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A Phase 1/2 First-in-human Study of BMS-986258 Alone and in Combination with Nivolumab in Advanced Malignant Tumors

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CLINICAL PROTOCOL CA031002

A Phase 1/2 First-in-human Study of BMS-986258 Alone and in Combination with Nivolumab in Advanced Malignant Tumors

Protocol Amendment 07

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 07	16-Jun-2021	Included the option for participants in cohort A1 who received subcutaneous BMS-986258 on Cycle 1 Day 1 to be subsequently treated with intravenous BMS-986258 in combination with nivolumab (standard dose of 480 mg) at the dose of BMS-986258 that has been shown to be safe and tolerable in the dose escalation. Deleted the requirement for imaging results prior to enrollment in participants with anti-PD-(L)1-resistant RCC, CRC, NSCLC, and SCCHN in Part C, Part A NSCLC PD, and Part B NSCLC PD cohorts. Clarified the definition of the end of treatment (EOT) visit.
Protocol Amendment 06	23-Dec-2020	Included a new BMS-986258 formulation [redacted]. Additional corrections in numbering of exclusion criterion 3, male contraception, [redacted] were included. [redacted] for inclusion in NSCLC PD cohorts. Candidates to NSCLC PD cohorts will be allowed to be enrolled in dose escalation cohorts (Part A and B) if the [redacted] is not fulfilled.
Revised Protocol 05	22-Oct-2020	Defined initial dose for Part A1 of the study, BMS-986258 at 1200 mg co-administered subcutaneously with recombinant human hyaluronidase PH20 (rHuPH20), at Cycle 1 Day 1. All subsequent doses of BMS-986258 will be administered as monotherapy IV, Q4W twice per cycle, for up to twelve 8-week cycles (96 weeks). Instructions and infusion rate for SC administration. Inclusion of SARS-CoV-2 language and EPE v6 updates. Additional editorial changes and minor clarifications.
Revised Protocol 04	27-Apr-2020	Defined [redacted] dose levels (1600 mg and 2400 mg) in Part A (monotherapy) and [redacted] dose level (1600 mg) in Part B (combination with nivolumab 480 mg). Reduced the number of NSCLC PD cohorts in Part B. Updated imaging and biopsy language for clarity. Updated text throughout to bring in line with current BMS standards. Incorporated Administrative Letter 01.
Revised Protocol 03	14-Mar-2019	Added pharmacodynamic (PD) cohorts of participants with non-small cell lung cancer (NSCLC), selected for [redacted], to Parts A and B, changed the planned highest dose level of BMS-986258 from 800 mg to 1200 mg for both monotherapy (Part A and A1) and combination therapy (Part B) [redacted]. See Key Changes table
Administrative Letter 01	02-Nov-2018	Removed the unit of dose strength of rHupH20 from the protocol.
Revised Protocol 02	12-Jun-2018	Added subcutaneous dosing cohort; see Key Changes table

Document	Date of Issue	Summary of Change
Revised Protocol 01	08-Jan-2018	See Key Changes table
Original Protocol	01-Dec-2017	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 07:

The rationale for this amendment was to include the option for participants in cohort A1 who have received subcutaneous BMS-986258 on Cycle 1 Day 1 to be subsequently treated with intravenous BMS-986258 in combination with nivolumab (standard dose of 480 mg) at the dose of BMS-986258 that has been shown to be safe and tolerable in the dose escalation.

In addition, in the inclusion criteria for participants with anti-PD-(L)1-resistant tumors, the documentation of the radiological progression from prior anti-PD-(L)1-containing regimen by submission of available scans before and after anti-PD-(L)1 treatment has been deleted from eligibility criteria.

The definition of end of treatment (EOT) visit has been further clarified.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07

Section Number & Title	Description of Change	Brief Rationale
Section 1 - Synopsis	Revised the synopsis to incorporate all changes described below	Updated to align with study protocol changes
[redacted] Section 5.1.4.1 -Safety Follow-up Period; [redacted]	Clarified definition of EOT visit	Defined EOT visit as the visit in which the participant receives the last dose of study treatment
[redacted]		
Section 3.3.3 - BMS-986258 Starting Dose for Part A1 (Monotherapy SC); Section 5.1.3 - Treatment Period; Section 5.4.2 - Rationale for Subcutaneous Administration of BMS-986258 (Part A1); Section 7.1 - Treatments Administered	Added the option for participants in cohort A1 to switch to combination therapy after receiving subcutaneous BMS-986258 on Cycle 1 Day 1	To give participants in cohort A1 the option to be treated in combination with nivolumab at the maximum tolerable dose of BMS-986258 observed in Part B
Section 3.3.6 - Safety Monitoring on Study Therapy	Added clarification that non-live COVID-19 vaccination is considered a simple concomitant medication within the study	To align with current BMS COVID-19 guidelines
Section 4 - Objectives and Endpoints	Revised [redacted]	To align with current BMS COVID-19 guidelines

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted] Section 5 - Study Design; Section 9.5 - Pharmacokinetics; [redacted]	[redacted] Table 9.5-3, [redacted]	Updated to align with study protocol changes
Section 6.1- Inclusion Criteria	Deleted documentation of the radiological progression from prior anti-PD-(L)1-containing regimen by submission of available scans before and after anti-PD-(L)1 treatment from inclusion criteria 2i(i[3]) and 2i(i[4]) (participants with anti-PD-[L]1-resistant RCC, CRC, NSCLC, and SCCHN in Part C, Part A NSCLC PD, and Part B NSCLC PD cohorts only)	Submission of imaging results from treatments prior to the clinical study is unfeasible
Section 6.2 - Exclusion Criteria	Clarified exclusion criteria 3e(xiv) related to previous receipt of SARS-CoV-2 vaccines	To align with current BMS COVID-19 guidelines
Section 7.3 - Blinding	Deleted text related to obtaining treatment assignment codes	Not relevant to open-label studies
Section 7.7.1- Prohibited and/or Restricted Treatments; [redacted]	Updated and clarified text related to receipt of authorized or approved SARS-CoV-2 vaccines while continuing on study [redacted]	To align with current BMS COVID-19 guidelines
Table 9.5-1: Pharmacokinetic Parameters	Corrected abbreviations and definitions for AI_AUC and T-HALFeff_AUC	Corrected for consistency
Section 10.3 - Statistical Analyses	Clarified that results will be presented by study part; participants who cross over from the SC cohort (A1) to IV monotherapy or combination treatment will be tabulated separately	To clarify statistical analysis of participants in cohort A1 who subsequently receive combination therapy
Appendix 2 - Study Governance Considerations	Added text regarding monitoring details and dissemination of clinical study data	Updated for consistency with current BMS protocol standards and policies
Entire document	Made additional corrections and editorial or formatting changes where appropriate	Added to provide clarity

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1 SYNOPSIS

Protocol Title: A Phase 1/2 First-in-human Study of BMS-986258 Alone and in Combination with Nivolumab in Advanced Malignant Tumors

Study Phase: 1/2

Rationale: Patients with metastatic or refractory solid tumors have very poor prognosis. The unmet need resides in the lack of effective treatments to deliver long-term survival, hence the need to test compounds that have novel mechanisms of action in clinical studies. T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) is expressed mostly on monocytes, macrophages, dendritic cells, and natural killer cells, as well as in endothelial cells; little expression of TIM-3 is detected in peripheral T cells in the majority of normal healthy donors or cancer patients, but it can be induced upon T-cell activation. Functional anti-TIM-3 monoclonal antibodies (mAbs), including BMS-986258 and the mouse surrogate anti-TIM-3 antibodies, all bind to the phosphatidylserine (PS)-binding loops of TIM-3, suggesting that PS might be a functional ligand of TIM-3 either by itself or associated with another unidentified molecule in dampening T cell responses. TIM-3 expression marks dysfunctional or exhausted cluster of differentiation 8 positive (CD8+) T cells in several cancer types. In tumor infiltrating lymphocytes (TIL) from patients with advanced metastatic melanoma, non-small cell lung cancer (NSCLC), and follicular B cell non-Hodgkin lymphoma, in vitro TIM-3 blockade improved T-cell responses with TIM-3/programmed cell death-1 (PD-1) co-blockade showing even greater responses than single agents. TIM-3 might also work as a mechanism of resistance to anti-PD-1 therapy, as TIM-3 expression was found to be upregulated in 2 lung cancer patients who developed secondary resistance to anti-PD-1 mAb treatment. Thus, an antagonistic antibody such as BMS-986258 that blocks TIM-3-mediated inhibitory signals in T cells and, perhaps, in other immune subsets as well, might provide therapeutic benefit to cancer patients.

Study Population:

Participants must be at least 18 years old and have histologic confirmation of a solid tumor that is advanced (metastatic, recurrent, and/or unresectable) with measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The tumor types to be evaluated in participants are NSCLC, renal cell carcinoma (RCC), colorectal cancer (CRC), triple negative breast cancer (TNBC), and squamous cell carcinoma of the head and neck (SCCHN). [redacted]

Objectives and Endpoints:

Objectives	Endpoints
Primary To assess the safety, tolerability, and to determine MTD or MAAD and RP2D of BMS-986258 administered as monotherapy and in combination with nivolumab in participants with select advanced solid tumors.	Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and death.
Secondary 1. To assess the preliminary anti-tumor activity of BMS-986258 as monotherapy and in combination with nivolumab in advanced solid tumors. 2. To explore the PK of BMS-986258 when administered IV as monotherapy and in combination with nivolumab. 3. To characterize the immunogenicity of BMS-986258 as monotherapy and in combination with nivolumab.	1. ORR, mDOR, and PFS rate at 6, 9, and 12 months. 2. Summary measures of PK parameters of BMS-986258 after monotherapy and combination treatment. 3. Incidence of ADA to BMS-986258.

[redacted]

Abbreviations: ADA, anti-drug antibody; AE, adverse event; BMS, Bristol-Myers Squibb; [redacted] DLT, dose-limiting toxicity; [redacted]; IV, intravenous; MAAD, maximum administered dose; mDOR, median duration of response; MTD, maximum tolerated dose; [redacted]; ORR: overall response rate; [redacted]; PFS, progression-free survival; PK, pharmacokinetics; [redacted]

[redacted]; RP2D, recommended Phase 2 dose; SAE, serious adverse event; [redacted]

Overall Design:

This is a Phase 1/2, open-label, non-randomized study of BMS-986258, administered as a single agent and in combination with nivolumab, in participants with select advanced solid tumors. The study is comprised of 4 parts: Part A (dose escalation of BMS-986258 monotherapy), Part A1 (subcutaneous [SC] BMS-986258 monotherapy), Part B (dose escalation of BMS-986258 in combination with nivolumab), and then Part C (BMS-986258 in combination with nivolumab cohort expansion). Data obtained from the analysis of the SC dose(s) in Part A1 may be used to inform route of administration and dose selection in Part C.

[redacted]

All participants will complete up to 4 study periods: Screening [redacted], Treatment for up to 12 cycles (56 days/cycle), Safety Follow-up (100 days), and Survival Follow-up [redacted]. The duration of the study will be approximately 4 years. Pre-screening for participants in Part A and B NSCLC PD cohorts will be completed prior to the screening period. All on-study images will be submitted to a central imaging vendor for collection. At the Sponsor's discretion, scans may undergo blinded independent central review. Sites should be trained prior to scanning the first study participant. Image acquisition guidelines and submission process will be outlined in the CA031002 Imaging Manual to be provided by the core lab.

Number of Participants:

The approximate number of participants will be up to [redacted] as shown below.

- Part A Monotherapy Escalation: The total sample size is up to approximately [redacted] participants including [redacted] to assess the maximum tolerated dose (MTD)/ maximum administered dose (MAAD) and an additional [redacted] in [redacted] NSCLC PD cohorts.
- Part A1: Subcutaneous (SC) Dose: The total sample size is up to approximately [redacted] participants to evaluate up to [redacted].

- Part B Combination Escalation: The total sample size is up to approximately [redacted] participants including [redacted] participants to assess the MTD/MAAD in combination and [redacted] in [redacted] NSCLC PD cohorts.
- Part C Cohort Expansion: Approximately up to [redacted] participants will be treated in each of the 5 tumor cohorts (up to a total of [redacted] across tumors).

Treatment Arms and Duration:

- The Dose Escalation Phase, where the dose level of BMS-986258 administered intravenously (IV) as monotherapy (Part A) or in combination with nivolumab (Part B) will be escalated to determine the MTD or MAAD.
  - Part A, BMS-986258 Monotherapy Dose Escalation: Dosing Q4W up to twelve 8-week cycles, administered as monotherapy; escalations will be based on dose-limiting toxicities, using a Bayesian Logistic Regression Model (BLRM) employing the escalation with overdose control principle.
  - Part A1 will be independent from the other treatment arms where BMS-986258 will be co-administered SC with recombinant human hyaluronidase PH20 (rHuPH20) for the first dose in Cycle 1. All subsequent doses of BMS-986258 will be administered as monotherapy IV, Q4W twice per cycle, for up to twelve 8-week cycles (96 weeks). Alternatively, participants in cohort A1 who have received SC BMS-986258 on Cycle 1 Day 1 will be offered the option to receive subsequent IV combination therapy of BMS-986258 with nivolumab (480 mg) at the highest dose of BMS-986258 that has been shown to be safe and tolerable in the dose escalation (Part B). Treatment will be given Q4W twice per cycle, for up to twelve 8-week cycles (96 weeks). The dose selected for Part A1 will not exceed a dose determined to be safe and tolerable in Part A. Once initiated Part A1 may be run in parallel with Part A and B.
  - Part B, BMS-986258 in Combination with Nivolumab Dose Escalation: Dosing Q4W, administered as combination up to twelve 8-week cycles, with escalation decisions based on dose-limiting toxicities, using a BLRM copula employing the escalation with overdose control principle.
  - During dose escalation, all the eligible participants will be initially assigned to Part A until the decision is made to escalate to the third dose cohort. Subsequently, treatment in Part B will be initiated, and dose escalation in the 2 parts will occur in parallel.
- Expansion Phase (Part C): Dosing Q4W, administered as combination up to twelve 8-week cycles. The dose(s) selected for Part C will not exceed the MTD (or MAAD if no MTD is determined) in Part B, and may incorporate assessment of other data including toxicities, PK, and PD data from Parts A and B.

Study Treatment:

Study Drug for CA031002		
Medication	**Potency**	**IP/Non-IP**
BMS-986258	[redacted]	IP
BMS-986258		IP
Nivolumab	10 mg/mL	IP
ENHANZE® Drug Product (rHuPH20)[a]	1 mg/mL	IP

Abbreviations: IP: investigational product; rHuPH20, recombinant human hyaluronidase PH20.

[a] ENHANZE® (rHuPH20) is referred to as rHuPH20 in the protocol

[redacted]

[redacted]

Pre-Screening for PD Cohort only (NSCLC)

Participants in Parts A and B NSCLC PD cohorts only must have tumor-associated [redacted] as measured by a [redacted] prior to completion of the remaining screening procedures. A participant is considered enrolled only when a main protocol-specific informed consent is signed. If allowed by institutional practices, sites are required to use a pre-screening consent for the [redacted] staining to evaluate [redacted] from biopsy samples. Participants must have a lesion that can be biopsied at an acceptable clinical risk as judged by the Investigator, in order to be eligible for the NSCLC PD cohorts.

Participants in Part A and B NSCLC PD cohorts will be allowed to sign the main ICF and continue with other screening procedures while the [redacted] result is available for the determination of participant eligibility in NSCLC PD cohorts.

Screening: The screening period will be [redacted] and begins by signing the main protocol informed consent form. Participants meeting all eligibility criteria will be enrolled in the study using an Interactive Response Technology according to the part and treatment arm availability.

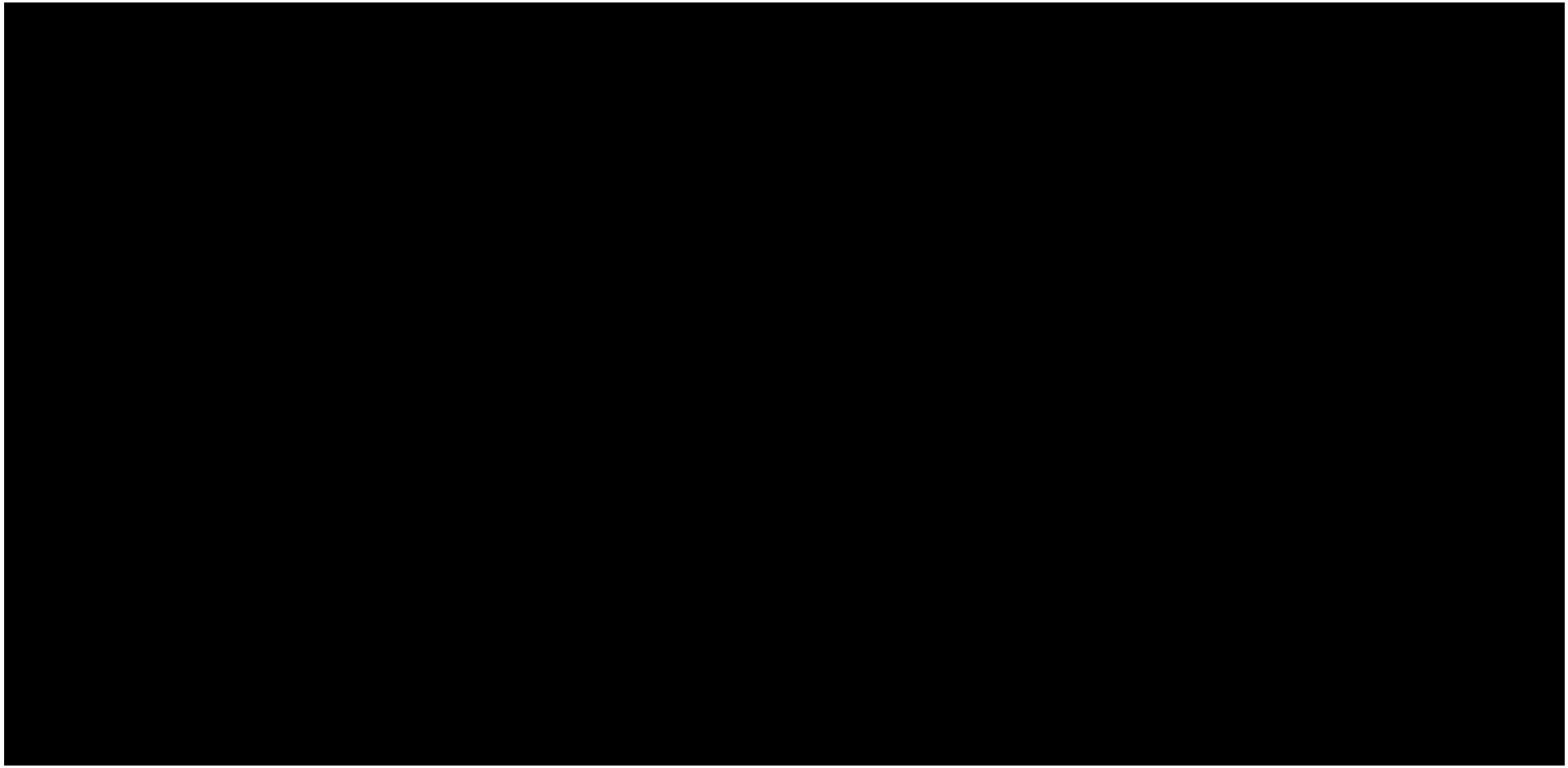
Treatment: The dosing regimen of BMS-986258 is Q4W. [redacted] Refer to Section 5.1 and [redacted] of the protocol. All participants will be treated for up to twelve 8-week treatment cycles, totaling 96 weeks. Continuous safety evaluation and tumor assessment (every 8 weeks) will guide the decision to treat a participant with additional cycles of study therapy if the participant has confirmed clinical benefit.

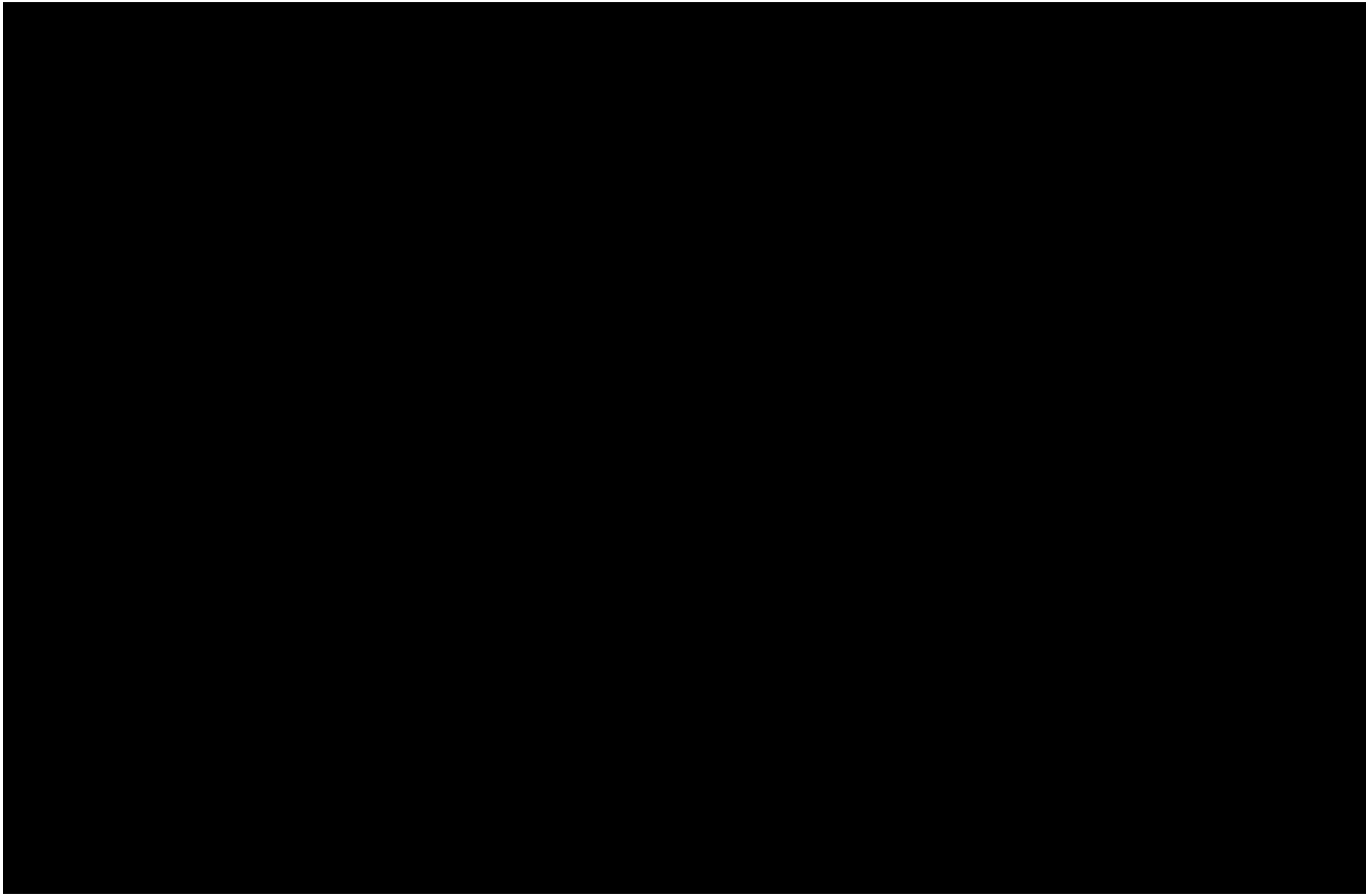
- In Part A (BMS-986258 Monotherapy Escalation), BMS-986258 will be administered Q4W. BMS-986258 will be infused according to dosing and infusion times in Table 7.1-1. Shorter infusion times may be used for initial dose panels and longer infusion times will be used for the higher dose panels. In Part A1 (BMS-986258 SC for first dose), BMS-986258 will be co-administered with rHuPH20 for the first dose of BMS-986258 in Cycle 1. All subsequent doses will be administered as monotherapy IV Q4W. Alternatively, participants in cohort A1 who have received SC BMS-986258 on Cycle 1 Day 1 will be offered the option to receive subsequent IV combination therapy of BMS-986258 with nivolumab (480 mg) at the highest dose of BMS-986258 that has been shown to be safe and tolerable in the dose escalation (Part B). Treatment will be given Q4W twice per cycle, for up to twelve 8-week cycles (96 weeks). [redacted]. Please refer to the Pharmacy Manual for dose-specific infusion times and sites of SC administration. BMS-986258 will require a [redacted] observation period following the completion of the infusion for the first 2 doses for each participant.
- In Part B (BMS-986258 in Combination with Nivolumab Escalation) and Part C (BMS-986258 in Combination with Nivolumab Cohort Expansion), nivolumab will be administered Q4W and will be infused over 30 minutes. When both BMS-986258 and nivolumab are given in combination, nivolumab will be given first, over 30 minutes, followed by a [redacted] observation period then BMS-986258, over approximately [redacted]. BMS-986258 infusion will begin at least [redacted] after completion of the infusion of nivolumab. BMS-986258 infusions will require a [redacted] observation period following the completion of the infusion for the first 2 doses for each participant. Shorter infusion times for BMS-986258 may be used for initial dose panels and longer infusion times [redacted] will be used for the higher dose panels. [redacted]. Please refer to the Pharmacy Manual for dose-specific infusion times and administration details for nivolumab and BMS-986258.
- Tumor progression and response endpoints will be assessed using RECIST v1.1 criteria for solid tumors.

