parts A, B, and C [redacted]	[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Laboratory Tests; [redacted]	[redacted]	[redacted]
Section 4 Objectives and Endpoints; Section 5.1.2 Treatment phase; Section 5.1.5 Treatment Beyond Progression; Section 6.1. Inclusion Criteria; Section 8.1 Discontinuation from Study Treatment; Section 8.1.2 Treatment Beyond Disease Progression; Section 8.1.3 Discontinuation Due to Further Progression (Confirmed Progression); Section 9.1 1 Method of Assessment; Section 9.1.3 Secondary Efficacy Assessments; Section 10.3 Statistical Analyses;	Added text to refer to Prostate Cancer Working Group 3 (PCWG 3) efficacy assessment criteria for prostate.	Modified efficacy assessment criteria to include PCWG 3 criteria in addition to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-2 On-treatment Procedural Outline (CA021002); Table 2-5: Retreatment and Extended Treatment Procedural Outline (CA021002); Section 5 Study design; Section 5.1 Overall Design; Section 5.1.2.2 BMS-986226 and Nivolumab Combination Therapy Cohort (Parts B1 and B2); Section 5.1.2.3 BMS-986226 and Ipilimumab Combination Therapy Cohort (Parts C1 and C2); Section 6.1 Inclusion Criteria; Section 7.1 Treatment Administered; Section 10.1.2 BMS-986226 and Nivolumab or Ipilimumab Combination Therapy Cohorts (Parts B and C)	Revised the study design and the text in this section to modify the combination escalation of BMS-986226 with either nivolumab (Part B) or ipilimumab (Part C) to include and prioritize a Q12W dosing schedule that will provide pharmacodynamic data to inform dose and schedule.	Prioritized BMS-986226 Q12W cohorts to determine optimal dose and schedule using selected [redacted] assays including ICOS and ICOS-L expression
Table 2-2 On-treatment Procedural Outline (CA021002); Table 2-5: Retreatment and Extended Treatment Procedural Outline (CA021002); Section 5 Study design; Section 5.1.2.4 Combination Expansion Arms (Parts D and E); Section 5.2 Number of Participants; Section 6.1. Inclusion Criteria; Section 7.1 Treatment Administered; Section 10.1.2 BMS-986226 and Nivolumab or Ipilimumab Combination Therapy Cohorts (Parts B and C)	New text has been added or modified in these sections related to dose expansion phase with either nivolumab (Part D) or ipilimumab (Part E)	Modification was made to align with the revised protocol study design. The purpose of the cohort expansion is to gather additional safety, tolerability, preliminary efficacy, PK, and PD information regarding BMS-986226 in combination with either nivolumab (Part D) or ipilimumab (Part E)
Section 5.1.3.1 Safety Follow-up; Section 5.1.5.1 Retreatment During Response Follow-up; Section 5.4.2.2;	Modified language to allow combination patients to receive study therapies for 2 years rather than 24 weeks	Modification was made to align with published data on the efficacy of treatment with nivolumab monotherapy for 2 years

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.2 Number of Participants	Total number of participants in this study was increased to 234 subjects.	Modification was made to fulfill the expected number of participants per revised study design.
Section 6 Inclusion criteria; Criteria 3d)	Modified inclusion criteria for prostate cancer tumor	Modification was made to clarify prior hormonal and chemotherapies allowed and to define progression as per the PCWG3 criteria.
Section 7.3.2 BMS-986226 Dose Limiting Toxicities	The dose-limiting toxicity (DLT) period was modified for the combination of BMS-986226 + nivolumab (Part B1) or ipilimumab (Part C1) to allow patients to be DLT eligible after 1 dose of BMS-986226.	The 5-week DLT period for Parts B and C covers 2 doses of nivolumab (Q4W) or ipilimumab (Q4W) and 1 dose of BMS-986226 (Q12W).
Section 9.5 Pharmacokinetic and Immunogenicity Assessments.	PK and immunogenicity sample scheduling tables for Parts A, B1, B2, C1 and C2 were modified to support the revised study design. Also new PK and immunogenicity tables were added to support the sample collections for participants in Parts D and E.	The tables in this section were modified and added to support assessment for PK and immunogenicity in subjects enrolled in Parts A, B1, B2, C1, C2, D and E.
[redacted]		
Appendix 10 Statistical Methodology	Updated	Updated the BLRM-RD languages and related prior distributions for the combination phase to align with the protocol text.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 11: Prostate Cancer Working Group 3 (PCWG 3) Guidelines (with Modified Response Evaluation Criteria in Solid Tumors (RECIST) Criteria for Soft Tissue Lesion Assessment)	Added new appendix for PCWG 3.	Appendix added to support inclusion of PCWG 3 criteria for efficacy assessments.
All	Minor formatting and typographical corrections.	Made corrections for clarity and consistency within the document.