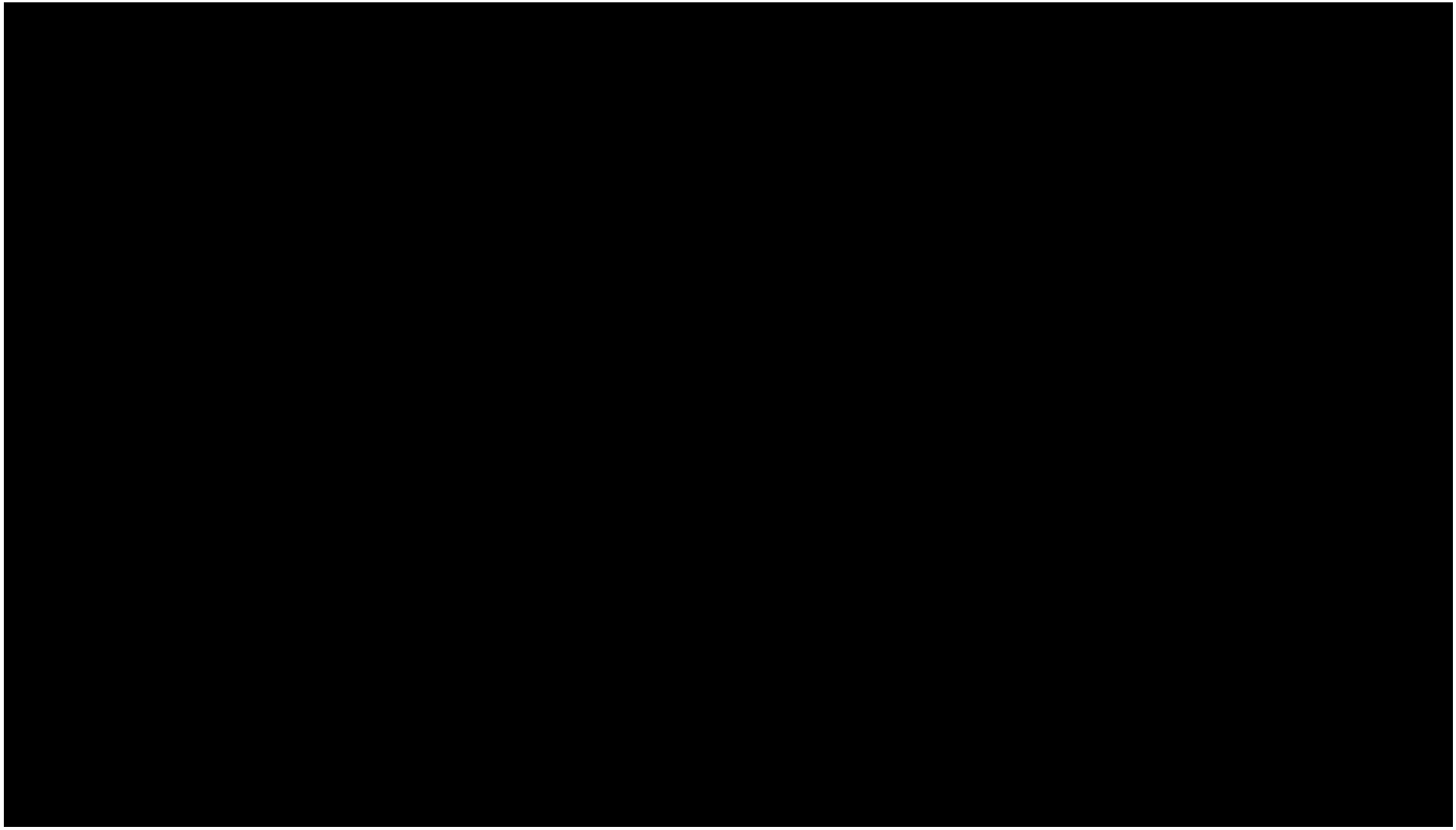
Follow-up:

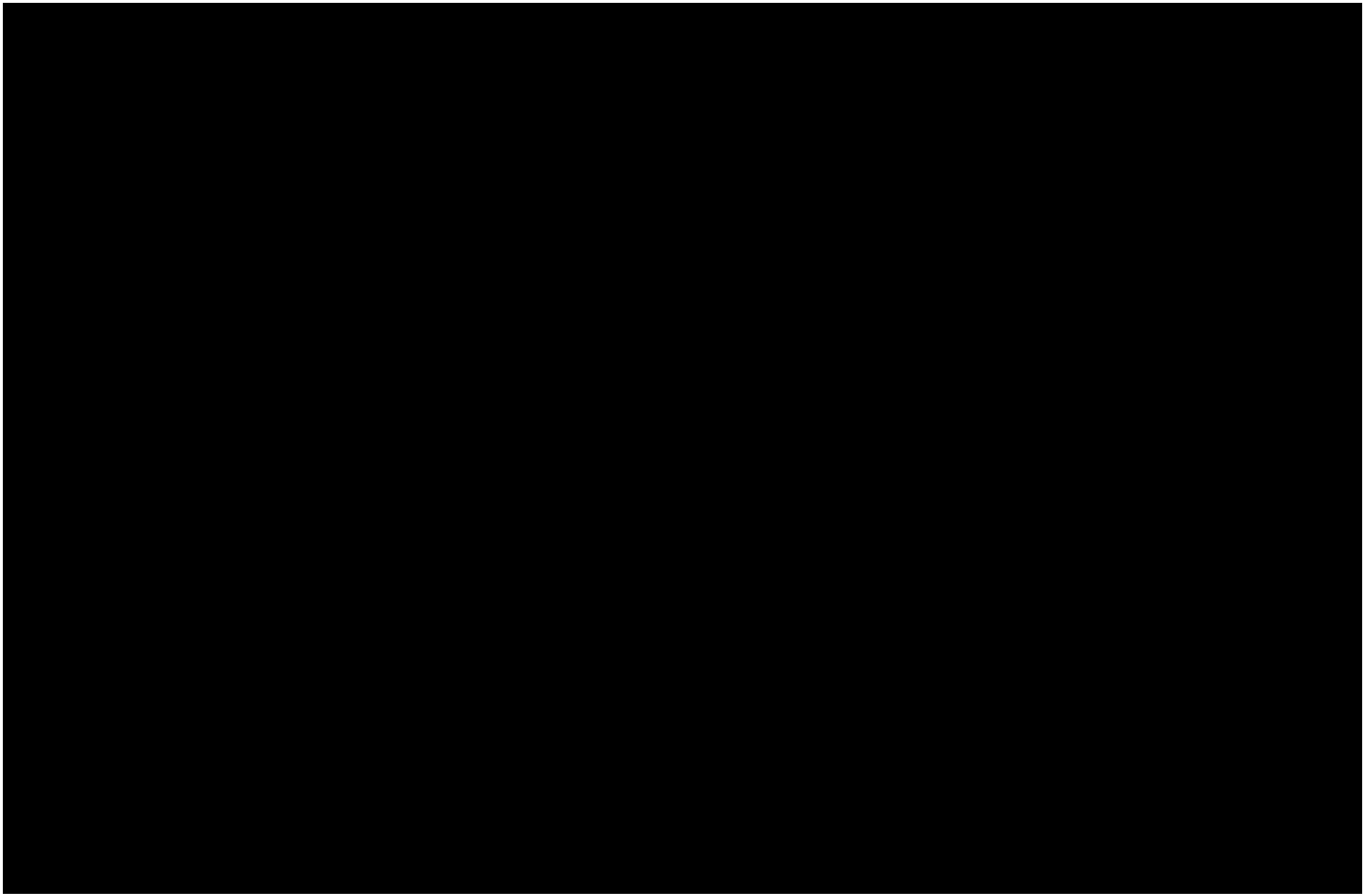
- Safety Follow-up Period:
  - Upon completion of study therapy (or up to a maximum of 96 weeks, if applicable), or once the participant has received the last administration of any study treatment (ie, at end of treatment), all participants will enter a safety follow-up period for 100 days.
  - For participants who complete all scheduled cycles of therapy, the end of treatment (EOT) visit will be the same visit as the last scheduled and completed on-treatment visit and will be the start of the safety follow-up period. 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 will not need to be repeated. Accordingly, for these participants, this visit will be considered the start of the safety follow-up period.
- Survival Follow-up Period:
  - In parallel with the safety follow-up period, all participants will continue on the survival follow-up period. Participants will be followed up for survival at each Safety Follow-up

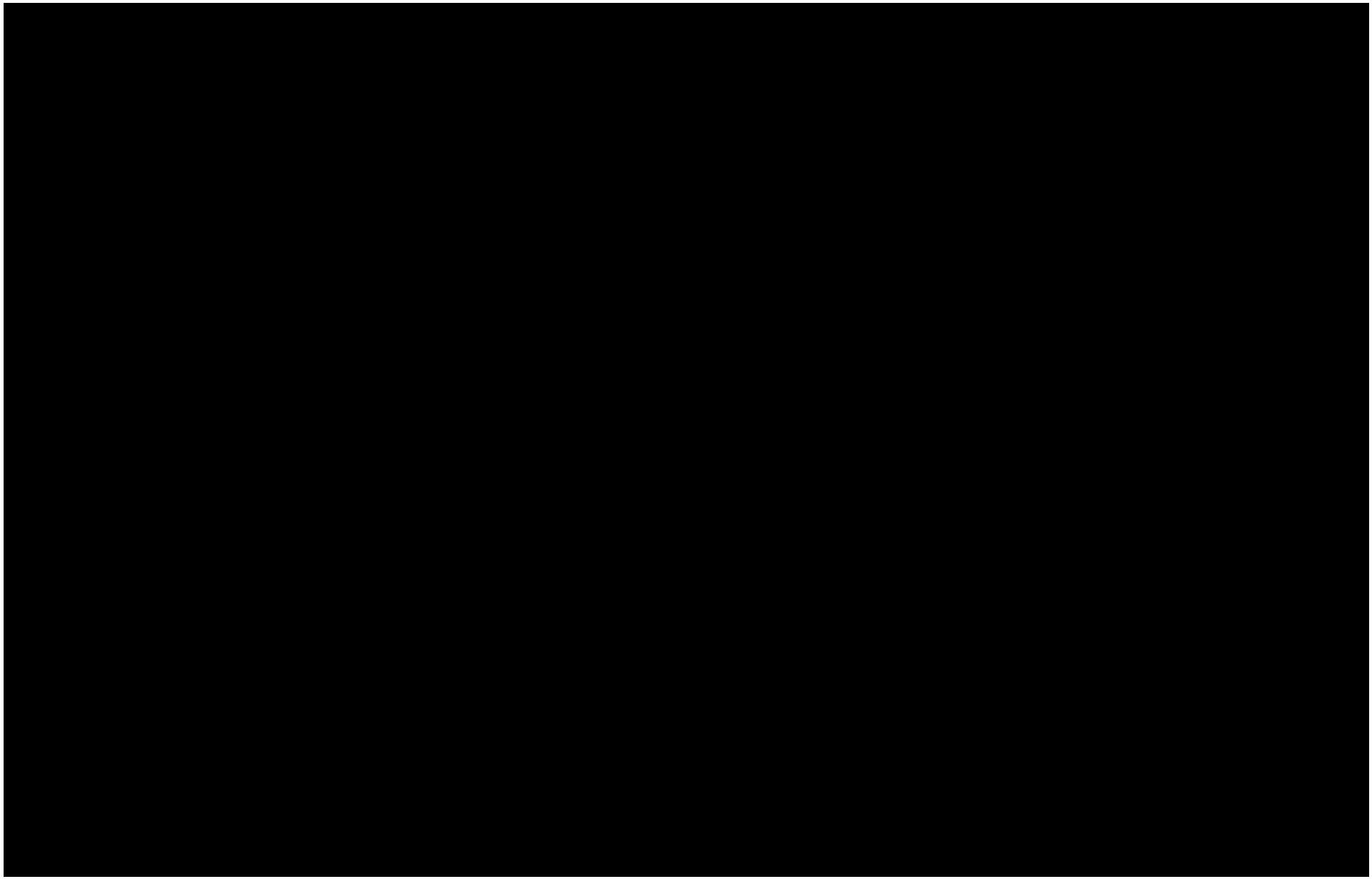
visit and then by telephone [redacted], loss to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first. Subsequent therapies will also be recorded in this survival follow-up period.

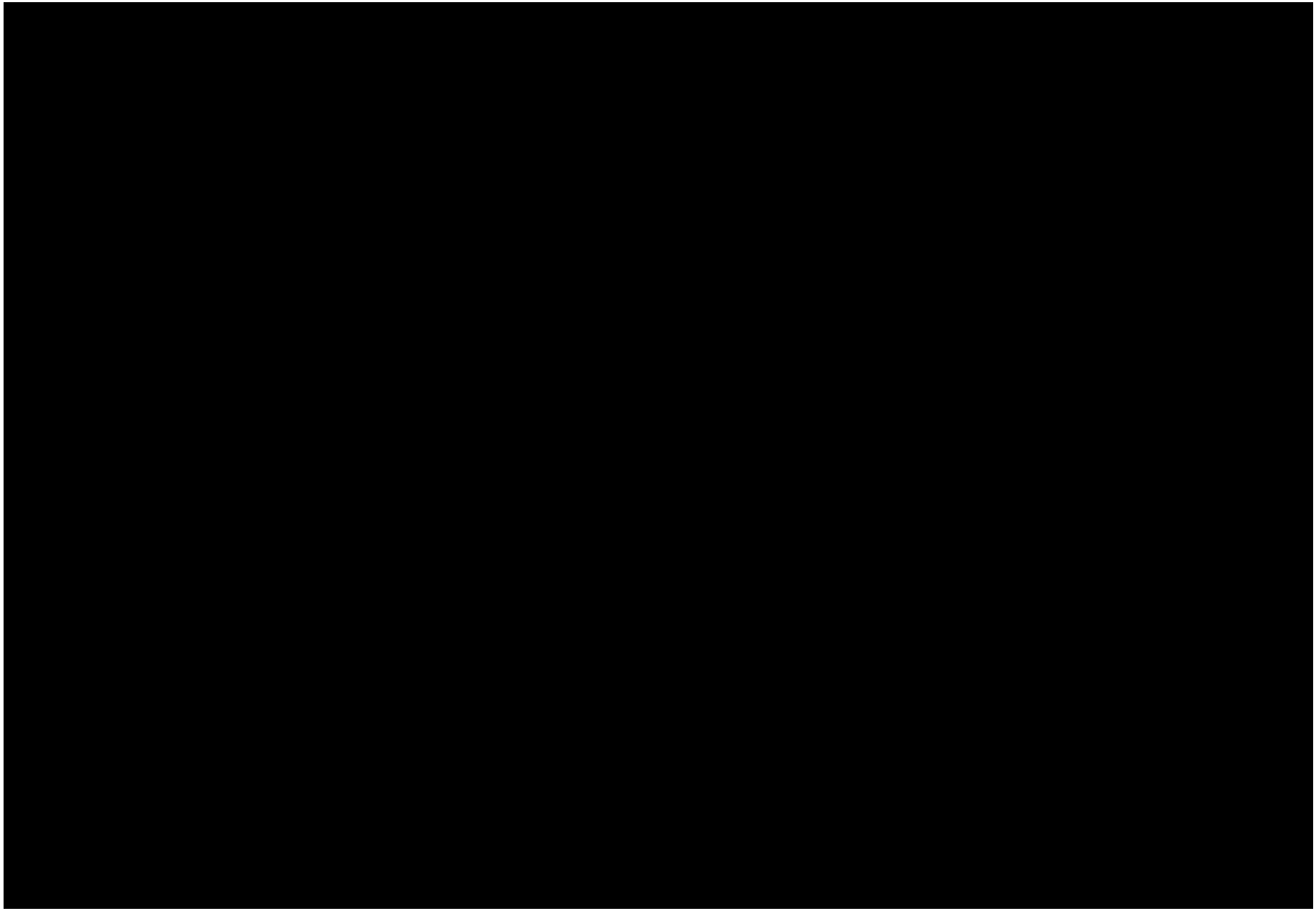












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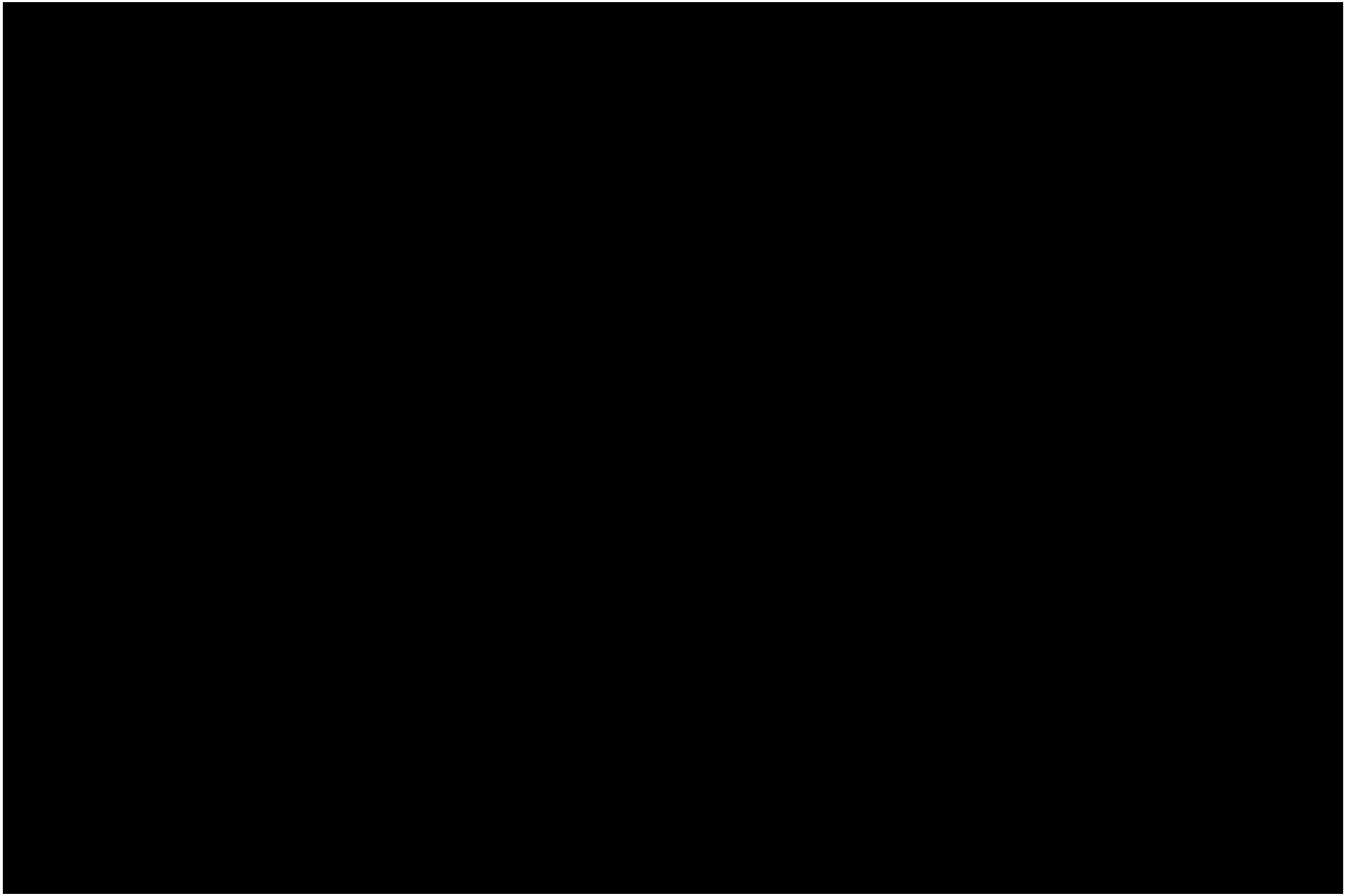

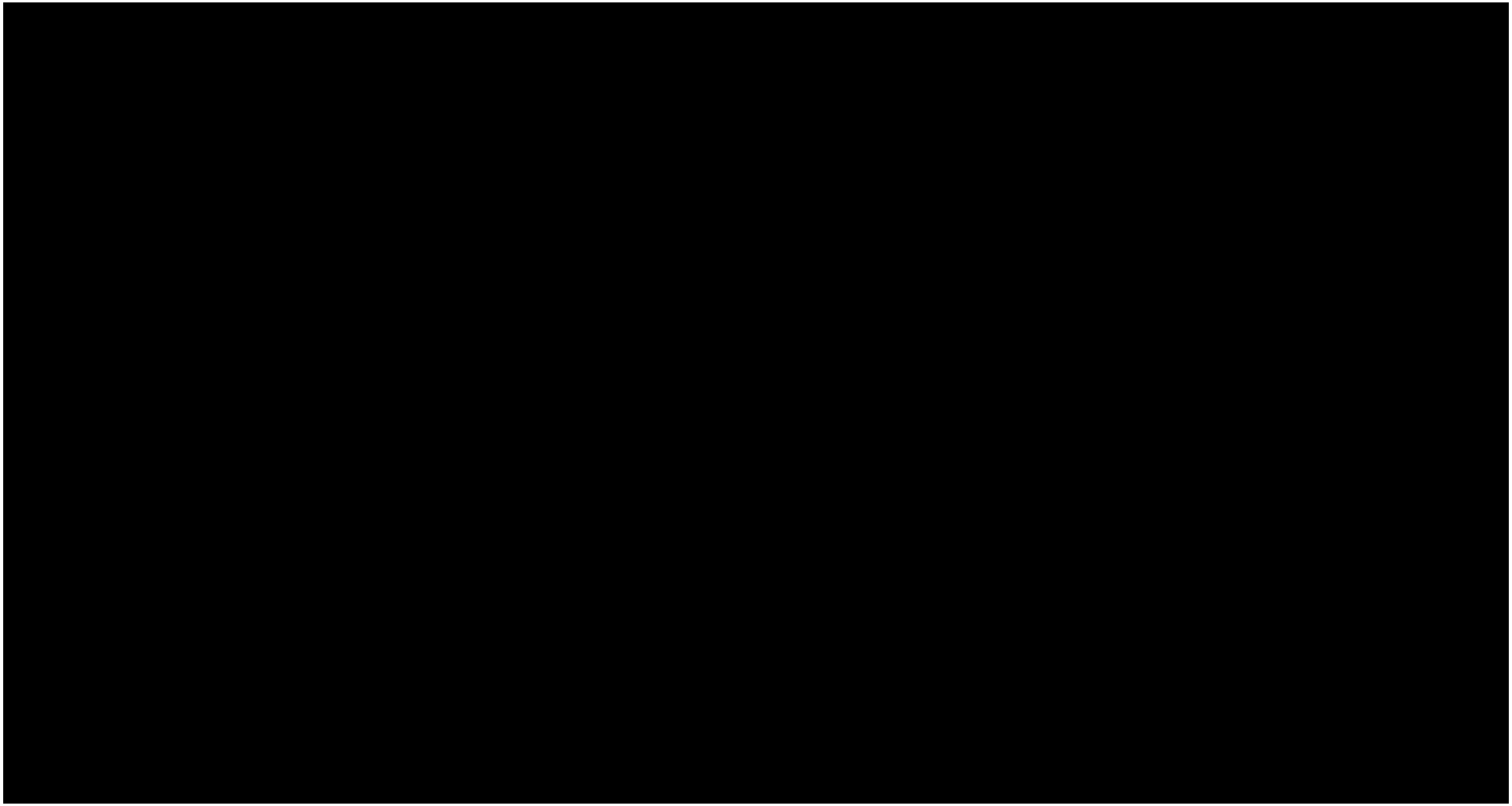

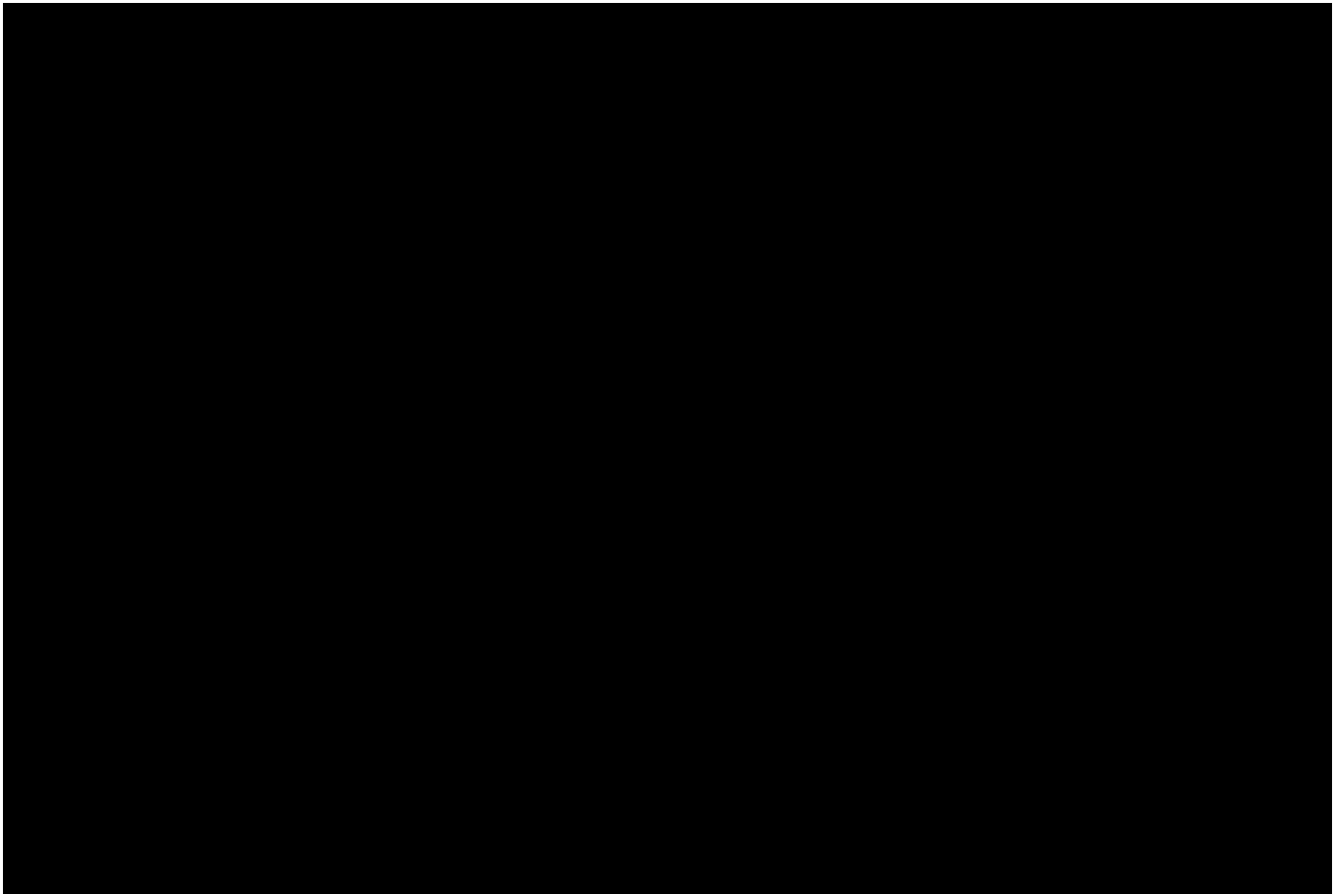

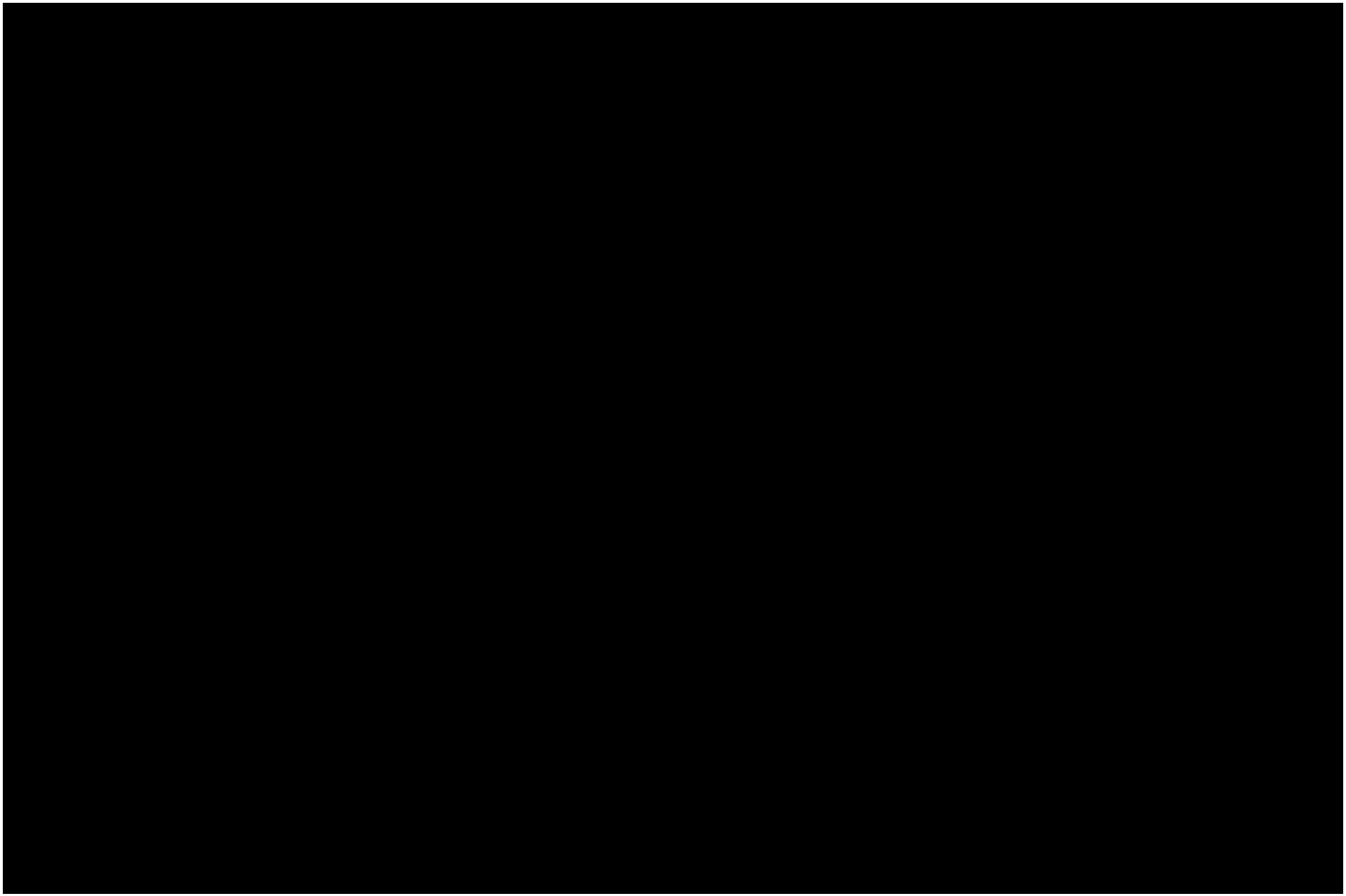

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3 INTRODUCTION

T-cell immunoglobulin (Ig) and mucin-domain containing-3 (TIM-3) is a protein that in humans is encoded by the hepatitis A virus cellular receptor 2 (HAVCR2) gene and works as an inhibitory receptor that suppresses activation and functional responses in T cells. TIM-3 is often co-expressed with programmed cell death 1 (PD-1) in cluster of differentiation 8 (CD8)+ T cells in different types of cancer. BMS-986258 is an antagonistic antibody to TIM-3 and its use as monotherapy or in combination with nivolumab will be explored in the CA031002 study, a Phase 1/2, first-in-human (FIH), ascending multiple-dose study, in humans with advanced/metastatic solid tumors – non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), colorectal cancer (CRC), triple negative breast cancer (TNBC), squamous cell carcinoma of the head and neck (SCCHN). This study will evaluate the safety profile, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of intravenous (IV) doses of BMS-986258 administered every 4 weeks (Q4W) as monotherapy and in combination with nivolumab in advanced solid tumors and is expected to determine the maximum tolerated dose (MTD)/maximum administered dose (MAAD) or an alternate dose(s) of BMS-986258 to be used in future trials. In addition, the study will evaluate the preliminary efficacy of BMS-986258 in combination with nivolumab in the following disease-restricted populations, as follows: RCC participants who received and progressed on or after anti-PD-1 therapy (combined or not with other immuno-oncology [I-O] agents); microsatellite instability-high (MSI-H) CRC participants who received and progressed on or after-anti-PD-1 therapy, and microsatellite stability (MSS) CRC participants; NSCLC participants who received and progressed on or after-anti-PD-1 therapy; SCCHN subjects who received and progressed on or after anti-PD-1 therapy; and participants with recurrent or metastatic TNBC.

3.1 Study Rationale

Patients with metastatic or refractory solid tumors have very poor prognosis.[1] Despite advances in multimodal therapy, increases in overall survival (OS) in this patient population have been limited. The unmet need resides in the lack of effective treatments to deliver long-term survival, hence the need to test compounds that have novel mechanisms of action in clinical studies.

The idea of harnessing the immune system to battle cancer is not new; in fact, it dates back to the 19th century with William Coley and his bacterial inoculations of several types of tumor, starting with sarcoma.[2] One hundred and twenty years later, immunotherapy was named breakthrough of the year by the Science Journal in 2013, not so much for the number of patients who had been successfully treated at that point, but for "a sense of paradigms shifting."[3] Immuno-oncology cancer drugs are able to alter the unfavorable balance between positive (co-stimulatory) and negative (co-inhibitory) T-cell surface molecules exploited by the tumors to escape immune surveillance.[4] The treatment focus, then, changes from targeting tumor cells to counteracting the resistance mechanisms developed by tumors, therefore enabling the endogenous immune system to reject tumors.

The most extensively studied immune-modulating molecules are agents blocking checkpoint molecules, such as PD-1 and cytotoxic T lymphocyte–associated antigen 4 (CTLA-4). Inhibition of these negative regulatory receptors, referred to as immune checkpoint blockade, results in the

enhanced activation of T-cell responses and potent antitumor activity in preclinical models. Trials with CTLA-4 blockade provided the first clinical evidence of improvement in OS with immune modulatory anticancer therapy in patients with metastatic melanoma.[5,6] Shortly after that, objective responses were obtained for NSCLC, melanoma, and RCC with anti-PD-1 antibody.[7] Moreover, metastatic melanoma patients treated with the combination of ipilimumab and an anti-PD-1 antibody (nivolumab) achieved an unprecedented 53% response rate and prolonged responses,[8] which demonstrated the potential of combination therapy. More recently, the benefit of combination therapy was also demonstrated in RCC.[9]

TIM-3 is a [redacted]. TIM-3 is expressed mostly on monocytes, macrophages, dendritic cells (DC) and natural killer (NK) cells, as well as in endothelial cells; little expression of TIM-3 is detected in peripheral T cells in the majority of normal healthy donors or cancer patients, but it can be induced upon T-cell activation.[10,11,12] Multiple ligands have been proposed for TIM-3 and include the following: galectin-9, phosphatidylserine (PS), high mobility group B1, and carcinoembryonic antigen-related cell adhesion molecule 1.[13] Functional anti-TIM-3 monoclonal antibodies (mAbs), including BMS-986258 and the mouse surrogate anti-TIM-3 antibodies, all bind to the PS-binding loops of TIM-3, suggesting that PS might be a functional ligand of TIM-3 either by itself or associated with another unidentified molecule in dampening T-cell responses (internal BMS data).

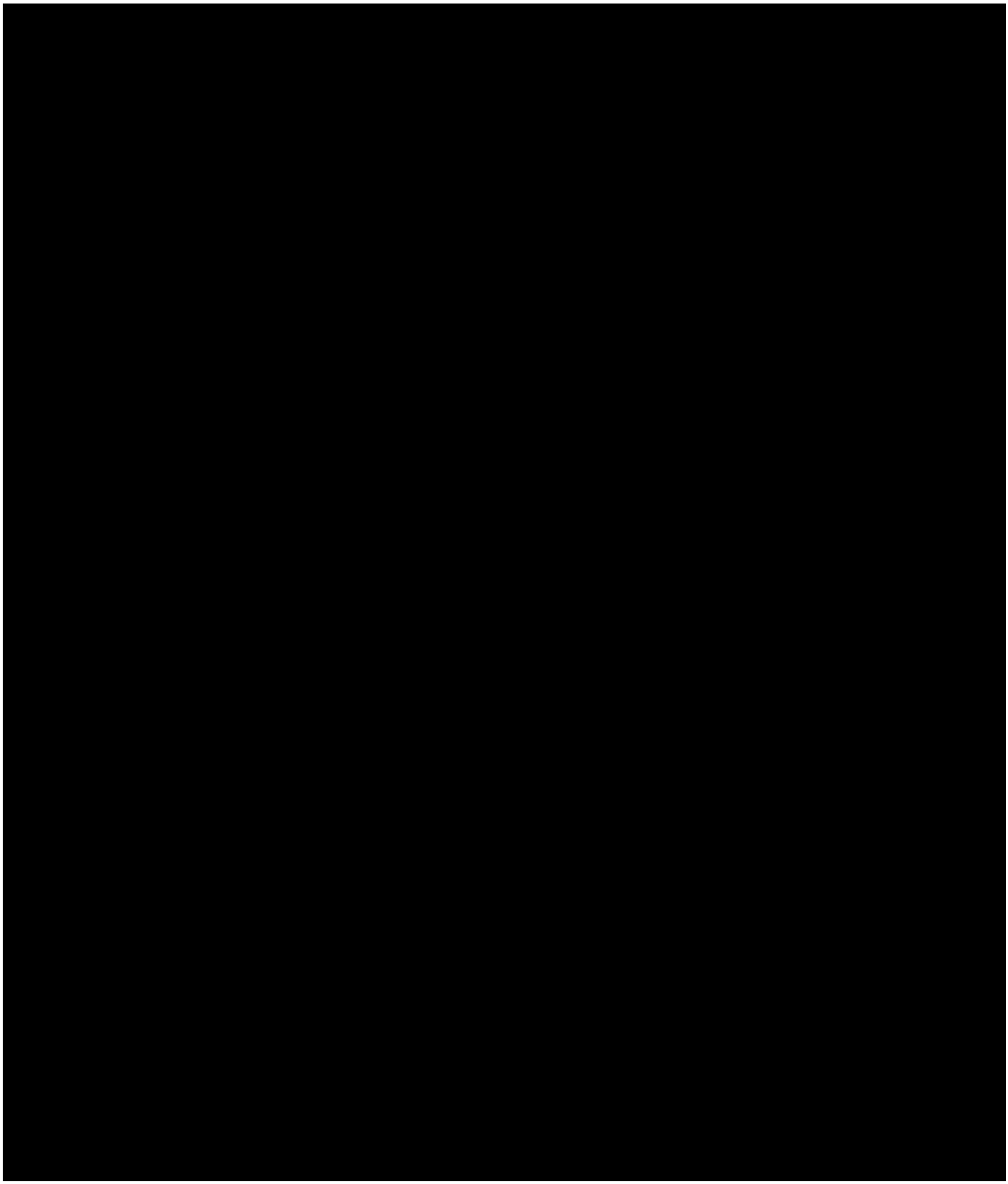
During chronic viral infections in mouse and humans, TIM-3 is expressed on dysfunctional or exhausted CD8+ T cells. Co-blockade of TIM-3 and PD-1 pathways results in greater restoration of T-cell responses in chronic viral infections than restoration of T-cell responses by PD-1 blockade alone.[14,15,16,17] TIM-3 expression also marks dysfunctional or exhausted CD8+ T cells in several cancer types. In tumor-infiltrating lymphocytes (TIL) from patients with advanced metastatic melanoma,[18] NSCLC[19] and follicular B cell non-Hodgkin lymphoma,[20] in vitro TIM-3 blockade improved T-cell responses with TIM-3/PD-1 co-blockade showing even greater responses than single agents. TIM-3 might also work as a mechanism of resistance to anti-PD-1 therapy, as TIM-3 expression was found to be upregulated in 2 lung cancer patients who developed secondary resistance to anti-PD-1 mAb treatment.[21]

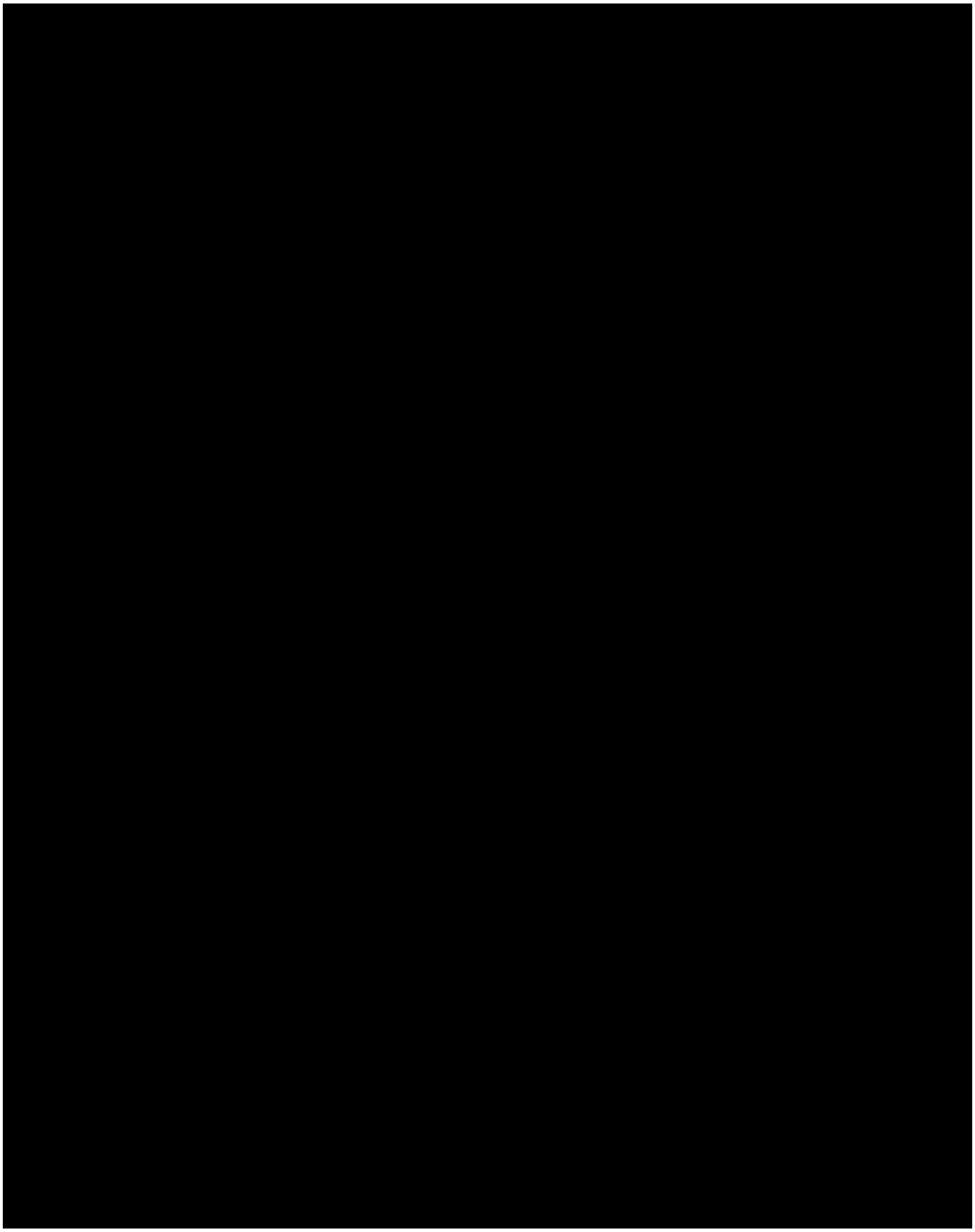
Thus, an antagonistic antibody such as BMS-986258 that blocks TIM-3-mediated inhibitory signals in T cells and, perhaps, in other immune subsets as well, might provide therapeutic benefit to cancer patients. Moreover, based on recent emerging clinical evidence of increased response rates with combination therapies, the association of BMS-986258 to anti-PD-1 may lead to greater depth of response and OS in advanced or metastatic solid tumors.

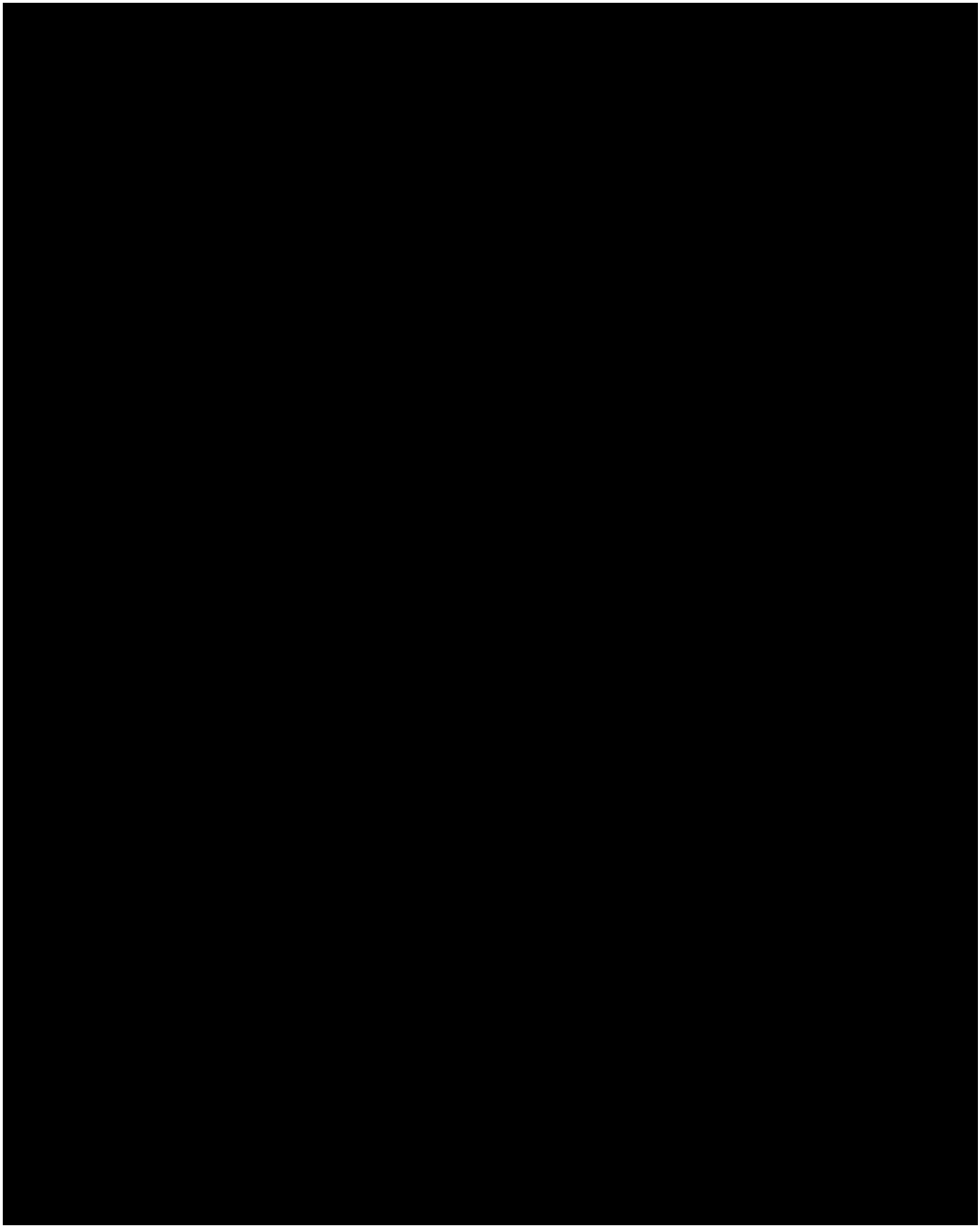
3.2 Background

A detailed description of BMS-986258 chemistry, pharmacology, and toxicology is provided in the BMS-986258 Investigator's Brochure (IB).[12]

3.2.1 BMS-986258







[redacted]

3.2.2 Nivolumab

Nivolumab is a fully human, IgG4 (kappa) isotype mAb that binds to PD-1 with nanomolar affinity (dissociation constant, 3.06 nM) and a high degree of specificity. Nivolumab blocks binding of

PD-1 to its ligands programmed death ligand 1 (PD-L1) and programmed death ligand 2. Nonclinical in vitro testing of nivolumab demonstrated that binding to PD-1 results in enhanced T-cell proliferation and release of IFN-γ in vitro in mixed lymphocyte reaction (MLR) and cytomegalovirus (CMV) assays.

The nonclinical safety of nivolumab was evaluated in a comprehensive toxicology program in mice and monkeys and was submitted as part of Biologics License Application 125527.[30] Details of the in vitro and in vivo nonclinical pharmacology studies conducted to support the development of nivolumab can be found in Section 4.1 of the nivolumab Investigator's Brochure (IB).[31]

While nivolumab was well tolerated in cynomolgus monkeys, there is a potential for enhanced toxicity when combined with other immunostimulatory agents. However, nonclinical studies with nivolumab did not predict clinically relevant adverse effects (eg, no evidence of immune-mediated adverse effects was observed in nonclinical toxicology studies with nivolumab). Therefore, combination nonclinical toxicology studies with BMS-986258 and nivolumab have not been conducted and are not required by the International Council for Harmonisation S9 Note for Guidance on Nonclinical Evaluation for Anticancer Pharmaceuticals.[32] The safety of the combination will be carefully monitored in this clinical trial.

The overall safety experience with nivolumab, as either monotherapy or in combination with other therapeutics, is based on experience in approximately 23,507 participants (see nivolumab IB).[31] Nivolumab has been approved by the United States (US) Food and Drug Administration (FDA) for the treatment of patients with unresectable or metastatic melanoma (as a single agent and in combination with ipilimumab), metastatic NSCLC after progression on or after platinum-based chemotherapy, metastatic SCLC after platinum-based chemotherapy, advanced RCC previously treated with anti-angiogenic therapy, recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy, classical Hodgkin lymphoma that has relapsed or progressed, advanced or metastatic urothelial carcinoma with disease progression on or after a platinum-based therapy, hepatocellular carcinoma (HCC) as single agent or in combination with ipilimumab that has previously been treated with sorafenib, MSI-H CRC that has progressed after chemotherapy in combination with ipilimumab and unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.[31]

For nivolumab monotherapy, the safety profile is similar across tumor types. The only exception is pulmonary inflammation adverse events (AEs), which may be numerically greater in participants with NSCLC. In NSCLC patients, it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes. There is no relationship between the incidence, severity, or causality of AEs and the nivolumab dose level. Additional details on the safety profile of nivolumab, including results from other clinical studies, are summarized in the nivolumab IB.[31]

3.3 Benefit/Risk Assessment

As of the reporting cut-off date of 12-Sep-2019, 25 participants have been treated with various doses of BMS-986258 as monotherapy (n = 3 at 8 mg, n = 3 at 24 mg, n = 4 at 72 mg, n = 4 at 200 mg, n = 4 at 480 mg, n = 4 at 800 mg, and n = 3 at 1200 mg). As of the data cutoff date of 12-Sep-2019, based on 25 participants treated with BMS-986258 IV monotherapy in doses 8 to 1200 mg, the majority of AEs observed were [redacted] in severity. [redacted] treatment-related AEs were reported. [redacted] no dose-limiting toxicities (DLTs) were observed. Therefore, BMS-986258 administered as monotherapy is considered to have a manageable safety profile in doses up to 1200 mg IV.[12] Additionally, there are preliminary data on 4 participants who have received at least 1 cycle of BMS-986258 480 mg IV combined to nivolumab 480 mg; none of them presented a DLT during the observation period of 28 days. At this time, no efficacy data are available. There is limited prior human experience with BMS-986258; therefore, clinical benefit in participants with advanced solid tumors has not been established, but the initial data support its continued development.

Extensive details on the safety profile of nivolumab are available in the IB and will not be repeated herein.

Overall, the safety profile of nivolumab monotherapy as well as in combination with ipilimumab is manageable and generally consistent across completed and ongoing clinical trials with no MTD reached at any dose tested up to 10 mg/kg. Most AEs were low-grade [redacted] with relatively few related [redacted] AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level. A pattern of immune-related AE (irAE) has been defined, for which management algorithms have been developed; these are provided in Appendix 8. 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, including results from other clinical studies, are also available in the nivolumab IB.[31]

Other TIM-3 inhibitors that have entered human trials, both as monotherapy and in combination with other immunotherapy drugs include MGB453 from Novartis, TSR-022 from Tesaro, and LY3321367 from Eli Lilly. Safety and efficacy data have been presented for TSR-022, showing safe dose escalation up to 10 mg/kg in participants with solid tumors and AEs consistent with other checkpoint inhibitors.[33] In follow-up presentation,[34] efficacy data were disclosed for NSCLC participants that had progressed on or after anti-PD-(L)1 treatment and then received dual TIM-3 and PD-1 blockade. Although data were reported for a small number of participants, it was suggested that responses were more frequent in participants treated with higher dose and in those who expressed PD-(L)1 ≥ 1%. Novartis reported results from a Phase 1/2 study of MBG453 as monotherapy or combined to an anti-PD-1 antibody in patients with solid tumors, in which MGB453 was escalated up to 1200 mg Q4W as monotherapy or in combination. AEs were mainly G1-2, constitutional symptoms, and no Grade 4 AEs were reported in more than 2% of participants. Overall response rate (ORR) of 4.7% and disease control rate of 44.2% were reported across all

different indications for the MBG453 combination therapy. The recommended Phase 2 dose (RP2D) of MBG453 was declared as 800 mg Q4W and Phase 2 studies are ongoing in participants with melanoma or NSCLC resistant to anti-PD-(L)1 therapy.[35] MBG453 is also under development for participants with acute myeloid leukemia (AML) or high-risk myelodysplastic syndrome (MDS), in combination with decitabine; Phase 1 results showed favorable efficacy in newly diagnosed AML and high-risk MDS.[36] A Phase 1a/1b study of LY3321367 as monotherapy or in combination with an anti-PD-L1 antibody, which enrolled 41 participants with solid tumors, investigated doses of LY3321367 up to 1200 mg every 2 weeks (Q2W). Results showed a favorable toxicity profile, with mostly Grade 1-2 treatment-emergent AEs and no DLTs. One participant with small cell lung cancer treated in the monotherapy arm showed a partial response (PR) in a post-PD-1 setting.[37]

In addition to the initial safety data observed for BMS-986258 in the current study, and the safety data reported by other companies for other TIM-3 inhibitors that demonstrated a safe profile as monotherapy or in combination with anti-PD-(L)1 agents, the evaluation of risk for this study is based on information from in vitro studies on human cell lines and from nonclinical studies in monkeys.