Overall Rationale for the Revised Protocol 01, 20-Jul-2017

The primary reason for this amendment is to incorporate the preliminary safety cohorts, intra-patient dose escalation, and revised inclusion/exclusion criteria for certain tumor types and to align the protocol with respect to these changes.

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-2: On-treatment Procedural Outline (CA021002); Table 2-5: Retreatment and Extended Treatment Procedural Outline for Preliminary Safety Cohorts and Parts A, B1, B2, and B3 Only (CA021002); Figure 5-1: Study Design Schematic; Section 5.1: Overall Design; Table 5.1-1:Study Cohorts per Part; Section 5.1.2: Treatment Phase; Section 5.1.2.1: Monotherapy Dose Escalation (Preliminary Safety Cohort and Part A); Section 5.1.2.1.1: Preliminary Safety Cohort; Section 5.1.2.1.2: Part A; Table 5.1-2: Dose Escalation (Preliminary Safety Cohort and Part A); Section 5.2; Number of Participants; Section 5.4.1: Rationale for BMS-986226 First-in-Human Dose (Preliminary Safety Cohort and Part A Monotherapy); Section 6.1: Inclusion Criteria; Table 7.1-1: Selection and Timing of Dose per Part; Section 7.1.1: Method of Treatment Assignment; Section 7.3: Dosage Modification; Section 7.3.1: Treatment Delay; Section 7.3.2: BMS-986226 Dose-limiting Toxicities; [redacted] Table 9.5-1:	A preliminary safety cohort of BMS-986226 administered at 2 mg and 8 mg every 4 weeks in a single participant with the possibility to offer intra-patient dose escalation was added to the protocol in all applicable areas, including procedural outlines, sampling schedules, inclusion criteria, study design, number of participants, rationale for study design, and rationale for dose.	Modified the starting monotherapy dose of BMS-986226 based on available in vitro and in vivo data.

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986226, Nivolumab, and Ipilimumab (Parts A, B1, B2, and B3); Table 9.5-4: Additional and Retreatment Cycles Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986226, Nivolumab, and Ipilimumab (Preliminary Safety Cohorts and Parts A, B1, B2, and B3 Only); [redacted] Section 10.1.1: Preliminary Safety Cohort and Dose Escalation (Part A)		
Section 6.1: Inclusion Criteria	The inclusion criteria were modified as follows: 2.c) Edited so that participants in the study should have progressed on, or been intolerant to, all standard therapies <u>Colorectal cancer (CRC)</u> 3.a.iv) Added: Participants must have incurable, metastatic disease (ie, patients with disease that is potentially curable by surgical resection are not eligible for treatment). <u>Non-small cell lung cancer (NSCLC)</u> 3.c.i.2) Edited: Platinum-based chemotherapy may have been given in the adjuvant, neoadjuvant, or chemoradiation setting. Participants with recurrent/metastatic disease that has recurred within 6 months of completing such treatment are considered eligible for study treatment. <u>Adenocarcinoma of the prostate (PRC)</u> 3.d.iii.a) Added: Participants with bone-only disease should have progression confirmed	Modified the eligibility criteria to the requirements for target disease characteristics and for participants with UCC, CRC, PRC, and NSCLC.