3.3.1 Recombinant Human Hyaluronidase PH20

Recombinant Human Hyaluronidase PH20 (rHuPH20) is a recombinant form of hyaluronidase, a human enzyme that increases the dispersion and absorption of co-administered therapeutics by locally depolymerizing interstitial hyaluronan in the SC space, thereby decreasing the viscosity of SC extracellular matrix. This facilitates administration of greater fluid volumes via the SC route and potentially allows more antibody to reach the systemic circulation as compared to SC administration without rHuPH20. The half-life of rHuPH20 in skin is < 30 minutes and hyaluronan in the SC space is restored via normal bodily processes within 24 to 48 hours.[38] Additional details are provided in version 08 of the rHuPH20 IB.[39]

3.3.2 BMS-986258 Starting Dose for Part A (Monotherapy)

The FIH dose for this study has been carefully selected based on a review of all available nonclinical data (see Section 5.4.2). To balance the potential for possible therapeutic benefit and need for reasonable safety in a cancer patient population, the starting dose of 8 mg [redacted] Q4W was selected. This dose is [redacted] the MRSD [redacted] based on a HNSTD/NOAEL and the projected human exposures (AUCs) at [redacted] are [redacted] than the exposures observed in cynomolgus monkeys at the HNSTD/NOAEL [redacted]).[40] Furthermore, BMS-986258 is a blocking antibody with no Fc mediated effector function and no in vitro human PBMC activation or cytokine release, suggesting very low potential for adverse PBMC activation or cytokine release in humans.

3.3.3 BMS-986258 Starting Dose for Part A1 (Monotherapy SC)

Treatment in Part A1 (SC dose[s] BMS-986258 with rHuPH20) will be initiated after a dose level of BMS-986258 has been cleared for safety in Part A (IV monotherapy). The starting dose of

BMS-986258 administered in Part A1 will not exceed IV doses of BMS-986258 that have demonstrated to be safe in the monotherapy dose escalation arm (Part A). The SC dose(s) of BMS-986258 for Part A1 will be selected taking into consideration preliminary safety and available PK and PD data from the initial cohorts and [redacted] may be evaluated. Once a dose has been determined to be safe and tolerable from Part A, Part A1 may be initiated independently of Parts B and C, using all available safety and PK data and may be run in parallel with Parts A and B.

The first cohort in Part A1 has a goal of obtaining preliminary data on feasibility of SC administration of BMS-986258 and preliminary bioavailability. The highest dose that has been demonstrated to be safe and tolerable in Part A to date is 1200 mg Q4W; therefore, this is the dose that will be tested in the first cohort in Part A1. Participants in this cohort will receive their first dose of BMS-986258 1200 mg in combination with rHuPH20 as an SC injection. All subsequent doses will be administered as monotherapy 1200 mg IV, Q4W until EOT. Alternatively, participants in cohort A1 who have received SC BMS-986258 on Cycle 1 Day 1 will be offered the option to receive subsequent IV combination therapy of BMS-986258 with nivolumab (480 mg) at the highest dose of BMS-986258 that has been shown to be safe and tolerable in the dose escalation (Part B). Treatment will be given Q4W twice per cycle, for up to twelve 8-week cycles (96 weeks). A second cohort may be opened upon analysis of the totality of data from Parts A and B, and the preliminary data from the first cohort in Part A1.

Data obtained from the analysis of the SC dose(s) in Part A1 may be used to inform route of administration and dose selection in Part C.

3.3.4 BMS-986258 Starting Dose for Part B (Combination with Nivolumab)

The starting dose of BMS-986258 in Part B (combination with nivolumab) was selected to be 480 mg IV Q4W. Part B was initiated only after both 800 mg Q4W and 1200 mg Q4W cohorts were determined to be safe in Part A. In participants treated with BMS-986258 in Part A, no drug-related serious adverse effects were observed up to the highest tested dose of 1200 mg Q4W. The choice of 480 mg as the starting dose for Part B was also supported by preliminary PK and biomarker data. Preliminary PK results from Part A demonstrated that PK was linear and dose proportional at doses 200 mg Q4W and higher (internal BMS data). Preliminary biomarker data showed sustained optimal peripheral RO throughout the dosing period at doses 72 mg Q4W and higher. Preliminary data also show dose-dependent increases in total soluble TIM-3 that appear to plateau at doses 480 mg Q4W and higher (internal data at BMS). Thus, given the totality of safety and preferred PK and biomarker characteristics of BMS-986258, 480 mg IV Q4W was considered as potentially therapeutic, and therefore was chosen as the starting dose in Part B. At no point will the dose of BMS-986258 administered in combination with nivolumab in Part B exceed doses of BMS-986258 that have been demonstrated previously to be safe in the monotherapy dose escalation arm (Part A), nor at any point during Part B escalation will the BMS-986258 dose exceed the highest dose determined to be tolerated in Part A.

3.3.5 Dose Escalation in Parts A and B

Bayesian Logistic Regression Model (BLRM) with overdose control (escalation with overdose control [EWOC]) principle will be employed to limit the risk of exposing participants to an unsafe or toxic dose. In addition, following the completion of [redacted] will be made in conjunction with the data available on all previously dosed participants (including clinical and laboratory safety assessments, PK, and PD data); escalation by more than [redacted] will not be permitted; and determination to escalate will be made after discussion and agreement between investigators and the Medical Monitor.

3.3.6 Safety Monitoring on Study Therapy

In the absence of a pre-clinically defined safety signal, safety monitoring, by way of complete blood counts and chemistry (including liver enzyme) tests will be carried out prior to administration of study therapy, every 2 weeks for the first cycle and every 4 weeks thereafter. In addition, complete physical examinations (PEs) will be conducted on Day 1 of each new cycle, along with Q4W symptom-directed targeted PEs prior to each administration of study treatment.

Because preclinical data show that mAbs have no effect on human ether-a-go-go-related gene (hERG) channel activity in the in vitro hERG assay, the potential for BMS-986258 to alter cardiac re-polarization will only be studied as part of this FIH trial with pre- and post-ECG studies on Cycle 1 Day 1 and Cycle 3 Day 1 of Part A. A single ECG will be required at other visits as specified [redacted] Nevertheless, participants with corrected QT (QTc) interval prolongation at baseline will be excluded and medications known to cause prolonged QT will be prohibited.

The mandated biopsies pose limited risk to the participant, which include discomfort, pain, and bleeding. Biopsies should be performed at minimal acceptable clinical risk as judged by the Investigator and not in a target lesion or a lesion in an area treated with prior radiation therapy. Tissue must be a core needle biopsy, excisional biopsy, or incisional biopsy. Fine needle biopsies are not considered adequate for biomarker analysis. Biopsies of bone lesions that do not have a soft tissue component are also not acceptable. Participants who do not have accessible tumor lesions in order to provide a fresh pre-treatment tumor biopsy are eligible. Participants in Parts A and B NSCLC PD cohorts whose pre-treatment biopsy yields inadequate tissue quantity or quality will not be eligible for NSCLC PD cohorts, but they can be enrolled in dose escalation (Part A and B) cohorts. Section 9.8.4 gives additional guidance on lesions that are appropriate for a research biopsy. Because of the need for development, investigation of selection using biomarkers for participants treated with BMS-986258, the limited risk of a research biopsy in low-risk participants is considered appropriate in a Phase 1 research setting.

As noted in the nonclinical studies in Section 3.2.1.3, BMS-986258 repeatedly administered to cynomolgus monkeys did not induce infusion-related or anaphylactoid reactions. However, because of the as yet unknown potential of infusion reactions with the administration of BMS-986258 in humans, although the first 25 participants treated with BMS-986258 monotherapy in doses ranging from 8 to 1200 mg did not present with infusion-related reactions, all participants receiving the first 2 doses of BMS-986258 monotherapy or in combination with nivolumab will

be closely monitored until [redacted] post infusion for potential infusion reactions that could occur after either first administration or from repeat dosing of a novel mAb. In addition, the administration of BMS-986258 as monotherapy or in combination with nivolumab will occur at sites with medical monitoring and capability to manage infusion reaction or anaphylaxis.

Frequent 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 regularly by the Medical Monitor/Study Director and the Pharmacovigilance group to look for trends and potential safety signals. Treatment of AEs will follow Institutional guidelines and recommended management algorithms as listed in the nivolumab prescribing information[30] and nivolumab IB[31] and provided as appendices to the protocol.

It is unknown if treatment with BMS-986258 or BMS-986258 in combination with nivolumab increases the risk for contracting symptomatic SARS-CoV-2 infection or increases the severity or duration of symptoms. This unknown risk must be considered when enrolling a subject.

No additional safety monitoring or routine screening tests for all participants will be implemented because of the SARS-CoV-2 pandemic. However, eligibility for this trial may be impacted in participants with a recent episode of SARS-CoV-2 infection (please refer to Section 6.2 Exclusion Criteria). [redacted]

Non-live COVID-19 vaccination is considered a simple concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in participants receiving BMS-986258 or BMS-986258 in combination with nivolumab is unknown.

3.3.7 Overall Benefit/Risk for Combination with Nivolumab

Nivolumab has demonstrated clinical activity in subjects with advanced NSCLC, RCC, melanoma, and lymphomas as well as other tumors. Nivolumab has demonstrated a manageable safety profile; the overall safety experience with nivolumab, as monotherapy or in combination with other therapeutics, is based on experience in approximately 23,507 subjects treated to date.[31] There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. The most common AEs included fatigue, rash, pruritus, diarrhea, and nausea. Side effects of nivolumab therapy may include those associated with immune-mediated activation, such as pneumonitis, thyroiditis, and transaminitis. To mitigate risk from serious immune-mediated AE (IMAEs), subject management algorithms for nivolumab-related AEs from prior collective nivolumab experience have been included (Appendix 8). For nivolumab monotherapy, the safety profile is similar across tumor types. The only exception is pulmonary inflammation AEs, which may be numerically greater in subjects with NSCLC because, in some cases, it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes.

The combination of nivolumab and BMS-986258 has potential for clinical benefit in participants who were refractory to or progressed after anti-PD-(L)1 therapy. TIM-3 is frequently co-expressed with PD-1 in TILs, and patients with the highest co-expression of PD-1 and TIM-3 generally have the highest frequencies of PD-1^+ and TIM-3^+ CD8 T cells. Furthermore, TIM-3 expression was found to be upregulated in 2 lung cancer patients who developed secondary resistance to anti-PD-1 mAb treatment.[21] Therefore, it is plausible that TIM-3 may have a role in resistance to anti-PD-1 blockade, and the association of both therapies is able to overcome resistance.

In general, the combination of nivolumab with other therapeutic agents results in a safety profile with similar types of AEs as either agent alone, but in some cases, with a greater frequency. In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve. Because BMS-986258 is a novel anti-TIM-3 antibody with potentially additive action with nivolumab and the 2 checkpoints are frequently co-expressed by T cells, augmented and/or unanticipated irAEs may occur. On the other hand, this potentially additive action justifies the exploration of the 2 drugs in combination, since clinical activity may be higher with BMS-986258 in combination with nivolumab compared to either drug administered as monotherapy.

3.3.8 Summary

An urgent need exists for new therapies for subjects with advanced cancer that have progressed after or not responded to other treatments. The lack of a safety signal in pre-clinical toxicology studies, the emerging role of combination immune-modulating therapies in producing deep and durable responses in a variety of tumor types, and the careful consideration for safety in designing this study support the exploration of BMS-986258 as monotherapy or in combination with nivolumab in participants with advanced solid tumors who have few treatment options.

4 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary To assess the safety, tolerability, and to determine MTD or MAAD and RP2D of BMS-986258 administered as monotherapy and in combination with nivolumab in participants with select advanced solid tumors.	Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and death.
Secondary 1. To assess the preliminary anti-tumor activity of BMS-986258 as monotherapy and in combination with nivolumab in advanced solid tumors. 2. To explore the PK of BMS-986258 when administered IV as monotherapy and in combination with nivolumab. 3. To characterize the immunogenicity of BMS-986258 as monotherapy and in combination with nivolumab.	1. ORR, mDOR, and PFS rate at 6, 9, and 12 months. 2. Summary measures of PK parameters of BMS-986258 after monotherapy and combination treatment. 3. Incidence of ADA to BMS-986258.

[redacted]

Abbreviations: ADA, anti-drug antibody; AE, adverse event; BMS, Bristol-Myers Squibb; [redacted]; DLT, dose-limiting toxicity; [redacted]; IV, intravenous; MAAD, maximum administered dose; mDOR, median duration of response; MTD, maximum tolerated dose; [redacted]; ORR, overall response rate; OS,

overall survival; PFS, progression-free survival; PK, pharmacokinetics; [redacted]; RP2D, recommended Phase 2 dose; SAE, serious adverse event; [redacted]; SC, subcutaneous; [redacted]

5 STUDY DESIGN

5.1 Overall Design

This is a Phase 1/2, open-label, non-randomized study of BMS-986258, administered as a single agent and in combination with nivolumab, in participants with select advanced solid tumors: NSCLC, RCC, CRC, TNBC, and SCCHN. The study comprises 4 parts: Part A (dose escalation of BMS-986258 monotherapy), Part A1 (SC BMS-986258 monotherapy), Part B (dose escalation of BMS-986258 in combination with nivolumab) where the dose is escalated to determine the MTD, and Part C (BMS-986258 in combination with nivolumab cohort expansion), where the cohort of participants is expanded to gather additional safety, tolerability, preliminary efficacy, PK, and PD information regarding BMS-986258 in combination with nivolumab. Data obtained from the analysis of the SC dose(s) in Part A1 may be used to inform route of administration and dose selection in Part C.

[redacted] Treatment in Part A1 (SC dose[s] BMS-986258 with rHuPH20) will be initiated independent of the Treatment Arms B and C but only after a dose level of BMS-986258 in Part A has cleared the DLT period.

[redacted] After preliminary evaluation of safety and PK data from these [redacted] re-escalating doses of BMS-986258 may be initiated. [redacted]. All participants will complete up to 4 study periods: Screening [redacted], Treatment (12 cycles, 56 days/cycle), Safety Follow-up (100 days), and Survival Follow-up [redacted]. The duration of the study will be approximately 4 years. Pre-screening for participants in Part A and B NSCLC PD cohorts will be completed prior to the screening period.

[redacted]

[redacted]

5.1.1 Pre-screening for PD Cohorts only (NSCLC)

Participants in Part A and B NSCLC PD cohorts only must have tumor-associated [redacted] as measured by a [redacted] prior to completion of the remaining screening procedures. A participant is considered enrolled only when a main protocol-specific informed consent is signed. If allowed by institutional practices, sites are required to use a pre-screening consent for the [redacted] staining to evaluate [redacted] from biopsy samples. Participants must have a lesion that can be biopsied at an acceptable clinical risk as judged by the Investigator in order to be eligible for the NSCLC PD cohorts.

Participants in Parts A and B NSCLC PD cohorts whose pre-treatment biopsy yields inadequate tissue quantity or quality will not be eligible for NSCLC PD cohorts, but they can be enrolled in dose escalation (Part A and B) cohorts.

Participants in Part A and B NSCLC PD cohorts will be able to sign the main ICF and continue with other screening procedures while the [redacted] result is available for the determination of participant eligibility in NSCLC PD cohorts.

5.1.2 Screening Period

The screening period will be up to [redacted] and begins by signing of the main protocol informed consent form (ICF). The screening assessments are shown in Table 2-2.

If a participant exceeds the [redacted] screening period due to a study-related procedure (eg, scheduling of a tumor biopsy or waiting for a study-related laboratory value), the participant must be re-consented but does not require a new patient identification number. In this situation, the fewest number of procedures from the initial screening should be repeated to qualify the participant, while maintaining participant safety and eligibility. Within a given disease type, participants meeting all eligibility criteria will be enrolled in the study using an Interactive Response Technology (IRT) according to the part and treatment arm availability.

5.1.3 Treatment Period

The dosing regimen of BMS-986258 is Q4W. [redacted] Refer to Section 5.1 and [redacted]. All participants will be treated for up to 96 weeks. The treatment period will consist of up to 12 treatment cycles (each cycle is 8 weeks in length). Following each treatment cycle, the decision to treat a participant with additional cycles of study therapy (up to a maximum of 12 cycles) will be based on response assessment at the end of each cycle. Continuous safety evaluation and tumor assessment (every 8 weeks [Q8W]) will guide the decision to treat a participant with additional cycles of study therapy if the participant has confirmed clinical benefit (up to a maximum of 96 weeks) for all study parts.

Study visits will be performed every 2 weeks for the first 8 weeks following the first dose of study treatment for the BMS-986258 Monotherapy Escalation (Part A), BMS-986258 with rHuPH20 SC for first dose (Part A1), and BMS-986258 in Combination with Nivolumab (Part B). Study visits at Cycle 2 and beyond will be every 4 weeks. During Cycles 1 and 3 of the treatment period, additional study visits to collect samples for intensive PK, ADA, [redacted] are required. See Section 9.5 [redacted] for further details. In Part C (BMS-986258 in

Combination with nivolumab Cohort Expansion), study visits will be performed every 2 weeks for the first cycle. Study visits at Cycle 2 and beyond will be every 4 weeks.

In Part A (BMS-986258 Monotherapy Escalation), BMS-986258 will be administered Q4W. BMS-986258 will be infused according to dosing and infusion times in Table 7.1-1. Shorter infusion times may be used for initial dose panels and longer infusion times will be used for the higher dose panels.

In Part A1 (BMS-986258 SC for first dose), BMS-986258 will be co-administered with rHuPH20 for the first dose of BMS-986258 in Cycle 1. All subsequent doses will be administered as monotherapy IV Q4W. Alternatively, participants in cohort A1 who have received SC BMS-986258 on Cycle 1 Day 1 will be offered the option to receive subsequent IV combination therapy of BMS-986258 with nivolumab (480 mg) at the highest dose of BMS-986258 that has been shown to be safe and tolerable in the dose escalation (Part B). Treatment will be given Q4W twice per cycle, for up to twelve 8-week cycles (96 weeks). [redacted]

BMS-986258 SC should be administered in the abdomen or alternatively in the thigh. ENHANZE® Drug Product (rHuPH20) should not be injected into or around an infected or acutely inflamed area because of the danger of spreading a localized infection. Clinical judgment should be used in determining the best site for SC drug administration. Please refer to the Pharmacy Manual for dose-specific infusion times and sites of SC administration. BMS-986258 will require a [redacted] observation period following the completion of the infusion for the first 2 doses for each participant.

In Part B (BMS-986258 in Combination with Nivolumab Escalation) and Part C (BMS-986258 in Combination with Nivolumab Cohort Expansion), nivolumab will be administered Q4W and will be infused over 30 minutes. When both BMS-986258 and nivolumab are given in combination, nivolumab will be given first, over 30 minutes, followed by a [redacted] observation period then BMS-986258, over approximately [redacted]. BMS-986258 infusion will begin [redacted] after completion of the infusion of nivolumab. BMS-986258 infusions will require [redacted] observation period following the completion of the infusion for the first 2 doses for each participant. Shorter infusion times for BMS-986258 may be used for initial dose panels and longer infusion times [redacted] will be used for the higher dose panels. [redacted]. Please refer to the Pharmacy Manual for dose-specific infusion times and administration details for nivolumab and BMS-986258.

During dose escalation, all eligible participants will be assigned to Part A until the decision is made to escalate to the third dose cohort. Subsequently, treatment in Part B may be initiated, and dose escalation in the 2 parts will occur in parallel. The dose(s) of BMS-986258 for Part A1 will be selected based on preliminary safety and available PK and PD data. Once a dose has been determined to be safe and tolerable from Part A, Part A1 can be initiated independently, using all available safety and PK data and may be run in parallel with Parts A and B. The dose(s) of BMS-986258 monotherapy or in combination with nivolumab for Part A and B NSCLC PD

cohorts will be selected based on preliminary safety and available PK and PD data. The doses selected for Part C will not exceed the MTD (or MAAD if no MTD is determined) in Part B, but may incorporate assessment of other data including toxicities and PK, PD data from Parts A and B, as well as feasibility and bioavailability (BA) of SC administration from Part A1.

Sentinel Participant:

During the dose escalation phase in Part A, Part A1, and Part B, a staggered dosing (sentinel participant) approach will be used. In Part A and Part A1, the first participant to be dosed at Cycle 1 Day 1 of the first dose level will be observed for 5 days before additional participants (ie, Participant 2 onward in that cohort) receive study treatments in the same dose level. In Part B, the first participant to be dosed at Cycle 1 Day 1 of each dose level will be observed for 5 days before additional participants (ie, Participant 2 onward in that cohort) receive study treatments in the same dose level.

Initially, 3 participants will be enrolled at the start of each cohort, in accordance with the sentinel participant approach cited above. However, to allow for any unforeseen discontinuations (such as disease progression) before the 4-week DLT period (28 days) is completed, an extra participant may be enrolled in each dose escalation cohort. Therefore, there may be a total of 4 participants (3 + 1) at the start of each cohort, provided that the fourth participant is able to start dosing within approximately 1 week of the third participant in the same dose escalation cohort. Additional information on DLTs can be found in Section 7.1.1.

5.1.3.1 BMS-986258 Monotherapy Dose Escalation (Part A) (Including NSCLC PD Cohorts) and Subcutaneous Dose (Part A1)

Approximately [redacted] participants are expected to be treated during the BMS-986258 Monotherapy Dose Escalation (Part A) of the study guided by BLRM for the primary objective. Additionally, approximately [redacted] participants are expected to be treated in the [redacted] NSCLC PD cohorts in Part A [redacted] per dose level in order to have at least [redacted] evaluable participants with baseline and on treatment biopsies considered as adequate tissue sample); and approximately [redacted] participants are planned to be treated in SC cohort(s) (Part A1). Therefore, a total of [redacted] participants are expected to be treated in Parts A and A1. Refer to Section 10 for additional details.

In dose escalation, each participant will be administered IV doses of BMS-986258 in planned dose levels of 8, 24, 72, 200, 480, 800, 1200, 1600, and 2400 mg Q4W twice per cycle, for up to 12 cycles (96 weeks) of study therapy.

[redacted] monotherapy dose cohorts may be [redacted] in the escalation phase based upon the BLRM analysis and clinical evaluation of all available safety and PK/PD data. Participants enrolled in the NSCLC PD cohorts will receive a dose level that has already been cleared for safety within the corresponding dose escalation cohort.

Prior to declaring the MTD, and in consultation with investigators, the Sponsor has the option to expand any dose level previously established to be tolerable in order to obtain [redacted] to those defined in the protocol. Planned dose levels may be modified, or [redacted] added, based upon the BLRM analysis and

clinical evaluation of all available safety and PK/PD data. Once the tolerability (during the DLT evaluation) of a dose level has been established, additional participants may be added at that dose level to better characterize the safety, PK, and PD profiles.

The dose escalation phase of the study will evaluate the safety and tolerability of BMS-986258, administered as monotherapy based on DLTs, using a BLRM (for the BMS-986258 Monotherapy Dose Escalation [Part A]). During the Monotherapy Dose Escalation phase, approximately 3 participants will be treated at each dose level. Cohort tolerability assessment and subsequent dose recommendation will occur when at least 2 evaluable participants within a cohort have completed the 4-week DLT period. Any toxicities that occur beyond the DLT period will be considered in making dose level decisions and/or dose level modifications. Additional information on DLTs can be found in Section 7.1.1.

If the potential DLT occurring in the third evaluable participant regarding any 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 reassessment of dose recommendation, by BLRM in the BMS-986258 Monotherapy Escalation (Part A) will be carried out for each dose level. Planned dose levels for dose escalation are provided in Section 5.5.

Approximately up to [redacted] participants are expected to be treated in the BMS-986258 monotherapy SC cohort(s) (Part A1). Refer to Section 10 for additional details. For each participant in Part A1, BMS-986258 will be co-administered SC with rHuPH20 for the first dose in Cycle 1. All subsequent doses of BMS-986258 will be administered as monotherapy IV, Q4W twice per cycle, for up to twelve 8-week cycles (96 weeks). Alternatively, participants in cohort A1 who have received SC BMS-986258 on Cycle 1 Day 1 will be offered the option to receive subsequent IV combination therapy of BMS-986258 with nivolumab (480 mg) at the highest dose of BMS-986258 that has been shown to be safe and tolerable in the dose escalation (Part B). Treatment will be given Q4W twice per cycle, for up to twelve 8-week cycles (96 weeks).

The dose selected for Part A1 will not exceed a dose determined to be safe and tolerable in Part A.

5.1.3.2 BMS-986258 in Combination with Nivolumab Dose Escalation and NSCLC PD Cohorts (Part B)

Approximately [redacted] participants are expected to be treated during the BMS-986258 combination with Nivolumab Dose Escalation (Part B) of the study guided by BLRM-copula for the primary objective. Additionally, approximately [redacted] participants are expected to be treated in the [redacted] NSCLC PD cohorts in Part B, with approximately up to [redacted] participants per cohort, in order to obtain [redacted] participants with evaluable biopsies per cohort. Refer to Section 10 for additional details. Therefore, a total of [redacted] participants are expected to be treated in Part B.

Based on preliminary safety, PK, and PD from Part A, the starting dose of BMS-986258 in Part B may be higher than the starting dose from Part A. Each dose level in Part B, including the starting dose, will only be opened after at least [redacted] higher dose levels in Part A have demonstrated tolerability during the DLT observation period. [redacted]. Each participant may be administered IV doses of

BMS-986258 in planned dose levels of 8, 24, 72, 200, 480, 800, 1200 and 1600 mg combined with 480 mg of nivolumab Q4W (twice per cycle), for up to twelve 8-week cycles of study therapy (96 weeks) unless criteria for study drug discontinuation are met earlier (see Protocol Section 8).

[redacted] during escalation based upon the BLRM analysis and clinical evaluation of all available safety and PK/PD data. Participants enrolled in the PD cohorts will receive a dose level that has already been cleared for safety within the corresponding dose escalation cohort. Upon completion of study therapy, all participants will enter the Safety Follow-up period.

The combination dose escalation phase (Part B) of the study will evaluate the safety and tolerability of BMS-986258, given in combination with nivolumab, based on DLTs, using a BLRM-copula. During the combination dose escalation phase, approximately [redacted] participants will be treated at each dose level. Cohort tolerability assessment and subsequent dose recommendation will occur when at least [redacted] evaluable participants within a cohort have completed a 4-week DLT period. Any toxicities that occur beyond the DLT period will be considered in making dose level decisions and/or dose level modifications. Additional information on DLTs can be found in Section 7.1.1.

If the potential DLT occurring in the third evaluable participant regarding a/any specific dose level does not influence the dose recommendation the BLRM-copula, 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, BLRM-copula in the Safety Evaluation of Combination Doses of BMS-986258 with Nivolumab (Part B), will be carried out for each dose level. Planned dose levels for dose escalation are provided in Section 5.5.

Planned dose levels may be modified, or [redacted] dose levels added, based upon the BLRM-copula analysis for combination and clinical evaluation of all available safety and PK/PD data. Once the tolerability (during the DLT evaluation) of a dose level has been established, additional participants may be added at that dose level to better characterize the safety, PK, and PD profiles.

5.1.3.3 BMS-986258 in Combination with Nivolumab Expansion Cohorts (Part C)

The purpose of the BMS-986258 cohort expansion is to gather preliminary efficacy information in specific patient populations regarding BMS-986258 in combination with nivolumab.

In the BMS-986258 cohort expansion in combination (Part C), the preliminary efficacy of BMS-986258 in combination with nivolumab may be explored in selected populations with RCC, NSCLC, CRC, TNBC, and SCCHN. Please refer to Section 5.4.7 and Section 6 Study Population for additional details.

Treatment in Part C will be initiated when the RP2D, MTD, or MAAD for BMS-986258 in combination with nivolumab has been determined based on evaluation of the totality of available clinical safety, PK, PD, and modeling data from Parts A, A1, and B, including information from the NSCLC PD cohorts. The dose(s) selected for Part C will not exceed the MTD or MAAD

determined in Parts A and B. Part C may begin while Part B continues to [redacted].

Participants with stable disease (SD), partial response (PR), or complete response (CR) 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:

- Confirmed progressive disease defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix 5) unless participants meet criteria for treatment beyond progression (Section 8.1.3).
- Clinical deterioration suggesting that no further benefit from treatment is likely.
- Intolerability to therapy.
- Participant meets criteria for discontinuation of study treatment as shown in Section 8.1.
- Completion of the maximum number of cycles (12 cycles).

Continuous evaluation of toxicity events in the BMS-986258 cohort expansions will be performed throughout enrollment for all expansion cohorts. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds [redacted] across all participants treated in cohort expansions, the findings will be discussed and further enrollment will be interrupted. Depending on the nature and grade of the toxicity, and after assessing the benefit/risk ratio, a new dose for all cohorts may be initiated at a previously tested lower dose level or at a dose level [redacted] to previously tested lower dose levels.

5.1.4 Follow-up

5.1.4.1 Safety Follow-up Period

Upon completion of study therapy (or up to a maximum of 96 weeks, if applicable), or once the participant has received the last administration of any study treatment (ie, at EOT), all participants will enter a safety follow-up period.

For participants who complete all scheduled cycles of therapy, the EOT visit will be the same visit as the last scheduled and completed on-treatment visit and will be the start of the safety follow-up period. 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 will not need to be repeated. Accordingly, for these participants, this visit will be considered the start of the safety follow-up period.

After the EOT visit, all participants will be evaluated for any new AEs for at least 100 days after the last dose of study treatment. [redacted] All participants will be required to complete the 3 clinical safety follow-up visits, regardless of whether new anti-cancer therapy is started, except those participants who withdraw consent for study participation.

5.1.4.2 Survival Follow-up

In parallel with the safety follow-up period, all participants will continue on the survival follow-up period. Participants will be followed up for survival at each Safety Follow-up visit and then by telephone [redacted]. The duration of this follow-up is up to [redacted] following the last dose of study treatment, although a longer follow-up period could be considered in selected cases if an efficacy signal is apparent. Tumor assessment scans, for participants who have ongoing clinical benefit beyond the [redacted] period following the end of treatment, may continue to be collected as part of standard-of-care treatment upon agreement between the Sponsor and Investigator. Subsequent therapies will also be recorded in this survival follow-up period.

5.1.5 Data Monitoring Committee and Other External Committees

BMS has in place a multi-layered process for ensuring patient safety through close collaboration of study site investigators, the BMS study team, and the BMS Global Pharmacovigilance and Epidemiology (GPVE)-led Medical Surveillance Team (MST). This collaborative process constitutes the Data Safety Monitoring Plan for the study as detailed below:

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

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

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

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

- This is an open-label study.

- The eligibility criteria exclude participants with disease characteristics that could predispose to higher risk of morbidity.
- Exclusion of participants with known autoimmunity also applies as they could be at risk for exacerbation of their condition by the administration of therapies that relieve immune suppression such as BMS-986258 and nivolumab.
- Participants will be observed frequently for clinical evaluation and blood counts during dose escalation.
- Well-defined discontinuation criteria are established in the protocol for individual participants for both safety and treatment futility with clear criteria for treatment discontinuation, dose delay, and toxicity management.
- For the combination therapy with nivolumab, management algorithms for immune-related events are well established based on the clinical experiences from the over 23,500 subjects who were exposed to nivolumab as either monotherapy or in combination with other agents, in the past as well as in ongoing studies.

5.2 Number of Participants

The approximate number of participants will be up to [redacted] as shown below.

Part A Monotherapy Escalation: The total sample size is up to approximately [redacted] participants including [redacted] to assess the MTD/MAAD and an additional [redacted] in [redacted] NSCLC PD cohorts.

Part A1: SC Dose: The total sample size is up to approximately [redacted] participants to evaluate up to [redacted] dose levels.

Part B Combination Escalation: The total sample size is up to approximately [redacted] participants, including [redacted] participants to assess the MTD/MAAD in combination and [redacted] in [redacted] NSCLC PD cohorts.

Part C Cohort Expansion: Approximately up to [redacted] participants will be treated in each of the 5 tumor cohorts (up to a total of [redacted] across tumors).

5.3 End of Study Definition

The start of the study is defined as the first visit for the first participant screened. Similarly, the end of the study is defined as the last visit or scheduled procedure shown in the Schedule of Activities ([redacted]) for the last participant. Primary study completion is defined as the final date on which data for the primary endpoint are expected to be collected, if this is not the same.

5.4 Scientific Rationale for Study Design

BMS-986258 will be evaluated in participants with RCC, CRC, NSCLC, SCCHN, and TNBC. These indications were chosen based on prevalence of TIM-3 expression on immune cells in the tumor microenvironment (internal data at BMS). [redacted]. TIM-3 expression marks exhausted T cells, therefore it is expected that TIM-3 blockade will promote T-cell activation, proliferation,

effector function, and survival. TIM-3 expression in tumor samples will be assessed retrospectively in this study.

The study design includes the following:

- Pre-Screening for [redacted] (Part A and B NSCLC PD cohorts only)
- [redacted] Screening period
- Treatment period of up to twelve 8-week cycles, totaling 96 weeks
- Dose escalation phases in monotherapy and combination with nivolumab
- Cohort expansion phase
- Safety follow-up period of 100 days
- Survival follow-up period of [redacted]

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

5.4.1 Rationale for the Monotherapy Dose Escalation (Part A)

[redacted]

BMS-986258 has never been tested in humans; however, the experiments described above suggest a role for BMS-986258 as monotherapy in advanced solid tumors. This study will evaluate the safety profile, tolerability, preliminary efficacy, PK, and PD of IV doses of BMS-986258 administered Q4W, and in combination with nivolumab (Q4W) in participants with select advanced solid tumors. Part A will provide data for BMS-986258 as monotherapy that may be used in future studies in association with drugs other than nivolumab.

5.4.2 Rationale for Subcutaneous Administration of BMS-986258 (Part A1)

rHuPH20 is a recombinant form of hyaluronidase, a human enzyme that degrades hyaluronan, an extracellular matrix component that poses a barrier to large injection volume and fluid flow at the SC injection site, therefore, decreasing the viscosity of SC extracellular matrix, and enabling a rapid delivery of large volume of study drug. It improves the SC absorption rate, thus it has the potential to improve bioavailability.

rHuPH20 has dose-dependent, usually local, mild, transient and reversible side effects. rHuPH20 has a local half-life < 30 minutes and systemic half-life < 5 minutes. Additional details are provided in version 08 of the rHuPH20 IB.[38]

Part A1 will be conducted to obtain preliminary data on the PK profile of BMS-986258 when administered SC combined with rHuPH20 in comparison to IV administered BMS-986258. This SC cohort will initiate after IV dose(s) and schedule(s) have been shown to be safe in Part A.

SC administration has the potential to reduce infusion time and provide greater convenience and comfort for oncology patients. Co-administration of rHuPH20 (a tissue permeability enhancer) may further enable to overcome barriers of SC drug delivery especially for large mAbs with regards to time and volume to be administered. As of 15-Nov-2019, rHuPH20 has been administered to 1592 participants in 30 clinical studies conducted under the US rHuPH20 IND. In these studies, individual doses have ranged from 15 to 96,000 U rHuPH20. Across all studies, SC injections of rHuPH20 were generally well tolerated in healthy subjects, dehydrated pediatric subjects, hospice and palliative care subjects, subjects with type 1 and 2 diabetes, and subjects with RA. Subcutaneous injections of rHuPH20 alone or in combination with lactated Ringer's, normal saline, co-injected drugs (morphine, ceftriaxone, insulin, and insulin analogs), or biologic products (IgG and adalimumab) have been well tolerated in all clinical trials. Adverse events were generally mild, transient injection site reactions, including erythema, pain, bruising, pruritus, burning, tenderness, edema, induration, irritation, paresthesia, numbness, and rash. Moderate injection site reactions, which have occurred less frequently, include burning, erythema, pain, and numbness. Mild-to-moderate headache was also commonly reported. Adverse events in these trials have otherwise generally reflected the adverse reaction profiles of the co-administered drug or have been associated with the rapid introduction of a relatively large volume of fluid in the SC space.

A large safety database exists for approved products coformulated with rHuPH20 SC is available, including Herceptin®SC, HYQVIA®, and RITUXAN HYCELA™/MabThera® SC/Rituxan®.[39] Public data presented to the FDA to support coadministration of rituximab (1400 mg and 1600 mg) and rHuPH20, summarizing data from randomized PK bridging trials in patients with follicular lymphoma, CLL, or DLBCL (SparkThera, SABRINA, SAWYER, MabEase, PrefMab) show: (1) comparable Ctrough and overall exposure; (2) comparable safety, aside from administration site reactions; and (3) comparable efficacy (ORR, CRR, PFS, EFS, and OS in various studies) for SC versus IV routes. Injection site reactions (discomfort, erythema) were increased following SC administration, occurring in 1.9% - 25.9% of subjects; these were generally mild and did not limit therapy. Importantly, patient preference and patient-reported outcomes were evaluated in a randomized crossover trial (PrefMab) of 743 previously untreated patients with DLBCL or FL receiving R-CHOP, R-CVP, or R-Bendamustine to SC versus IV administration. Over 80% of patients preferred SC administration, due to reduced time for administration and greater comfort.[40]

Studies have shown that the BA of mAbs following SC administration approximates 70% (50% to 80%), with lower Cmax and a delayed time of maximum observed concentration (Tmax) compared

to IV. The doses evaluated in these studies ranged from 2 to 1400 mg administered with or without rHuPH20.[38,41,42,43] Drugs administered with rHuPH20 provide an added advantage of faster Tmax as compared to when administered without rHuPh20. The PK of BMS-986258 is expected to follow a similar profile as other IgG mAbs and hence the BA is expected to be approximately 70% in the dose range planned in Part A when administered SC.

Overall, these data suggest that SC administration of BMS-986258 with rHuPH20, at a dose previously shown to be safe intravenously, should be feasible and tolerable. [redacted]

For each participant in Part A1, 1200 mg of BMS-986258 will be co-administered with rHuPH20 SC for the first dose in Cycle 1. All subsequent doses of BMS-986258 will be administered as monotherapy 1200 mg IV, Q4W twice per cycle, for up to twelve 8-week cycles (96 weeks). Alternatively, participants in cohort A1 who have received SC BMS-986258 on Cycle 1 Day 1 will be offered the option to receive subsequent IV combination therapy of BMS-986258 with nivolumab (480 mg) at the highest dose of BMS-986258 that has been shown to be safe and tolerable in the dose escalation (Part B). Treatment will be given Q4W twice per cycle, for up to twelve 8-week cycles (96 weeks). The dose selected for Part A1 is based on the safety and tolerability observed in Part A. Based on the expected bioavailability of [redacted] for SC administered mAbs, the 1200 mg SC dose is expected to produce exposures similar to IV 800 mg Q4W, which has been found to be within the range of linear PK. Dose-dependent increases in soluble TIM-3 were observed in Part A, and preliminary data suggest that target engagement is suboptimal at doses below 800 mg IV Q4W. Thus, given the totality of safety and PK and biomarker characteristics of BMS-986258 IV, 1200 mg SC Q4W is considered as potentially therapeutic, and therefore was chosen as starting dose in Part A1. Additional cohorts at higher doses may be tested depending on the safety and PK data of the dose at 1200 mg level.

5.4.3 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 compared to rule-based methods (such as 3 + 3 design) by incorporating external information from preclinical studies as well as historical clinical trials. The 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. After completing the monotherapy phases (Part A), the drug-associated dose-toxicity

profiles are characterized and incorporated as prior knowledge into the drug combination phase of the study (Part B) or used in future studies.

5.4.5 Rationale for the Combination of BMS-986258 with Nivolumab

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA-4, inducible costimulator (ICOS), and B and T-lymphocyte attenuator (BTLA).[45] PD-1 signaling has been shown to inhibit CD28-mediated upregulation of interleukin(IL)-2, IL-10, IL-13, IFN-γ, and Bcl-xL. PD-1 expression has also been noted to inhibit T-cell activation and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[46] 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 (half-maximal effective concentration [EC50] 0.39-2.62 nM) and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4, and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the MLR. Using a 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).[47]

The power of combining immune-oncology drugs to broaden responses has been demonstrated for metastatic melanoma[48] and for RCC.[9] Given that TIM-3 is frequently co-expressed with PD-1, and that patients that had the highest co-expression of PD-1 and TIM-3 were generally those with the highest frequencies of PD-1+ and TIM-3+ CD8 T cells, the combination of BMS-986258 and nivolumab may result in stronger clinical activity compared to either agent. In fact, in an evaluation of antitumor activity in staged CT26 syngeneic CRC model of treatment with anti-mouse TIM-3 antibodies, both anti-TIM-3 and anti-PD-1, while neither surrogate antibody alone demonstrated efficacy, the combination of anti-TIM-3 and anti-PD-1 antibodies showed a greater effect in reducing median tumor volume than either antibody alone. In a human Th1 assay, BMS-986258 was tested with nivolumab in co-culture using irradiated CHO-OKT3 cells co-expressing PD-L1 (CHO-OKT3-PD-L1). While both PD-1 and anti-TIM-3 antibodies promoted Th1 cell proliferation as single agents, co-blockade of TIM-3 and PD-1 showed an additive effect.

Prior experience with the combination of nivolumab and ipilimumab and the pre-clinical data utilizing the combination of BMS-986258 and nivolumab support the investigation of this combination in the clinic.

5.4.6 Rationale for 2-Year Duration of Treatment

The optimal duration of immunotherapy is an important question and continues to be investigated. Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long-term benefit. CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with previously treated advanced solid tumors (including 129 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.[49]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% to 18% for squamous and non-squamous NSCLC, respectively).[50]

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

In contrast, a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated patients with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153, patients with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 patients still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in

progression-free survival (PFS) compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached versus 10.3 months, respectively; hazard ratio (HR) = 0.42 (95% confidence interval [CI], 0.25 to 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for patients on continued treatment to live longer (OS HR = 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (ie, 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years.[51]

Collectively, these data suggest that there is minimal if any benefit derived from continuing I-O treatment beyond 2 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 CA031002, treatment with BMS-986258 and nivolumab will be administered for up to 2 years. Participants may receive a total of 12 cycles, which corresponds to approximately 96 weeks.

5.4.7 Rationale for Tumor Selection for Expansion (Part C)

Five tumor types were chosen for the study. The following specific populations may be chosen for Part C:

- RCC participants who received and progressed on or after anti-PD-1 therapy as monotherapy or in combination with other I-O agents)
- MSI-H CRC participants who received and progressed on or after-anti-PD-1 therapy, and MSS CRC participants
- NSCLC participants who received and progressed on or after-anti-PD-1 therapy
- SCCHN participants who received and progressed on or after anti-PD-1 therapy
- Recurrent or metastatic TNBC participants

The precise indications that will be evaluated in these tumor types were defined based on current results (or lack of) with immune-oncology agents, but also on the premise that TIM-3 and PD-1 are frequently co-expressed and TIM-3 may arise as a mechanism of resistance for anti-PD-1 therapy.

Given its inherent immunogenic characteristics, RCC was among the first tumor types to be studied in the context of immunotherapy. High-dose IL-2 was approved in 1992 for the treatment of RCC and remained an important treatment option for 2 decades.[52] More recent discoveries of molecular and immunological alterations led to the approval of nivolumab for previously treated advanced RCC, based on an ORR of 25% in comparison with 5% for everolimus.[53] Recently published results demonstrated response rates of around 40% with the combination of nivolumab and ipilimumab for patients with metastatic RCC.[51] Progress is being made, but despite recent advances, most patients with advanced RCC will succumb to their disease.

The current standard treatment for patients with metastatic CRC is fluorouracil-based chemotherapy regimens combined with agents targeting angiogenesis or epidermal growth factor receptor (EGFR).[54] Based on results from the Phase 2 CheckMate-142 trial, nivolumab was

approved for the treatment of patients with MSI-H or mismatch repair-deficient (MMR-D) metastatic CRC[55] but MSI-H patients correspond to 5% of the patient population with metastatic CRC. MSS colon cancers, which make up the majority of the tumors, do not respond to anti-PD-1 monotherapy. TIM-3 is expressed in the immune infiltrate in CRC; therefore, BMS-986258 may be active in this indication.

Lung cancer is the leading cause of cancer death in the US. In 2017, an estimated 222,510 new cases are expected to be diagnosed, and 155,870 deaths are estimated to occur because of the disease, making it the leading cause of death due to cancer.[56] Most lung cancers (80%) are NSCLC[57]; of these patients, more than 65% present with locally advanced or metastatic disease.[58] Patients with metastatic NSCLC have a median survival of approximately 10 months and a 5-year survival rate of less than 5%.[54] Treatment options are pembrolizumab with chemotherapy in first line, chemotherapy-based, and anaplastic lymphoma kinase (ALK) and EGFR inhibitors for patients that carry these mutations. Nivolumab was approved for the management of previously treated advanced squamous and non-squamous NSCLC after there was demonstrable survival difference compared to chemotherapy.[59] TIM-3 has been demonstrated to be upregulated in patients that develop secondary resistance to anti-PD-1 therapy, therefore participants in this situation may benefit from treatment with BMS-986258.

The incidence and primary site of head and neck cancers present large geographic variability, likely caused by the ethnic and genetic differences among populations, but also related to differences in the prevalence of risk factors like tobacco and alcohol consumption. Human papillomavirus (HPV) infection plays an increasingly prominent role as a causative agent for head and neck cancer. HPV-associated head and neck cancers occur primarily in the oropharynx (tonsils and base of tongue), account for the younger age of patients with oropharyngeal squamous cell carcinoma and define a subset of patients with improved treatment outcome. However, the use of HPV status in clinical decision making remains investigational at this time, and treatment is the same as for patients without an HPV-associated tumor.[60,61,62,63,64,65,66] Radiation and platinum-based chemotherapy remain the backbone of treatment for advanced cases. Nivolumab was approved for recurrent or metastatic SCCHN based on increased OS when compared to standard treatment.[67] The combination of BMS-986258 and nivolumab may be able to rescue patients that progress after anti-PD-1 therapy.

TNBCs are usually more aggressive and harder to treat than hormone receptor-positive tumors; they are associated with a higher risk of early relapse and metastasis after surgery, chemotherapy, and/or radiotherapy.[68] The lack of estrogen receptor, progesterone receptor, and human EGFR 2 expression precludes the use of targeted therapies in advanced stages, and the only approved systemic treatment option is chemotherapy with or without bevacizumab.[69] In patients with advanced TNBC, responses to chemotherapy occur but are often of short duration and prognosis is poor. No I-O agent is approved for TNBC. However, some findings support the investigation: the elevated numbers of TAM in breast cancer and its negative association to clinical evolution[70];

TILs work as a prognostic factor for disease-free survival and OS in TNBC patients[71]; and data in mouse models that suggest that major TIL populations in breast tumors express TIM-3.[72]

5.4.8 Rationale for Treatment Beyond Progression

Immunotherapeutic agents produce atypical clinical response patterns that are not usually observed in conventional chemotherapy. Accumulating clinical evidence indicates 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 non-conventional 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, 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 drug that might induce a non-conventional response pattern in some patients.

5.5 Justification for Dose

5.5.1 Rationale for BMS-986258 Starting Dose

A flat dose of 8 mg [redacted] IV once Q4W was selected to render possible therapeutic benefit to patients while maintaining adequate safety. At the [redacted] Q4W starting dose, the anticipated steady-state trough concentration (Cminss) of 0.90 µg/mL approximates the 90% maximal effective concentration (EC90) determined from in vitro TIL function assay to ensure adequate target coverage for possible therapeutic effects to patients. In addition, the starting dose is [redacted] the MRSD [redacted] based on a [redacted] HNSTD/NOAEL and the projected human exposures (AUCs) at [redacted] (AUC = [redacted]) are [redacted] than the exposures observed in cynomolgus monkeys at the HNSTD/NOAEL (AUC = [redacted]). Furthermore, BMS-986258 is a blocking antibody with no Fc mediated effector function with no in vitro human PBMC activation or cytokine release, suggesting very low potential for adverse PBMC activation or cytokine release in humans.

5.5.2 Rationale for Dose Selection and Dosing Schedule

5.5.2.1 BMS-986258

In the Monotherapy Dose Escalation (Part A), SC Monotherapy (Part A1), Combination with Nivolumab Dose Escalation (Part B), and the Cohort Expansion - Combination (Part C), BMS-986258 will be administered Q4W. This dosing frequency is supported by the projected human T-HALF for BMS-986258 of [redacted]. In addition, this dosing regimen complements the

Q4W schedule of nivolumab, planned for Part B and C, thereby simplifying study logistics for both participants and investigators. Doses up to [redacted] have been tested in a definitive (GLP-compliant) pre-clinical 1-month IV toxicity study with good tolerance. Therefore, proposed doses of BMS-986258 to be tested in this study will be 8, 24, 72, 200, 480, 800, 1200, 1600, and 2400 mg IV Q4W as monotherapy and 8, 24, 72, 200, 480, 800, 1200, and 1600 mg IV Q4W in combination with nivolumab 480 mg IV Q4W.

5.5.2.2 Nivolumab

The nivolumab dose of 480 mg Q4W was selected for this study based on clinical data and modeling and simulation approaches using population PK (PPK) and exposure-response (ER) analyses examining relationships between nivolumab exposures and efficacy (eg, OS and overall response) and safety responses, using data from studies in multiple tumor types (melanoma, NSCLC, and RCC) with body weight-normalized dosing (mg/kg). A flat dose is expected to reduce prescription dosing errors, shorten pharmacy preparation time, and improve ease of administration. Extending the dosing interval to 4 weeks provides numerous benefits to patients, as they would have increased flexibility between clinical visits. The PPK analyses have shown that exposure to nivolumab increased dose proportionally over the dose range of 0.1 mg/kg to 10 mg/kg administered Q2W, and no clinically meaningful differences in PK across ethnicities and tumor types were observed. Nivolumab clearance and volume of distribution were found to increase as body weight increases but less than proportionally with increasing weight, indicating that milligram-per-kilogram dosing represents an over-adjustment for the effect of body weight on nivolumab PK.

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

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

Nivolumab 480 mg Q4W is predicted to have approximately 16% lower Cminss compared to nivolumab 3 mg/kg Q2W. While these exposures are predicted to be lower, they are on the flat part of the ER curves and are not predicted to affect efficacy. Exposure-efficacy analyses of multiple PK measures and efficacy endpoints (eg, OS and overall response) indicated that, following administration of nivolumab 480 mg Q4W, efficacy is predicted to be similar to that following administration of nivolumab 3 mg/kg Q2W across multiple tumor types. Based on these data, nivolumab 480 mg Q4W is expected to have similar efficacy and safety profiles to nivolumab 240 mg Q2W or nivolumab 3 mg/kg Q2W.

Of note, as an immunoglobulin G4 mAb, nivolumab does not interact directly with cytochrome P450 (CYP) enzyme systems. Systemic cytokine modulation data indicated that there were no meaningful changes in cytokines known to have indirect effects on CYP enzymes across all dose levels of nivolumab (0.3, 2, and 10 mg/kg) during the course of treatment. Therefore, it is unlikely that nivolumab administered at 480 mg Q4W will affect the systemic exposures of BMS-986258.