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	as per PCWG2 criteria and require confirmatory scans. 3.d.iv) Added: Participants must have received abiraterone and enzalutamide. Urothelial carcinoma (UCC) 3.e.iii) Removed: All participants must have measurable disease by CT or MRI per RECIST v1.1 criteria. 3.e.iv.1) Edited so that participants with UCC must have progression or recurrence after treatment with at least 1 platinum-containing chemotherapy regimen (if platinum eligible) but no more than 2 regimens for metastatic or surgically unresectable locally advanced urothelial cancer 3.e.v) Removed: Participants that have received more than 2 prior lines of chemotherapy must not have liver metastases.	
Section 7.3.2: BMS-986226 Dose-limiting Toxicities; Section 7.3.5: Exceptions to Permanent Discontinuation Criteria	1) The following dose limiting toxicity (DLT) criteria were edited/added: Isolated Grade 3 fever not associated with hemodynamic compromise (eg, hypotension, clinical or laboratory evidence of impaired end-organ perfusion) or with other symptoms of infusion-related reactions that returns to ≤Grade 1 with standard treatment in ≤ 1 hour Grade 3 infusion reaction that returns to Grade 1 in ≤ 1 hour 2) The following DLT criterion has been added: Grade 4 rash of any duration 3) A 4-week DLT observation period for the Preliminary Safety Cohort was added. 4) Consideration to permanently discontinue study therapy, on a case-by-case basis, for participants with any severe Grade 3 drug-related adverse event (AE) that recurs was added to Section 7.3.5.	Clarified specific requirements for DLT criteria, and modified ***the DLT requirements consistent with the introduction of preliminary safety cohort***.
Table 2-2: On-treatment Procedural Outline (CA021002); Section 3.3: Benefit/Risk Assessment; Table 7.1-1: Selection and Timing of Dose per Part	Instructions were added for participants to be observed for at least 60 minutes following completion of BMS-986226 infusion.	Extended the post-infusion observation period to monitor for potential infusion-related reactions.

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Table 2-2: On-treatment Procedural Outline (CA021002); Table 9.5-4: Additional and Retreatment Cycles Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986226, [redacted]	Edits were made to the procedural outline table, pharmacokinetic and immunogenicity sample schedule table [redacted] to clarify which procedures and sampling schedules are to be followed for additional cycles and that participants in Parts C1 and C2 are not eligible for additional cycles.	Updated the study procedural outline table to align with the description of additional cycles in *Section 5.1.4: Treatment with Additional Cycles beyond 24 Weeks.*
Table 2-2: On-treatment Procedural Outline (CA021002); Table 2-5: Retreatment and Extended Treatment Procedural Outline for Parts A, B1, B2, and B3 Only (CA021002); Table 9.5-4: Additional and Retreatment Cycles Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986226, [redacted]	Edits were made to the procedural outline table, pharmacokinetic and immunogenicity sampling schedule table [redacted] to clarify which procedures and sampling schedules are to be followed for retreatment cycles and that participants in Parts C1 and C2 are not eligible for extended treatment.	Updated the study procedural outline tables to align with the description of retreatment in *Section 5.1.5.1: Retreatment During Response Follow-up.*
Table 2-5: Retreatment and Extended Treatment Procedural Outline for Parts A, B1, B2, and B3	Edits were made to the procedural outline table to clarify which procedures are to be followed for extended treatment cycles and that participants in Parts C1 and C2 are not	Updated the study procedural outline table to align with the description of extended

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Only (CA021002); Table 2-6: Retreatment and Extended Treatment Follow-up Procedural Outline (CA021002); Section 5.1.6: Extended Treatment	eligible for extended treatment. Section 5.1.6 was added.	treatment in *Section 5.1.6: Extended Treatment.* Added *Section 5.1.6 Extended Treatment* to clarify this phase of treatment, which permits participants who have completed the maximum duration of study treatment to have an extended treatment up to an additional 24 weeks.
Table 9.5-3: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986226 (Parts C1 and C2)	Grade 3/4 hypersensitivity reaction sampling time point was added for pharmacokinetic (PK) and anti drug antibody (ADA) sampling in Parts C1 and C2.	Added PK and ADA sampling for Grade 3/4 hypersensitivity to better evaluate any drug-related AEs, infusion reactions, or hypersensitivity reactions.
Table 9.5-1: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986226, [redacted] Table 9.5-2: Pharmacokinetic and Immunogenicity Post-DLT Period Sampling Schedule for BMS-986226, [redacted] Table 9.5-3: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986226 (Parts C1 and C2); Table 9.5-4: Additional and Retreatment Cycles Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986226, [redacted]	Dose delay sample collection timepoints were added for PK and ADA sampling in the event that a dose is delayed.	Updated the PK and ADA sampling tables to align with procedural requirements described in the body of the protocol.
Table 2-3: Follow-up Procedural Outline (CA021002)	Tumor assessments were added for all participants in survival follow-up until beginning a new anti-cancer therapy.	Updated the study procedural outline table to align with the requirements for tumor assessments in *Section 5.1.3.3: Response Follow-up.*
Table 2-1: Screening Procedural Outline	Oxygen saturation procedure was removed from the assessments to be collected.	Updated the study procedural outline table to align with

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
(CA021002); Table 2-4: Retreatment Day 0 Procedural Outline (CA021002)		procedural requirements described in the body of the protocol.
All	Minor formatting and typographical corrections.	Made corrections for clarity and consistency within the document.