5.5.2.3 Rationale for 30-Minute Dose Administration of Nivolumab

Long infusion times place a burden on participants and treatment centers. Using shorter infusion times of 30-minute duration in participants will diminish the burden provided there is no change in safety profile. Nivolumab is currently approved for IV administration over 60 minutes. Clinical studies show that nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg over a long treatment duration. For example, in Study CA209010 (a Phase 2, randomized, double-blinded, dose-ranging study of nivolumab in participants with advanced/metastatic, clear cell RCC, N = 167), a dose association was observed for infusion site reactions and hypersensitivity reactions (5.1% at 0.3 mg/kg, 3.7% at 2 mg/kg, and 18.5% at 10 mg/kg).[68] All the events were Grade 1/2 and were manageable.

The impact of infusion time on nivolumab safety was assessed in a substudy conducted as part of an ongoing community based trial (ie, CheckMate 153) in patients with previously treated advanced or metastatic NSCLC.[73] In the substudy, 322 patients received nivolumab 3 mg/kg IV Q2W as a 30-minute infusion, and 355 patients received the same nivolumab regimen as a 60-minute infusion.

Overall, the safety profiles between the 30- and 60-minute infusion groups were similar. Any grade treatment-related AEs were reported in 53% and 51% of patients given 30- or 60-minute infusions, respectively. Grade 3 to 4 treatment-related AEs were reported in 12% of patients in each infusion group. Among select AEs of any cause, Grade 3 to 4 events were comparable between infusion groups in the pulmonary (3% and 2%), hepatic (2% and 3%), and gastrointestinal (2% and 2%) categories. Hypersensitivity/infusion reactions of any cause were reported in 8 (2%) and 5 (1%) patients administered 30- and 60-minute infusions, respectively. The incidence of Grade 3 to 4 hypersensitivity/infusion reactions was < 1% in each infusion group. Hypersensitivity/infusion reactions were managed either through dosing interruptions (8 patients given 30-minute infusions and 3 patients given 60-minute infusions), discontinuations (1 patient given a 30-minute infusion and 2 patients given 60-minute infusions), or administration of systemic corticosteroids (3 patients given 30-minute infusions and 1 patient given a 60-minute infusion). In addition, PPK modelling

demonstrated similar predicted Cmax after the first nivolumab dose and at steady state in both infusion groups, suggesting that a 30-minute infusion does not pose an increased safety risk due to an increase in nivolumab Cmax.

In conclusion, nivolumab can be safely administered as a 30-minute infusion, with a low incidence of infusion-related AEs. Given these findings, 30-minute infusion is being implemented across the nivolumab development programs, including the FIH study CA031002.

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

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

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

2) Type of Participant and Target Disease Characteristics

a) Participants must be at least 18 years old and have histologic confirmation of one of the 5 tumors described below (metastatic, recurrent, and/or unresectable), with measurable disease per RECIST v1.1 (Appendix 5).

b) Eastern Cooperative Oncology Group Performance Status of 0 or 1 (Appendix 6).

c) Participants with controlled brain metastases are eligible. 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), and no longer taking steroids for at least 2 weeks prior to first dose of study treatment, and with no new or progressive neurological signs and symptoms.

d) Participants with RCC:

i) Advanced or metastatic RCC with a clear cell component.

ii) Participants must have received at least 1 but not more than 2 prior anti-angiogenic therapy regimens (including but not limited to sunitinib, sorafenib, pazopanib, axitinib, tivozanib, and bevacizumab) in the advanced or metastatic setting. Prior cytokine therapy (eg, IL-2, IFN-γ), vaccine therapy, or treatment with cytotoxics is allowed.

iii) Participants must have received no more than 3 total prior systemic treatment regimens in the advanced or metastatic setting and 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 received and progressed on or after anti-PD-(L)1 therapy, if available, for enrollment. Other I-O agents previously used in association with anti-PD-(L)1 therapy are allowed.

v) *Not applicable per Protocol Revision 04. See inclusion criterion 2, d, iv.*

vi) Participants in Part C only must have been resistant to anti-PD-(L)1 therapy. Refer to inclusion criteria 2) i) for the definition of anti-PD-(L)1 resistance.

e) Participants with CRC
   i) Histologically confirmed CRC that is metastatic or recurrent.
   ii) Participants with MSS CRC must have received and then progressed on or after, or have been intolerant or refractory to, at least 1 standard systemic therapy for metastatic and/or unresectable disease (or have progressed within 6 months of adjuvant therapy), including oxaliplatin and irinotecan.

   Participants must have known microsatellite instability or mismatch repair status. V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog, and B-Raf proto-oncogene status, if known, should be documented; if unknown, participants must consent to allow their submitted archived tumor tissue sample (block or unstained slides) to be tested, in addition to the required fresh tumor biopsies.
   iii) Participants who have received prior anti-angiogenic therapy (eg, bevacizumab) and/or anti-EGFR therapy (eg, cetuximab or panitumumab) are eligible.
   iv) Participants with MSI-H or MMR-D status must have received and progressed on or after anti-PD-(L)1 therapy, if available, for enrollment.
   v) Participants in Part C only, with MSI-H or MMR-D status, must have been resistant to anti-PD-(L)1 therapy. Refer to inclusion criteria 2) i) for the definition of anti-PD-(L)1 resistance.
f) Participants with NSCLC
   i) Histologically confirmed NSCLC meeting stage criteria for Stage IIIB, Stage IV, or recurrent disease.
   ii) Participants must have recurrent or progressive disease during or after platinum doublet-based chemotherapy for advanced or metastatic disease.

   OR

   Must have recurrent or progressive disease within 6 months after completing platinum-based chemotherapy for local disease.
   iii) Status for actionable mutations (eg, EGFR, ALK, ROS1, RET, etc.) must be known [when testing is available as per country/region standard of care practices]; participants with actionable mutations must have received and progressed on, have been intolerant to, or not be a candidate for, standard tyrosine kinase inhibitors [as available per country/region standard of care practices].
   iv) Participants must have received and progressed on or after anti-PD-(L)1 therapy, if available, for enrollment.
   v) Participants in Part A and B NSCLC PD cohorts and Part C only must have been resistant to anti-PD-(L)1 therapy. Refer to inclusion criteria 2) i) for the definition of anti-PD-(L)1 resistance.
g) Participants with SCCHN
   i) Histologically confirmed, recurrent, or metastatic SCCHN (oral cavity, pharynx, larynx) and not amenable to local therapy with curative intent.
   ii) Participants who progressed on or after, or were intolerant to, a platinum-containing regimen.

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

iv) Documentation of p16 is sufficient to determine HPV status of tumor for SCCHN of the oropharynx. Note: If results are not available, then a sample (tissue on microscopic slides, tissue block, or a fresh tissue biopsy in formalin) should be sent to the central laboratory for analysis.

v) Participants must have received and progressed on or after anti-PD-(L)1 therapy, if available, for enrollment.

vi) Participants in Part C only must have been resistant to anti-PD-(L)1 therapy. Refer to inclusion criteria 2) i) for the definition of anti-PD-(L)1 resistance.

h) Participants with TNBC

i) Males and females with histologically confirmed TNBC as defined by American Society of Clinical Oncology/College of American Pathologists guidelines[74].

ii) Participants must have received and progressed on or after, or have been intolerant or refractory to, at least 1 standard chemotherapy regimen containing anthracycline and taxane; in addition, the participant must have received at least 1 regimen for the treatment of metastatic or locally advanced disease.

i) Participants with anti-PD-(L)1 resistant RCC, CRC, NSCLC, and SCCHN, participating in Part C, Part A NSCLC PD, and Part B NSCLC PD cohorts only.

i) Participants must have received prior anti-PD-1/PD-L1 therapy and have radiologically or clinically documented disease progression or recurring disease on or within 3 months following last dose of anti-PD 1/PD-L1 therapy for their advanced (metastatic and/or unresectable) cancer and have been considered for all other potentially efficacious therapies prior to enrollment.

(1) One intervening systemic therapy is allowed between anti PD-(L)1 therapy and enrollment.

(2) Anti-PD-(L)1 therapies may have been received in sequential or combination regimens.

(3) Required documentation includes start and stop dates of prior anti-PD-(L)1 therapy and a progression date no more than 3 months after the last dose of anti-PD-(L)1 therapy.

(4) At screening, the Investigator should document on the electronic case report form (eCRF) the progression date and criteria used in determining disease progression from prior anti-PD-(L)1 therapy (eg, RECIST v1.1, irRC, irRECIST, and/or iRECIST).

[redacted]

[redacted]

3) Physical and Laboratory Findings

a) Adequate hematologic function for participants as defined by the following:

i) Neutrophils ≥ 1500/μL (use of growth factors to achieve this level is not permitted within 2 weeks prior to screening laboratories).

ii) Platelets ≥ 80 × 10^3/μL (transfusion to achieve this level is not permitted within 2 weeks prior to screening laboratories).

iii) Hemoglobin ≥ 8 g/dL (transfusion to achieve this level is not permitted within 2 weeks prior to screening laboratories).

b) Adequate hepatic function

i) Alanine aminotransferase (ALT) and aspartate aminotransferase (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) Clinically stable thyroid function per Investigator assessment.

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

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

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

e) Ability to comply with treatment, PK and PD sample collection, and required study follow-up periods.

4) Age and Reproductive Status

a) Males and females ages 18 years, or age of majority, or older at time of consent.

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study treatment. An extension up to 72 hours prior to the start of study treatment is permissible in situations where results cannot

be obtained within the standard 24-hour window. Additional requirements for pregnancy testing during and after study intervention are located in [redacted] Schedule of Activities.

c) WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) and as described below and included in the ICF. WOCBP are permitted to use hormonal contraception methods (as described in Appendix 4).

d) WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements but should still undergo pregnancy testing as described in this section.

e) *Not applicable per Protocol Amendment 06.* Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception and fetal protection (Appendix 4) during BMS-986258 monotherapy or in combination treatment with study treatment BMS-986258 and nivolumab, for a total of 90 days post-treatment completion (duration of sperm turnover). In addition, male participants must be willing to refrain from sperm donation during this time.

f) *Not applicable per Protocol Revision 05.* Azoospermic males are exempt from contraceptive requirements unless the potential exists for fetal toxicity due to study drug being present in seminal fluid, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

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

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

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

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

(1) Is not a WOCBP.

OR

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

Investigators shall counsel WOCBP on the importance of pregnancy prevention, the implications of an unexpected pregnancy, and the potential of fetal toxicity occurring due to transmission of study drug to a developing fetus.

6.2 Exclusion Criteria

1) Medical Conditions

a) Women who are pregnant or breastfeeding.

2) Prior/Concomitant Therapy

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

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 therapy.

c) Prior immune therapy 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 therapy.

d) Prior participation in an anti-TIM-3 clinical study.

e) Treatment with botanical preparations (eg, herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment. Refer to Section 7.7.1 for prohibited therapies.

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

3) Medical History and Concurrent Diseases

a) Participants with concomitant second malignancies (except adequately treated nonmelanomatous skin cancers or in situ bladder, breast, or cervical cancers) are excluded unless a complete remission was achieved at least 2 years prior to study entry, and no additional therapy is required or anticipated to be required during the study period.

i) In addition, in Part C, participants with concurrent malignancies that do not require treatment and are clinically stable and anticipated to be followed in an active surveillance manner for the next 12 months are eligible. Treatment should not be required at timing of consent and not be expected to be needed not only for the concurrent malignancy, but also for complications caused by it. The Investigator should inform the participant that the study treatment is not intended and not expected to be considered as treatment for the concurrent malignancy.

b) Participants with other active malignancy requiring concurrent intervention.

c) Prior organ or tissue allograft.

d) 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 (National Cancer Institute [NCI] common Terminology Criteria for Adverse Events [CTCAE] v4.03)

e) 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 on stable conditions under insulin treatment.

(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 drug).

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

ii) History of life-threatening toxicity related to prior immune therapy (eg, anti-CTLA-4 or anti-PD-(L)1 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).

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

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

(1) Myocardial infarction or stroke/transient ischemic attack within the past 6 months

(2) Uncontrolled angina within the past 3 months

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

(4) History of other clinically significant heart disease (eg, cardiomyopathy, congestive heart failure with New York Heart Association functional classification III to IV [Appendix 7])

(5) Cardiovascular disease-related requirement for daily supplemental oxygen therapy

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

(7) History of myocarditis, regardless of etiology

v) History of or with active interstitial lung disease

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

(1) Positive test for hepatitis B surface antigen

(2) Positive test for qualitative hepatitis C viral load by polymerase chain reaction (PCR)

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

(4) Additional testing or substitute testing per institutional guidelines to rule out infection is permitted.

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

viii) Human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome:

(1) For Parts A, A1, and B, known history of testing positive for HIV or known acquired immunodeficiency syndrome constitutes an exclusion criterion.

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

(2) For Part C, HIV infection does not constitute an exclusion criterion if the following conditions are satisfied:

(a) Subject is in use of an antiretroviral therapy regimen for > 4 weeks.

(b) HIV viral load is undetectable or below the lower limit of detection as per local testing standards.

(c) CD4+ T-cell counts >= 350 cells/mL, up to 4 weeks prior to enrollment.

(d) Subject has no history of AIDS-defining opportunistic infections.

ix) Any major surgery within 4 weeks of the first dose of study drug. Participants must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study drug.

x) Receipt of non-oncology vaccines containing live virus for prevention of infectious diseases within 4 weeks prior to first dose of study drug.

(1) The use of inactivated seasonal influenza vaccines (eg, Fluzone®) will be permitted on study without restriction.

xi) Receipt of packed red blood cells or platelet transfusion within 2 weeks of the first dose of study drug unless agreed by the Medical Monitor.

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

xiii) Previous SARS-CoV-2 infection within 10 days for mild or asymptomatic infections or 20 days for severe/critical illness prior to Cycle 1 Day 1.

(1) Acute symptoms must have resolved and based on investigator assessment in consultation with the Medical Monitor, there are no sequelae that would place the participant at a higher risk of receiving study treatment.

xiv) Previous SARS-CoV-2 vaccine within 14 days of Cycle 1 Day 1. For vaccines requiring more than one dose, the full series (eg, both doses of a two-dose series) should be completed prior to Cycle 1 Day 1 when feasible and when a delay in Cycle 1 Day 1 would not put the study participant at risk.

xv) Symptomatic central nervous system (CNS) metastases. Participants are eligible if CNS metastases are asymptomatic and do not require immediate treatment or have been treated and participants have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment). In addition, participants must have been either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to treatment assignment. In case of past or suspect CNS metastases, imaging performed [redacted] prior to treatment

assignment must document radiographic stability of CNS lesions and be performed after completion of any CNS-directed therapy.

xvi) Leptomeningeal metastases.

4) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug 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 participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and Bristol-Myers Squibb (BMS) approval is required).

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

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and that the results of the study can be used. It is imperative that participants fully meet all eligibility criteria and confirmed prior to Cycle 1 Day 1.

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently treated 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 publishing requirements, as applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs. If re-enrolled, the participant must be reconsented.

6.4.1 Retesting During Screening or Lead-In Period

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

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

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

Laboratory parameters and/or assessments that are included in [redacted] may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

Testing for asymptomatic SARS-CoV-2 infection by reverse transcription polymerase chain reaction (RT-PCR) or viral antigen is not required. However, some participants may develop suspected or confirmed symptomatic SARS-CoV-2 infection or be discovered to have asymptomatic SARS-CoV-2 infection during the screening period. In such cases, participants may be considered eligible for the study after meeting all inclusion/exclusion criteria related to active infection, and after meeting the following criteria:

- At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive RT-PCR or viral antigen test result
- At least 24 hours have passed since last fever without the use of fever-reducing medications
- Acute symptoms (eg, cough, shortness of breath) have resolved
- In the opinion of the investigator, there are no SARS-CoV-2 infection sequelae that may place the participant at a higher risk of receiving investigational treatment

In the instance of a SARS-CoV-2 infection during screening, the screening period may be extended beyond the protocol-specified timeframe with Medical Monitor approval.

- Any screening tests already performed which could potentially be affected by the SARS-CoV-2 infection or its complications on an individual basis and agreed upon with the Medical Monitor (eg, safety labs, oxygen saturation, chest CT scan) should be repeated.

7 TREATMENT

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

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

- BMS-986258
- Nivolumab
- ENHANZE® Drug Product (rHuPH20)

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

Drugs used in this open-label study qualify as IPs. Their description and storage information are described in Table 7-1. Please refer to the Pharmacy Manual for additional information.

Table 7-1: Study Treatments for CA031002

Product Description/Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
BMS-986258	[redacted]	IP	Open Label	Kit	Refer to Product label
BMS-986258		IP	Open Label	Kit	Refer to Product label
Nivolumab	100 mg/vial (10 mg/mL)	IP	Open Label	Kit	Refer to Product label
ENHANZE® Drug Product (rHuPH20)[a]	1 mg/mL	IP	Open Label	Vial and various packaging configurations	Refer to the label on container or package insert

Abbreviations: IP, Investigational Product; IMP, Investigational Medicinal Product; rHuPH20, recombinant human hyaluronidase PH20

[a] ENHANZE® (rHuPH20) is referred as rHuPH20 in the protocol

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.

7.1 Treatments Administered

The selection and timing of dose (Table 7.1-1) for each participant is as follows:

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit Dose Strength(s)/Dosage Level(s)	Dosage Formulation Frequency of Administration	Route of Administration	Infusion Time
BMS-986258	8, 24, and 72 mg[a,b]	Q4W	IV	See note[b]
	200, 480, and 800 mg[b]	Q4W	IV	[redacted]
	1200 mg[b]	Q4W	IV	
	1600 mg[b]	Q4W	IV	
	2400 mg[b]	Q4W	IV	
Nivolumab	480 mg[b]	Q4W	IV	30 minutes
BMS-986258 + ENHANZE® Drug Product (rHuPH20)	1200 mg [redacted]	Once	SC	[redacted]

Abbreviations: IV, intravenously; Q4, every 4 weeks; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous.

[a] [redacted]

[b] For study drugs preparation and infusion times, please refer to the Pharmacy Manual.

Intravenous (IV) BMS-986258:

Participants in Part A, Part A1 (after the first dose), and NSCLC PD cohorts will receive IV BMS-986258 as monotherapy at doses ranging from 8 mg to 2400 mg. After the first dose, participants in cohort A1 will be offered the option to receive subsequent IV BMS-986258 in combination with nivolumab (480 mg) at the highest dose of BMS-986258 that has been shown to be safe and tolerable in the dose escalation (Part B). Treatment will be given Q4W twice per cycle, for up to twelve 8-week cycles (96 weeks).

There will be no dose escalations or reductions of BMS-986258 allowed. For Q4W dosing cycles, participants may be dosed within a ±3-day window.

BMS-986258 will be administered through an IV line. For details in study drug preparation and administration, refer to Pharmacy Manual.

Subcutaneous (SC) BMS-986258:

Participants in Part A1 will receive BMS-986258 plus rHuPH20 as an SC injection. BMS-986258 + rHuPH20 will be administered subcutaneously [redacted] via a syringe pump (refer to Pharmacy Manual) on Cycle 1 Day1.

Nivolumab:

Participants in Part A1 who have received combination therapy and participants in Part B, Part B NSCLC PD, and Part C cohorts should receive nivolumab at a dose of 480 mg as a 30-minute infusion on Day 1 of each treatment cycle every 4 weeks until progression, unacceptable toxicity, withdrawal of consent, completion of [redacted] of treatment, or the study ends, whichever occurs first. Participants should begin study treatment within 3 calendar days of treatment assignment.

There will be no dose escalations or reductions of nivolumab allowed. For Q4W dosing cycles, participants may be dosed within a ±3-day window. Premedications are not recommended for the first dose of nivolumab.

Participants should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.3.

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed. Nivolumab injection will be administered as an IV infusion over approximately 30 minutes.

7.1.1 Dose-Limiting Toxicities

For the purpose of guiding decisions regarding dose escalation in Parts A and B, 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 start on the first day of Cycle 1 and end at Day 28 (therefore, 4 weeks) in Parts A and B. The severity of AEs will be graded according to NCI CTCAE v4.03.

For the purpose of participant management, DLTs that occur at any time, whether during dose escalation (Part A or B), SC dose(s) (Part A1), or cohort expansion (Part C), will result in study drug being held pending evaluation of the event being related to study drug, in accordance with Section 7.4.

A participant is considered DLT evaluable if receiving 1 dose of BMS-986258 in Part A or 1 dose of BMS-986258 and nivolumab 480 mg in Part B and completing the DLT observation period. Participants who withdraw from the study 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. The incidence of DLT(s) during the 4-week DLT evaluation period will be used in dose escalation decisions and to define the MTD/RP2D in monotherapy and in combination with nivolumab. AEs occurring after the 4-week DLT period will be considered for the purposes of defining the RP2D upon agreement between the Sponsor and Investigators. Participants experiencing a DLT will not be retreated with study drug and will enter the safety follow-up period of the study.

7.1.1.1 Hepatic Dose-Limiting Toxicity

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

[redacted]

7.1.1.2 Hematologic Dose-Limiting Toxicity

Any of the following events will be considered a DLT:

[redacted]

7.1.1.3 Dermatologic Dose-Limiting Toxicity

Any of the following events will be considered a DLT:

[redacted]

7.1.1.4 Other Dose-Limiting Toxicities

Any of the following events will be considered a DLT:

[redacted]

[redacted]

[redacted]

7.1.2 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology agents are associated with irAEs that can differ in severity and duration from AEs caused by other therapeutic classes. BMS-986258 and nivolumab 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 nivolumab to assist investigators in assessing and managing the following groups of irAEs:

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

The clinical nature of AEs noted with BMS-986258 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 8.

7.2 Method of Treatment Assignment

During the screening visit, the investigative site will call into the enrollment option of the IRT designated by BMS for assignment of a 5-digit participant number that will be unique across all sites. Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with [redacted]. The patient identification number (PID) will ultimately be comprised of the site number and participant number. For example, the first participant screened (ie, enrolled) at site number [redacted] will have a PID of [redacted]. Once it is determined that the participant meets the eligibility criteria following the screening visit, the investigative site will call the IRT to assign the participant into the open dose panel.

Participants will not be replaced if they are discontinued from the study secondary to an AE unless the AE can be determined to be unrelated to treatment.

During dose escalation, all participants will be assigned to Part A until the decision is made to escalate to the third dose cohort. Subsequently, treatment in Part B will be initiated, and dose escalation in the 2 parts will occur in parallel. In addition, Part A1 can be initiated independently, using all available safety and PK data and may be run in parallel with Parts A and B. Treatment assignments for participants eligible for Part A, Part A1, and Part B will alternate between the 3 parts, with consecutively treated participants assigned to different parts through IRT whenever possible and according to the corresponding inclusion criteria. If there are no openings available in the part to which the subject would be assigned by this algorithm, then the subject will be assigned to the next open part/cohort.

In addition, participants enrolled in monotherapy or combination PD cohorts will be assigned to dose levels that are already established as safe based on data coming from the corresponding dose

escalation cohort. The participants assigned in Part A and B NSCLC PD cohorts will need to pass eligibility for selection based on [redacted] at baseline (see Section 5.1 and Inclusion Criteria Section 6.1).

7.3 Blinding

This is an open-label, non-randomized study. The specific treatment to be taken by a participant will be assigned using an IRT. The site will contact the Interactive Response System prior to the start of study treatment administration for each participant. The site will record the treatment assignment on the applicable case report form (CRF).

7.4 Dosage Modification

Intra-participant dose escalation/reduction of BMS-986258 or nivolumab is not permitted in this study in order to allow better evaluation of the safety and efficacy at individual dose levels and schedules. No dose reductions of BMS-986258 or nivolumab will be allowed.

7.4.1 Dose Delays Due to Toxicity

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

- Potential DLTs, until DLT relatedness is defined.
- Select AEs and laboratory abnormalities:

[redacted]

- AE, laboratory abnormality, or concurrent illness that, in the judgment of the Investigator, warrants delaying study drug administration.
- Confirmed SARS-CoV-2 infection.

Criteria for participants who are required to permanently discontinue both study drugs 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 7.4.2. Participants eligible to resume study therapy will resume study therapy at the nominal treatment visit following their last received study medication dose.

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

7.4.2 Criteria to Resume Treatment

Subsequent dosing with study therapy may resume once drug-related non-DLT AEs resolve to Grade 1 or baseline. Participants experiencing AEs not meeting criteria for permanent discontinuation as outlined in Section 8.1 may resume treatment with study medication under the following criteria:

Participants may resume treatment with study drug 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 7.1.1.4) must resolve to baseline prior to resuming study therapy
- 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 7.1.1.1) should have treatment permanently discontinued
- Participants with confirmed SARS-CoV-2 infection may resume treatment after 1) at least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive RT-PCR viral antigen test result, 2) resolution of acute symptoms (including at least 24 hours has passed since last fever without fever reducing medications), 3) evaluation by the Investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment, and 4) consultation by the Medical Monitor. For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled-out and other criteria to resume treatment are met.

  Prior to re-initiating on-study treatment in a participant with a dosing delay lasting 8 weeks due to SARS-CoV-2 infection, the Medical Monitor/designee must be consulted.

7.4.3 Management of Drug-related Infusion Reactions

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, pulmonary infiltrates]; Grade 4: life-threatening; pressor or ventilatory support indicated):

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the participant as follows: recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for SC administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the Investigator is comfortable that the symptoms will not recur. Study drug 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. Remain at bedside and monitor participant until recovery of the symptoms.

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

7.5 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 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 BMS should be contacted immediately.

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

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

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

Please refer to the current version of the IBs and/or Pharmacy Manual for complete preparation, storage, and handling information.

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

7.5.1 Retained Samples for Bioavailability/Bioequivalence/Biocomparability

Not applicable.

7.6 Treatment Compliance

Not applicable.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

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

- Immunosuppressive agents

- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 6.2 and Section 7.7.2)
- Any concurrent anti-neoplastic therapy (eg, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy)
- Any botanical preparation (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.
- Administration of investigational SARS-CoV-2 vaccines is not allowed during the study. Participants may receive authorized or approved SARS-CoV-2 vaccines while continuing on study treatment at the discretion of the investigator.
- Treatment of active SARS-CoV-2 infections or high-risk exposures, including use of investigational therapies, is allowed and should be discussed with the Medical Monitor.

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

7.7.2 Other Restrictions and Precautions

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

For participants who need to undergo elective surgery (not tumor related) during the study, it is recommended to hold study drug(s) for at least 2 weeks before and 2 weeks after surgery, or until the subject recovers from the procedure, whichever is longer. Prior to resuming study drug treatment, surgically-related AEs should resolve to ≤ Grade 1 or baseline and participants must meet relevant eligibility criteria as determined by the BMS Medical Monitor in discussion with the Investigator. The BMS Medical Monitor must be consulted prior to re-initiating treatment in a subject with a dosing interruption lasting > 8 weeks after the last dose.

7.7.2.1 Vaccinations

Any vaccination containing attenuated or inactivated virus may be permitted if clinically indicated. However, this must be discussed and documented with the BMS Medical Monitor prior to administration and may require a study drug washout period prior to and after administration of the vaccine. Inactivated influenza vaccination will be permitted on study without restriction. Any vaccination containing live virus, including live SARS-CoV-2 vaccines, is prohibited.

7.7.2.2 Imaging Restriction and Precautions

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

The ultimate decision to perform MRI in an individual participant in this study rests with the site radiologist, the Investigator, and the standards set by the local Ethics Committee.

7.7.3 Permitted Therapy

Participants are permitted the use of the following treatments:

- Topical, ocular, intra-articular, intra-nasal, and inhalational corticosteroids
- Adrenal replacement steroid doses ≤ 10 mg daily prednisone equivalent
- A brief (less than 1 week) 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)

7.7.3.1 Radiotherapy

Palliative and supportive care for disease-related symptoms may be offered to all participants on the trial; however, investigators should consult with the BMS Medical Monitor prior to initiating palliative radiation in participants who have not yet completed the DLT evaluation interval (Parts A and B).

The potential for overlapping toxicities with radiotherapy and BMS-986258 administered as monotherapy or in combination with nivolumab is currently not known. Therefore, palliative radiotherapy is not recommended while receiving any of these drugs, alone or in combination. If palliative radiotherapy in short courses and for isolated fields is required to control symptoms not clearly related to disease progression, then drug administration should be withheld, if possible, for at least 1 week before radiation and for at least 1 week after its completion. Participants should be closely monitored for any potential toxicity during and after receiving radiotherapy. Prior to resuming study drug treatment, radiotherapy-related AEs should resolve to ≤ Grade 1 or baseline and participants must meet relevant eligibility criteria as determined by the BMS Medical Monitor in discussion with the Investigator. The BMS Medical Monitor must be consulted prior to re-initiating treatment in a subject with a dosing interruption lasting > 8 weeks after the last dose.

Details of palliative radiotherapy should be documented in the source records and eCRF. Details in the source records should include: dates of treatment, anatomical site, dose administered and

fractionation schedule, and AEs. Symptoms requiring palliative radiotherapy should be evaluated for objective evidence of disease progression. Participants receiving palliative radiation of target lesions will have the evaluation of best overall response (BOR) just prior to radiotherapy but such participants will no longer be evaluable for determination of response subsequent to the date palliative radiation occurs.

7.8 Treatment After the End of the Study

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS-supplied study treatment up to the maximum duration of 12 cycles as specified in Section 7.1. Study treatment will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee, or through another mechanism at the discretion of BMS.

BMS reserves the right to terminate access to BMS-supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of BMS-986258 is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government-sponsored or private health program. In all cases, BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation From Study Treatment

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.
- Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Documented disease progression as defined by RECIST v1.1 (Appendix 5) unless participants meet criteria for treatment beyond progression (Section 8.1.3).
- Clinical deterioration while receiving active study therapy that, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Any drug-related AE occurring at any time that meets DLT criteria as outlined in Section 7.1.1 will require permanent discontinuation. Exceptions to permanent discontinuation are listed in Section 7.4.2.
- Inability to comply with protocol.
- Discretion of the Investigator.
- Pregnancy.

- Termination of the study by BMS.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. Note: Under specific circumstances 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.
- Individual participants with confirmed CR will be given the option to discontinue study therapy on a case-by-case basis after specific consultation and agreement between the Investigator and BMS Medical Monitor in settings where benefit/risk justifies discontinuation of study therapy.

Any event that leads to delay in dosing lasting > 8 weeks from the previous dose requires discontinuation, with the following exceptions:

- Dosing delays for prolonged steroid tapers to manage drug-related AEs are allowed.
- Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor.

The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of BMS-986258. Although there is overlap among the discontinuation criteria, if a participant in any of the combination arms meets criteria for discontinuation and the Investigator is unable to determine whether the event is related to both or one study drug, the participant should discontinue both nivolumab and BMS-986258 and be taken off the treatment phase of the study. An exception to the discontinuation of BMS-986258 can be made in the case of a nivolumab-related hypersensitivity or infusion reaction.

Specifically, for hypersensitivity or infusion-related reactions, because nivolumab is administered first, if a participant presents with a reaction before the administration of BMS-986258 has started, treatment with BMS-986258 may continue after the hypersensitivity or infusion-related reactions have been resolved. For other IMAEs, when signs or symptoms have developed after administration of both study drugs, if discontinuation criteria are met, both study drugs should be discontinued.

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

In the case of pregnancy, the Investigator must immediately notify the BMS Medical Monitor/designee of this event. In the event a female participant becomes pregnant during a clinical trial, the study treatment must be discontinued immediately. Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy. If the Investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the Investigator and the BMS Medical Monitor/designee must occur. Refer to Section 9.2.5 Pregnancy.

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

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

8.1.1 Temporary Discontinuation

Not applicable.

8.1.2 Rechallenge

Not applicable.

8.1.3 Treatment Beyond Progression

As described in Section 5.4.8, accumulating evidence indicates that a minority of patients with tumors treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease. The decision to continue treatment beyond investigator-assessed progression according to RECIST v. 1.1 should be discussed with the BMS Medical Monitor and documented in the study records. Participants with progressive disease may be permitted to continue study therapy provided the following criteria are met:

- Subject is deriving clinical benefit as assessed by the Investigator.
- Disease progression is not rapid as assessed by the Investigator.
- Subject continues to meet relevant eligibility criteria as determined by the BMS Medical Monitor in discussion with the Investigator.
- Subject tolerates study treatment.
- Subject has stable performance status.
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, central nervous system metastases).
- Participant provides written informed consent prior to receiving any additional nivolumab or BMS-986258 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 treatments, the participant should remain on the trial and continue to receive monitoring according to the Schedule of Activities [redacted]. All decisions to continue treatment beyond initial progression must be discussed with the BMS Medical Monitor, and an assessment of the

benefit/risk of continuing with study therapy must be documented in the study records (see Appendix 2).

For the participants who continue BMS-986258 (as a monotherapy or in combination with nivolumab) study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the time of initial PD. Nivolumab treatment should be discontinued permanently upon documentation of further progression.

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

8.1.3.1 Discontinuation Due to Further Progression (Confirmed Progression)

Participants that meet the above criteria and continue on study therapy beyond initial progressive disease must discontinue BMS-986258 (and nivolumab, if part of the combination cohorts) upon the next documented event of progressive disease. A follow-up efficacy assessment should be performed at the next scheduled evaluation 8 weeks later (but no sooner than 4 weeks later) to determine whether there is continued progressive disease.

Subjects should discontinue study therapy upon further evidence of further 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). The tumor burden volume from 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:

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-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

Subjects should continue to receive monitoring according to Study Assessments and Procedures described in Section 9. Radiographic assessment by CT (preferred) or MRI described in Section 9.1.1 is required when participants continue post-progression treatment. For participants that

discontinue post-progression treatment with study therapy, no additional radiographic assessments will be required.

8.1.4 Exceptions to Permanent Discontinuation Criteria

Any drug-related AE occurring at any time that meets DLT criteria as outlined in Section 7.1.1 will require permanent discontinuation, with the exception of the following:

Any event that leads to a delay in dosing for BMS-986258 monotherapy or BMS-986258 in combination with nivolumab, lasting > 8 weeks from the previous dose, requires discontinuation, with the exception of the following:

- Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks from the previous dose, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 8 weeks, or more frequently if clinically indicated, during such dosing delays.
- Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug-related reasons may not require discontinuation, if approved by the BMS Medical Monitor. Prior to

re-initiating treatment in a participant with a dosing delay lasting > 8 weeks, the BMS Medical Monitor must be consulted.

- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued nivolumab dosing.

All participants who discontinue IP should comply with protocol-specified follow-up procedures [redacted]. 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, 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 CRF page.

8.1.5 Post-Study Treatment Follow-up

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

8.2 Discontinuation From the Study

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

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

8.3 Lost to Follow-up

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

9 STUDY ASSESSMENTS AND PROCEDURES

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

- If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, and 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 Appendix 8.
- Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

9.1 Efficacy Assessments

Data for the tumor assessments specified in this protocol should be submitted to BMS. Additional assessments may be performed as part of standard of care; however, data for these assessments should remain in the subject's medical record and should not be provided to BMS unless specifically requested by the Sponsor. The Sponsor can request scans for review at any time during or after the study.

[redacted]

9.1.1 Imaging Assessment for the Study

All on-study images will be submitted to a central imaging vendor for collection. At the Sponsor's discretion, scans may undergo blinded independent central review. Sites should be trained prior to scanning the first study participant. Image acquisition guidelines and submission process will be outlined in the CA031002 Imaging Manual to be provided by the core lab.

Screening images should be acquired [redacted]. On-study images should be acquired [redacted] from the date of first dose.

Tumor assessments at other time points may be performed if clinically indicated and should be submitted to the central imaging vendor. Unscheduled CT/MRI should be submitted to central imaging vendor. X-rays and bone scans that clearly demonstrate interval progression of disease (eg, most commonly as unequivocal lesions that are unmistakably new since the prior CT/MRI)

should be submitted to central imaging vendor. Otherwise, they do not need to be submitted centrally.

9.1.1.1 Methods of Assessment

Contrast-enhanced CT of the chest, abdomen, pelvis, and all other known/suspected sites of disease should be performed for tumor assessments. For participants with SCCHN, a CT or MRI of the neck is required. For participants with TNBC without measurable lesions outside of the breast, contrast-enhanced MRI of the breasts should also be performed. Images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging time points. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Change in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the Investigator using the RECIST v1.1 criteria.

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

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

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

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

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

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

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

9.1.1.2 Imaging and Clinical Assessment

Tumor assessments should continue on the protocol-defined imaging schedule regardless if dosing is delayed or discontinued. Changes in tumor measurements and tumor responses will be assessed by the same investigator or designee using RECIST v1.1 criteria. Investigators will report the number and size of new lesions that appear while on study. The time point of tumor assessments will be reported on the eCRF based on the investigator's assessment using RECIST v1.1 criteria (see Appendix 5 for specifics of RECIST v1.1 criteria to be used in this study). Assessments of PR and CR must be confirmed at least 4 weeks (28 days) after initial response. A BOR of SD requires a minimum of 49 days on study from date of first dose.

9.2 Adverse Events

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

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

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

Contacts for SAE reporting specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

Section 7.1 in the IB[12] represents the Reference Safety Information to determine expectedness of SAEs for expedited reporting. After the participant signs the Pre-Screen ICF for [redacted], all SAEs related to the biopsy must be collected and followed until resolution or stabilization. After the participant signs the main ICF to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

<u>After the Pre-Screen ICF is signed:</u>

- Only SAEs related to the screening biopsy will be collected and followed until resolution or stabilization.
- All related SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of this being available.

After the Main ICF is signed:

- All SAEs related to the screening biopsy will be followed until resolution or stabilization.
- All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within 100 days of discontinuation of dosing except in cases where a study participant has started a new anti-neoplastic therapy. Any SAE occurring after the start of a new anti-neoplastic therapy that is suspected to be related to study treatment by the Investigator will be reported.
- For participants assigned to treatment and never treated with study drug, 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 drug or protocol-specified procedure (eg, follow-up).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF 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 or designee within 24 hours of updated information being available.
- All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected from time of consent.
- All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment.

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

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

9.2.3 Follow-up of AEs and SAEs

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled-out.

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

9.2.4 Regulatory Reporting Requirements for SAEs

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

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

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least for 5 half-lives after study product administration, the Investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

Study treatment will be permanently discontinued in an appropriate manner. Please call the BMS Medical Monitor 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.

9.2.6 Laboratory Test Result Abnormalities

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

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

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

9.2.7 Potential Drug Induced Liver Injury

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

Potential drug-induced liver injury is defined as:

1) Aminotransferases (AT) (ALT or AST) elevation > 3 times ULN

AND

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

AND

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

The key responsibilities for investigators during DILI assessment include (1) early detection, medical evaluation (including the exclusion of other potential causes), and rapid laboratory confirmation of liver-related abnormalities and (2) BMS notification of DILI cases via SAE forms. Following the gathering and assessment of relevant clinical information, BMS is responsible for (1) timely evaluation and triaging of DILI cases, (2) expedited reporting of DILI cases, and (3)

expanded review of 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 DILI criteria. They are expected to promptly notify BMS of all DILI cases. Drug-induced liver injury 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 DILI criteria is a candidate for study treatment discontinuation. Any confirmed DILI events 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, non-exhaustively and by way of example only, the following: infectious diseases (such as active hepatitis A, B, and C), congenital diseases (such as Gilbert's syndrome), neoplastic diseases, 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 Immune-mediated Adverse Events

Immune-mediated AEs 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. Immune-mediated AEs 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.

9.2.9 Other Safety Considerations

Any significant worsening noted during interim or final PEs, ECG, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

9.3 Overdose

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

For this study, any dose of study drug greater than the assigned dose and considered excessive and medically important by the Investigator will be considered an overdose.

In the event of an overdose, the Investigator should:

1) Contact the Medical Monitor immediately.

2) Closely monitor the participant for AEs/SAEs and laboratory abnormalities until BMS-986258 can no longer be detected systemically.
3) Obtain a serum sample for PK if requested by the Medical Monitor (determined on a case-by-case basis).
4) Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications secondary to an overdose will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

9.4 Safety

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

[redacted]

9.4.2 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- A local laboratory will perform the analyses and will provide reference ranges for these tests. Results of clinical laboratory tests performed on Day -1 must be available prior to dosing.
- The laboratory tests that will be performed for study participants are shown in Table 9.4.2-1.
- 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.

Table 9.4.2-1: Clinical Laboratory Assessments

Hematology
Hemoglobin and hematocrit
Total leukocyte count, including differential
Platelet count
Prothrombin time, activated partial thromboplastin time, and *international normalized ratio* (at screening only)
Coagulation (screening only)

Table 9.4.2-1: Clinical Laboratory Assessments	
Serum Chemistry	
Aspartate aminotransferase Alanine aminotransferase Total bilirubin Direct bilirubin (reflex only)[a] Alkaline phosphatase Lactate dehydrogenase Creatinine Creatine kinase/ Creatine phosphokinase C-reactive protein Blood urea nitrogen or urea Uric acid Glucose Lipase Amylase Gamma glutamyl transferase (reflex only)[b] Thyroid stimulating hormone Free T3 and T4 (screening and reflex only)[c]	Total protein Albumin Sodium Potassium Chloride Calcium Phosphorus Magnesium Creatinine clearance (Cockcroft-Gault method) (screening only) Troponin
Urinalysis	
Protein	
Glucose	
Blood	
Leukocyte esterase	
Specific gravity	
pH	
Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick	
Serology	
Serum for hepatitis C Ab, hepatitis B surface antigen, HIV-1 and HIV-2 Ab (at screening, and as mandated by local requirement)	
Other Analyses	
Pregnancy test (WOCBP only: screening, predose, discharge). FSH (screening only and women only)	

[a] Reflex testing to be performed only if total bilirubin is abnormal.

[b] Reflex testing to be performed only if liver function test is abnormal.

[c] Reflex testing to be performed only if TSH is abnormal.

9.4.3 Imaging Safety Assessment

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

9.4.4 Physical Examinations

Refer to the Schedule of Activities for timing of assessments [redacted]

9.4.5 Vital Signs

Refer to the Schedule of Activities for timing of assessments [redacted].

9.5 Pharmacokinetics

The PK of BMS-986258 and nivolumab will be derived, if feasible, from serum concentrations versus time data in monotherapy and in combination with nivolumab. The PK parameters that will be assessed following serial PK collection are shown in Table 9.5-1. Sparse nivolumab concentration-time data will be collected and may be used in an integrated PPK or ER analysis along with data from other nivolumab studies, which would be the subject of a separate report. [redacted]

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

Table 9.5-1: Pharmacokinetic Parameters

Abbreviation	Definition
Parameters to be Reported Separately in Cycle 1 for Parts A, A1, and B	
Cmax	Maximum observed serum concentration
Tmax	Time of maximum observed serum concentration
AUC(0-T)	Area under the serum concentration-time curve from time zero to time of last quantifiable concentration
Ctau	Concentration at the end of the dosing interval
AUC(TAU)	Area under the concentration-time curve in one dosing interval
[redacted]	
Parameters that May Potentially be Assessed Following the Dose Administration in Cycle 3 for Parts A and B	
CLT	Total body clearance
Css-avg	Average concentration over a dosing interval (AUC[TAU]/tau)
AI_AUC	AUC accumulation index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
T-HALFeff_AUC	Effective elimination half-life that explains the degree of accumulation observed
[redacted]	

Table 9.5-1: Pharmacokinetic Parameters

[redacted]

Table 9.5-2, Table 9.5-3, Table 9.5-4, and Table 9.5-5 list the sampling schedule to be followed for the assessment of the PK and immunogenicity of BMS-986258 and nivolumab. All time points are relative to the start of BMS-986258 administration. Pre-dose samples should be taken within 30 minutes before the start of any dose administration. End-of-infusion samples should be taken just prior to the end of infusion (preferably within 2 minutes). On-treatment PK samples are intended to be drawn relative to actual dosing days. 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. Treatment assignments will be released to the bioanalytical laboratory, as needed, in order to minimize unnecessary analysis of samples.

Table 9.5-2: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986258 Q4W in Monotherapy Dose Escalation (Part A)

Study Day of Sample Collection (1 Cycle = 8 Weeks)	Event	Time (Relative to BMS- 986258 Dose) Hour:Min	PK Serum Samples for BMS-986258	ADA Samples for BMS-986258
Cycle 1 Day 1	Predose[a]	00:00	X	X
Cycle 1 Day 1	EOI[b]	EOI[b]	X	
Cycle 1 Day 1		04.00	X	
Cycle 1 Day 2		24:00	X	
Cycle 1 Day 3-Day 5		48:00-96:00	X	
Cycle 1 Day 8		168:00	X	
Cycle 1 Day 15		336:00	X	
Cycle 1 Day 22		504:00	X	
Cycle 1 Day 29	Predose[a]	00:00	X	X
Cycle 1 Day 29	EOI[b]	EOI[b]	X	
Cycle 2 Day 1	Predose[a]	00:00	X	X
Cycle 2 Day 29	Predose[a]	00:00	X	X

Table 9.5-2: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986258 Q4W in Monotherapy Dose Escalation (Part A)

Study Day of Sample Collection (1 Cycle = 8 Weeks)	Event	Time (Relative to BMS- 986258 Dose) Hour:Min	PK Serum Samples for BMS-986258	ADA Samples for BMS-986258
Cycle 3 Day 1	Predose[a]	00:00	X	X
Cycle 3 Day 1	EOI[b]	EOI[b]	X	
Cycle 3 Day 1		04.00	X	
Cycle 3 Day 2		24:00	X	
Cycle 3 Day 3-Day 5		48:00-96:00	X	
Cycle 3 Day 8		168:00	X	
Cycle 3 Day 15		336:00	X	
Cycle 3 Day 22		504:00	X	
Cycle 3 Day 29	Predose[a]	00:00	X	X
Cycle 5 and every other cycle (i.e., cycle 7, 9, ..) Day 1	Predose[a]	00:00	X	X
EOT		00:00	X	X
30 day follow up			X	X
60 day follow up			X	X
100 day follow up			X	X

Abbreviations: ADA, anti-drug antibody; EOI, end of infusion; EOT, end of treatment; PK, pharmacokinetics.

[a] Predose: All predose samples should be taken within 30 minutes prior to the start of any treatments.

[b] The EOI occurs when the entire BMS-986258 dose in the infusion bag is administered to the patient. If diluent is used to flush the dose remaining in the infusion line, then the EOI will occur when there is no dose is remaining in the infusion line after a flush. A PK sample should be taken immediately prior to the EOI (preferably within 2 minutes prior to the EOI). If the EOI is delayed to beyond the nominal infusion duration (30 minutes), 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.

Table 9.5-3: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986258 Q4W in Subcutaneous PK Sub-study (Part A1)

Study Day of Sample Collection (1 Cycle = 8 Weeks)	Event	Time (Relative to BMS-986258 Dose) Hour:Min	PK Serum Samples for BMS-986258	ADA Samples for BMS-986258
Subcutaneous Administration				
Cycle 1 Day 1	Predose[b]	00:00	X	X
Cycle 1 Day 2		24:00	X	
Cycle 1 Day 4- Cycle 1 Day 5		72:00-96:00	X	
Cycle 1 Day 8		168:00	X	
Cycle 1 Day 15		336:00	X	
Cycle 1 Day 22		504:00	X	
Intravenous Administration				
Cycle 1 Day 29	Predose[b]	00:00	X	X
Cycle 1 Day 29	EOI[c]	EOI[c]	X	
Cycle 1 Day 31- Cycle 1 Day 33		48:00- 96:00	X	
Cycle 1 Day 36		168:00	X	
Cycle 1 Day 43		336:00	X	
Cycle 1 Day 50		504:00	X	
Cycle 2 Day 1	Predose[a]	00:00	X	X
Cycle 2 Day 29	Predose[a]	00:00	X	X
Cycle 3 Day 1	Predose[a]	00:00	X	X
Cycle 3 Day 1	EOI[c]	EOI[c]	X	
Cycle 3 Day 29	Predose[a]	00:00	X	X
Cycle 5 and every other cycle (i.e., cycle 7, 9, ..) Day 1	Predose[a]	00:00	X	X
EOT		00:00	X	X
30 day follow up			X	X
60 day follow up			X	X
100 day follow up			X	X

Abbreviations: ADA, anti-drug antibody; EOI, end of infusion; EOT, end of treatment; IV, intravenous; PK, pharmacokinetics; Q4W, every 4 weeks.

[redacted]

[b] Predose: All predose samples should be taken within 30 minutes prior to the start of any treatments.

[c] The EOI occurs when the entire BMS-986258 dose in the infusion bag is administered to the patient. If diluent is used to flush the dose remaining in the infusion line, then the EOI will occur when there is no dose is remaining in the infusion line after a flush. A PK sample should be taken immediately prior to the EOI (preferably within 2 minutes prior to the EOI). If the EOI is delayed to beyond the nominal infusion duration (30 minutes), 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.

Table 9.5-4: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986258 Q4W in Combination with Nivolumab Q4W in Dose Escalation (Part B)

Study Day of Sample Collection (1 Cycle = 8 Weeks)	Event	Time (Relative To BMS-986258 Dose) Hour:Min	PK Serum Samples for BMS-986258	[redacted]	ADA Samples for BMS-986258	[redacted]
Cycle 1 Day 1	Predose[a]	00:00	X		X	
Cycle 1 Day 1	EOI[b]	EOI[b]	X			
Cycle 1 Day 1		04.00	X			
Cycle 1 Day 2		24:00	X			
Cycle 1 Day 3-Day 5		48:00-96:00	X			
Cycle 1 Day 8		168:00	X			
Cycle 1 Day 15		336:00	X			
Cycle 1 Day 22		504:00	X			
Cycle 1 Day 29	Predose[a]	00:00	X		X	
Cycle 1 Day 29	EOI[b]	EOI[b]	X		X	
Cycle 2 Day 1	Predose[a]	00:00	X		X	
Cycle 2 Day 29	Predose[a]	00:00	X		X	
Cycle 3 Day 1	Predose[a]	00:00	X		X	
Cycle 3 Day 1	EOI[b]	EOI[b]	X			
Cycle 3 Day 1		04.00	X			
Cycle 3 Day 2		24:00	X			
Cycle 3 Day 3-Day 5		48:00-96:00	X			
Cycle 3 Day 8		168:00	X			

Table 9.5-4: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986258 Q4W in Combination with Nivolumab Q4W in Dose Escalation (Part B)

Study Day of Sample Collection (1 Cycle = 8 Weeks)	Event	Time (Relative To BMS-986258 Dose) Hour:Min	PK Serum Samples for BMS-986258	[redacted]	ADA Samples for BMS-986258	[redacted]
Cycle 3 Day 15		336:00	X			
Cycle 3 Day 22		504:00	X			
Cycle 3 Day 29	Predose[a]	00:00	X		X	
Cycle 5 and every other cycle (i.e., cycle 7, 9, ..) Day 1	Predose[a]	00:00	X		X	
EOT			X		X	
30 day follow up			X		X	
60 day follow up			X		X	
100 day follow up			X		X	

Abbreviations: ADA, anti-drug antibody; EOI, end of infusion; EOT, end of treatment; PK, pharmacokinetics.

[a] Predose: All predose samples should be taken within 30 minutes prior to the start of any treatments.

[b] The EOI occurs when the entire BMS-986258 dose in the infusion bag is administered to the patient. If diluent is used to flush the dose remaining in the infusion line, then the EOI will occur when there is no dose is remaining in the infusion line after a flush. A PK sample should be taken immediately prior to the EOI (preferably within 2 minutes prior to the EOI). If the EOI is delayed to beyond the nominal infusion duration (30 minutes), 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.

Table 9.5-5: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986258 Q4W in Combination with Nivolumab Q4W in Dose Expansion (Part C)

Study Day of Sample Collection (1 Cycle = 8 Weeks)	Event	Time (Relative To BMS-986258 Dose) Hour:Min	PK Serum Samples for BMS-986258	[redacted]	ADA Samples for BMS-986258	[redacted]
Cycle 1 Day 1	Predose[a]	00:00	X		X	
Cycle 1 Day 1	EOI[b]	EOI[b]	X			
Cycle 1 Day 29	Predose[a]	00:00	X		X	
Cycle 1 Day 29	EOI[b]	EOI[b]	X			
Cycle 2 Day 1	Predose[a]	00:00	X		X	
Cycle 2 Day 29	Predose[a]	00:00	X		X	
Cycle 3 Day 1	Predose[a]	00:00	X		X	
Cycle 3 Day 29	Predose[a]	00:00	X		X	
Cycle 5 and every other cycle (i.e., cycle 7, 9, ..) Day 1	Predose[a]	00:00	X		X	
EOT			X		X	
30 day follow up			X		X	
60 day follow up			X		X	
100 day follow up			X		X	

Abbreviations: ADA, anti-drug antibody; EOI, end of infusion; EOT, end of treatment; PK, pharmacokinetics.

[a] Predose: All predose samples should be taken within 30 minutes prior to the start of any treatments.

[b] The EOI occurs when the entire BMS-986258 dose in the infusion bag is administered to the patient. If diluent is used to flush the dose remaining in the infusion line, then the EOI will occur when there is no dose is remaining in the infusion line after a flush. A PK sample should be taken immediately prior to the EOI (preferably within 2 minutes prior to the EOI). If the EOI is delayed to beyond the nominal infusion duration (30 minutes), 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.

9.6 Pharmacodynamics

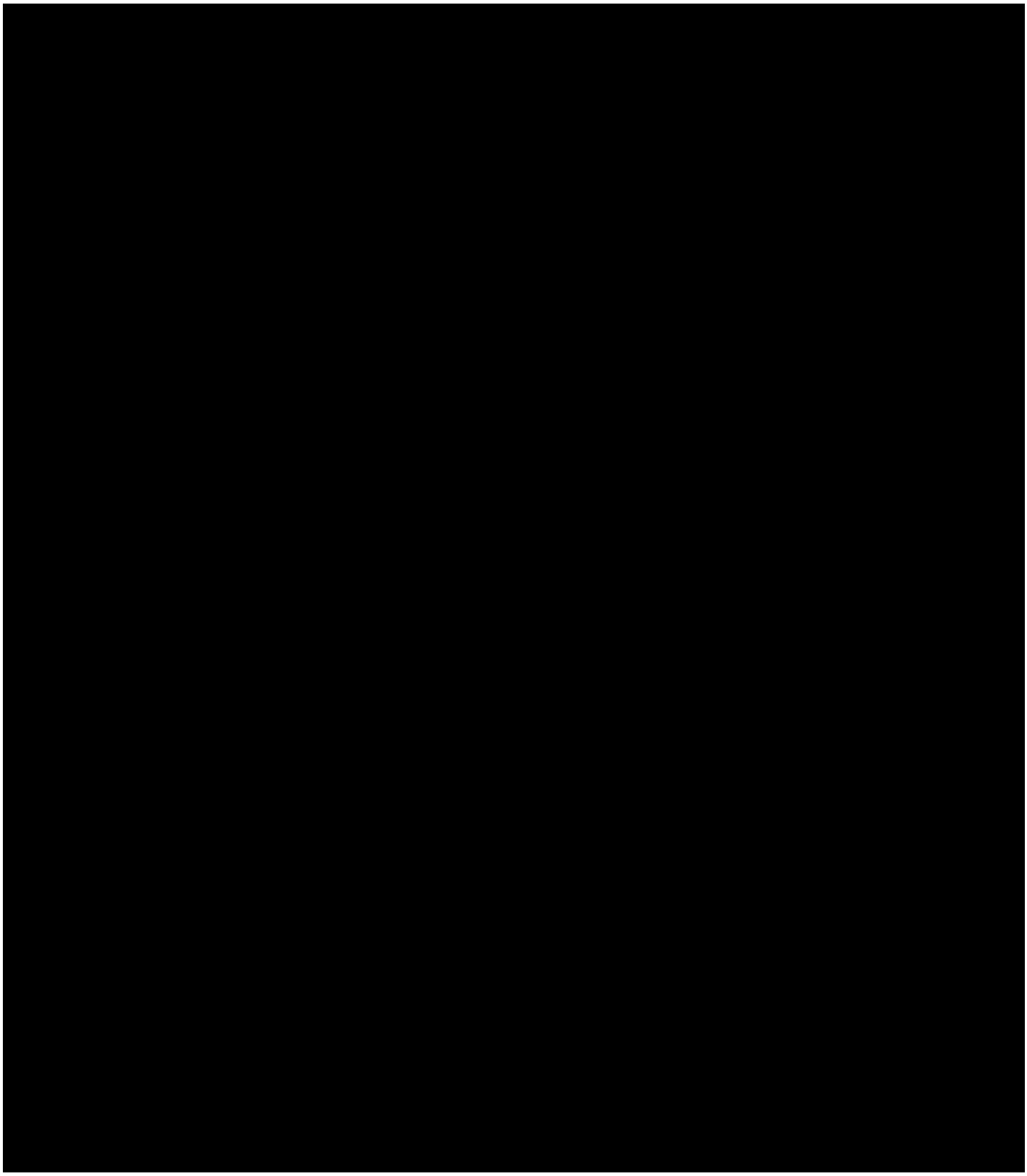
For details about biomarkers, please see Section 9.8.

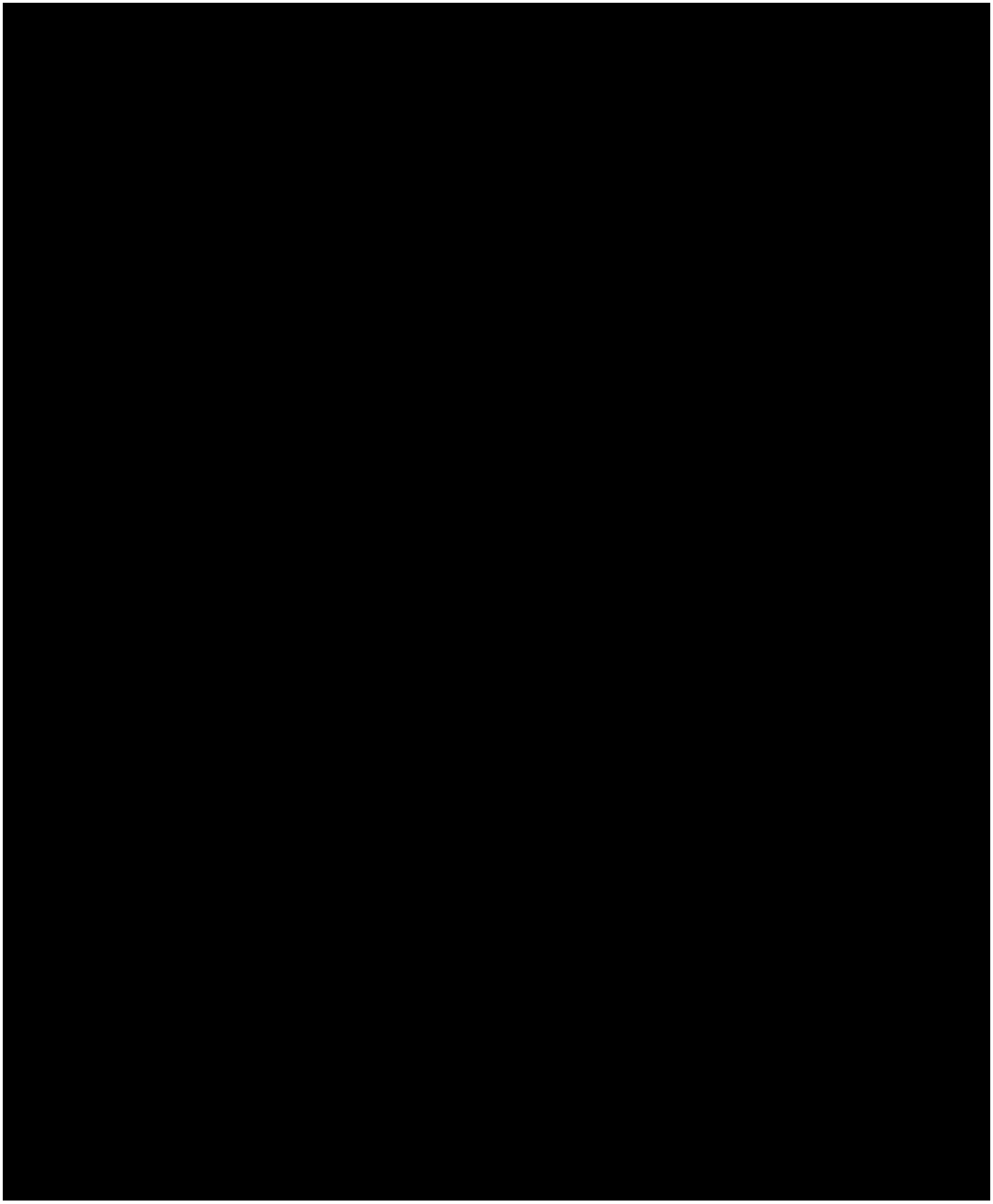
9.7 Pharmacogenomics

Not applicable.

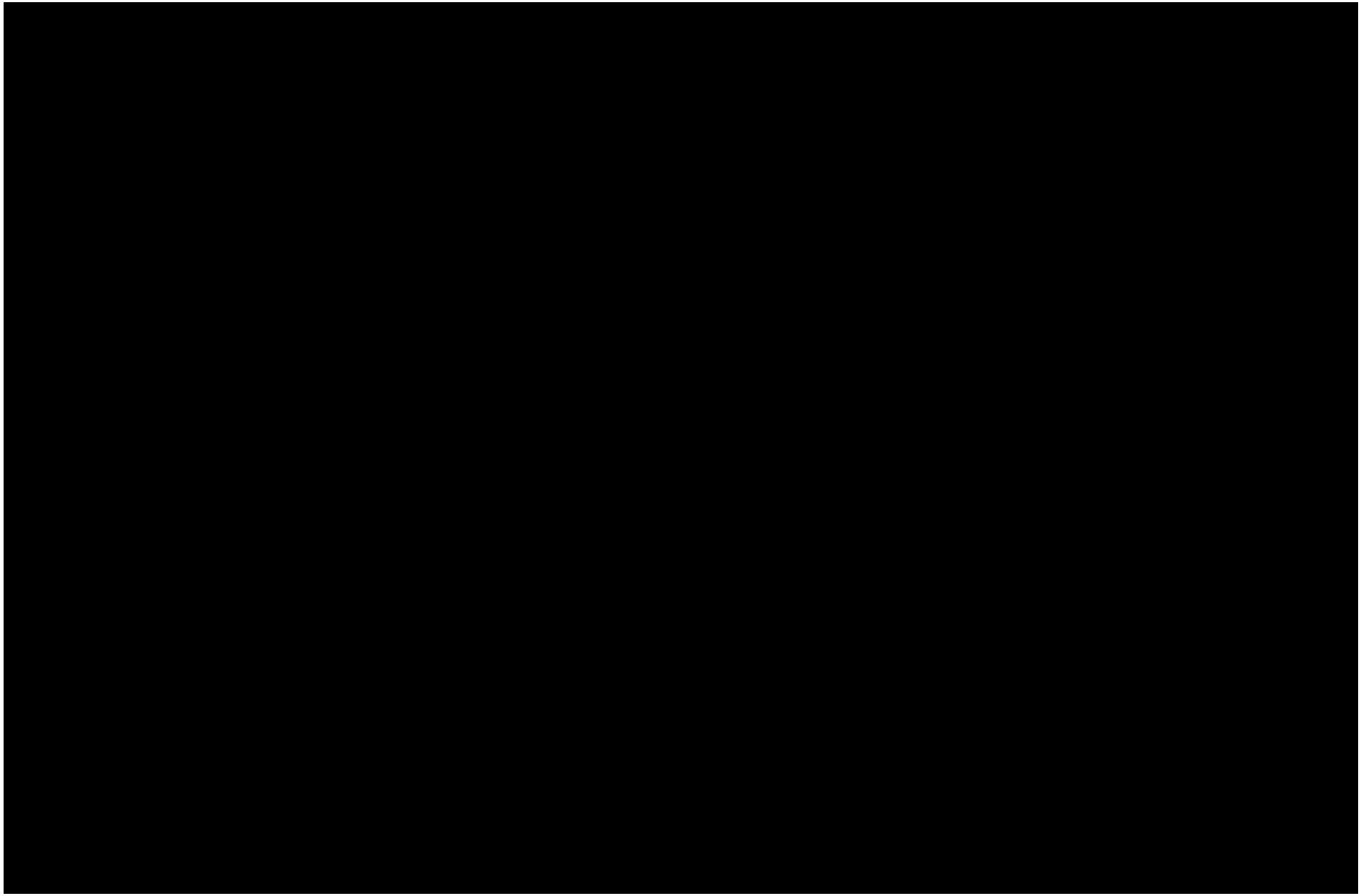
9.7.1 ADME Sampling

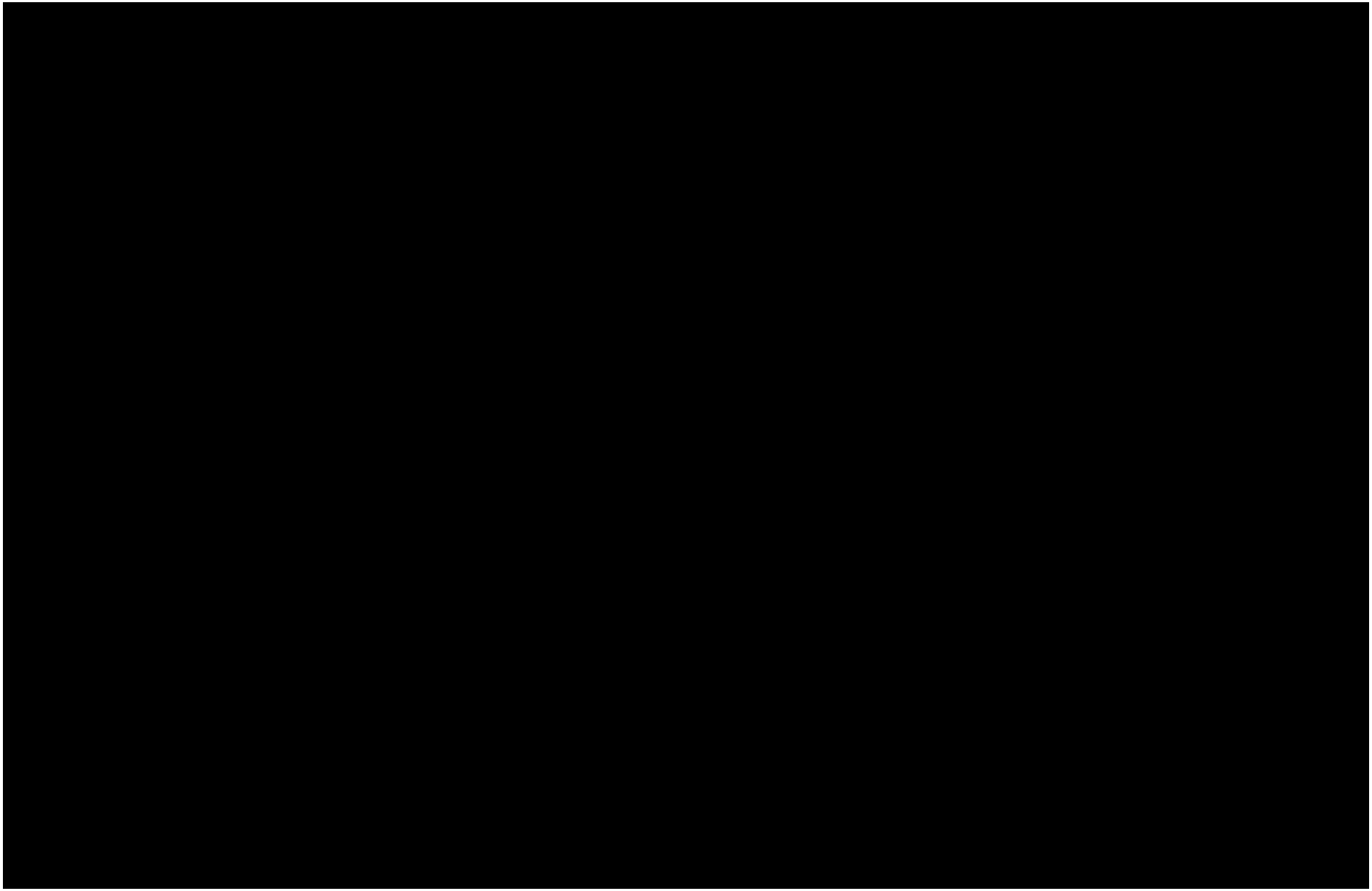
Not applicable.

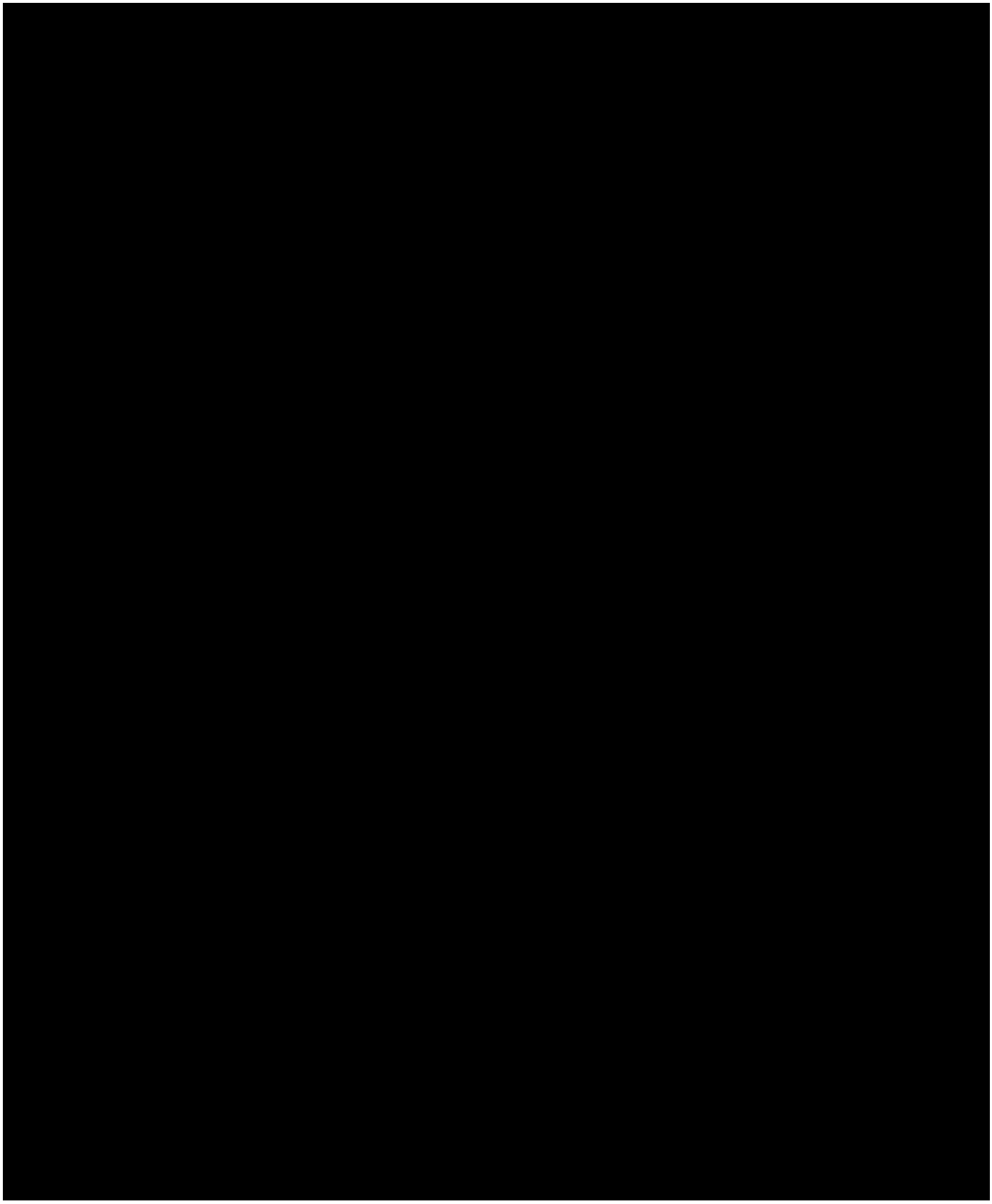




[redacted]







[redacted]

9.9 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/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 Dose Escalation

During the dose escalation phase, an adaptive dose escalation scheme (BLRM for monotherapy and BLRM-copula for combination therapy) employing the 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. [redacted] The operating characteristics of BLRM for monotherapy escalation and BLRM-copula for combination therapy escalation were studied in various scenarios through simulations in [redacted].

The maximum number of participants treated will be [redacted] for dose escalation Part A (BMS-986258 monotherapy) and [redacted] for Part B (BMS-986258 in combination with nivolumab).

Approximately [redacted] participants will be treated at the starting dose levels of BMS-986258 or BMS-986258 in combination with nivolumab. 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 [redacted] participants. At least [redacted] DLT-evaluable participants will be treated at the MTD. At most [redacted] DLT-evaluable participants will be treated at each dose level. Additional participants may be treated at or any dose level below the estimated MTD for further evaluation of safety, PK, or PD parameters as required for a total of up to [redacted] across doses for monotherapy and [redacted] for combination therapy.

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

[redacted]

The final recommended MTD/RP2D will be based on the recommendation from the BLRM/BLRM-copula and overall clinical assessment of all available safety, PK, PD and efficacy data. Lower doses of BMS-986258 may be tested if none of the planned doses are found to be tolerable as monotherapy or in combination with nivolumab. Such decisions will be made after discussion and agreement between the Investigators and the BMS Medical Monitor.

Sample size calculations for the SC study (Part A1) are based on width of the confidence interval for the geometric mean ratio (GMR) of exposure measures for SC and IV dosing. For each dose to be tested in Part A1, the PK parameters are assumed to be distributed log-normally, [redacted] To account for potential missing data, approximately [redacted] subjects will be treated for each dose to be tested in Part A1.

In addition, up to [redacted] participants will be enrolled in each of the Part A and B NSCLC PD cohorts in monotherapy and combination, with the goal of obtaining at least [redacted] participants with evaluable pairs of screening and on-treatment biopsies, in order to evaluate PD changes in NSCLC tumors with minimum [redacted].

[redacted]

For example, assuming a [redacted] intra-participant standard deviation, about [redacted] participants per dose level will be needed to estimate the change from baseline with the above precision; However, in order to account for non-evaluable biopsy samples or lack of repeat biopsy due to early dropouts, about [redacted] more participants would be needed (eg, in order to have [redacted] evaluable participants, up to [redacted] will need to be treated per dose level).

10.1.2 Cohort Expansion

The purpose of cohort expansion is to gather additional safety, tolerability, preliminary efficacy, PK, and PD information regarding BMS-986258 in combination with nivolumab. However, the sample size is strictly based on efficacy, specifically on the target ORR relative to historic response rate.

Part C will be an expansion phase for BMS-986258 in combination with nivolumab and may include participants with RCC, CRC, NSCLC, SCCHN, and TNBC. Enrolled participants with RCC, SCCHN, NSCLC and CRC MSI-H will be relapsed or refractory to prior PD-(L)1 treatment. Participants with a diagnosis of RCC, CRC, NSCLC, and SCCHN may be selected [redacted]. Each disease cohort expansion will be handled independently and there will be no multiplicity adjustment. Up to [redacted] participants may be treated per expansion cohort (for a total of [redacted] in Part C overall) to allow for [redacted] if needed per tumor cohort, although a total of up to [redacted] participants need to be treated across tumor cohorts based on the sample size assumptions and characteristics in the 2-stage design shown below.

[redacted]

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined in Table 10.2-1 below:

Table 10.2-1: Population for Analyses

Population	Description
Enrolled	All participants who sign informed consent and are registered into the IRT.
Treated	All participants who take at least 1 dose of study treatment.
Response-evaluable	All treated participants with measurable disease at baseline and one of the following: (a) at least 1 post-baseline tumor assessment, (b) clinical progression, (c) death.
Pharmacokinetic	All treated participants who have concentration-time data.
Immunogenicity	All treated participants who have baseline and at least 1 post baseline pre-infusion immunogenicity assessment.

Abbreviations: IRT, Interactive Response Technology.

10.3 Statistical Analyses

The Statistical Analysis Plan will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses. Below is a summary of planned

statistical analyses. Results will be presented by study part; data for participants who cross over from the SC cohort (A1) to IV monotherapy or combination treatment will be tabulated separately.

10.3.1 Efficacy Analyses

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

Table 10.3.1-1: Efficacy - Statistical Analyses

Endpoint	Statistical Analysis Methods
ORR is defined as the proportion of population of interest whose BOR is either CR or PR per RECIST v1.1 BOR for a participant will be assessed per RECIST v1.1.	Estimate of ORR and corresponding 2-sided exact 95% CI [redacted] by treatment for each tumor type.
Median DOR DOR for a participant with a BOR of CR or PR is defined as the time between the date of first response and the date of the first objectively documented tumor progression per RECIST v1.1 or death, whichever occurs first.	Median duration of response using the Kaplan-Meier method and corresponding 2-sided 95% CI [redacted] by treatment for each tumor type.
PFS rate at 6, 9, and 12 months 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 [redacted] for each tumor type.

Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response; DOR, duration of response; ORR, overall response rate; PFS, progression free survival; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors.

10.3.2 Safety Analyses

All safety analyses 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, and death	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 PT level, (2) once at the system organ class level, and (3) once in the 'total participant' row at their worst CTC grade, regardless of system organ class or PT.
Laboratory abnormalities Laboratory values will be graded according to CTCAE v4.03.	Laboratory shift table using the worst CTC grade on treatment per participant

Abbreviations: AE, adverse event; CTC, common terminology criteria; CTCAE, common terminology criteria for adverse events; DLTs, dose-limiting toxicities; PT, preferred term; SAE, serious adverse event.

10.3.3 Pharmacokinetic Analyses for BMS-986258 and Nivolumab

Parameters will be reported separately in Parts A, A1, and B in Cycle 1.

Endpoint	Statistical Analysis Methods
BMS-986258	
Parameters and Plots to Be Reported Separately for Cycle 1 in Parts A, A1, and B	
Cmax, AUC(0-T), AUC(TAU), Ctau	Summary statistics: geometric means and coefficients of variation
Tmax	Summary statistics: medians and ranges
Parameters that May potentially be Assessed Following the Dose Administration for Cycle 3 in Parts A and B	
CLT, Css-avg, AI_AUC, and T-HALFeff_AUC	Summary statistics: geometric means and coefficients of variation
Cmax, AUC(TAU)	Scatter plots versus dose for each cycle measured; dose proportionality based on a power model and a CI around the power coefficient
[redacted]	

Abbreviations: AI_AUC, accumulation index ratio of AUC at steady state to that after the first dose; 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; [redacted]; CI, confidence interval; CLT, total body clearance; Cmax, maximum observed concentration; Css-avg, average concentration over a dosing interval (AUC(TAU)/tau); Ctau, observed concentration at the end of a dosing interval; [redacted]; T-HALFeff_AUC, effective elimination half-life that explains the degree of accumulation observed for a specific exposure measure; Tmax, time of maximum observed concentration.

Summary statistics will be tabulated for each PK parameter, if feasible, and wherever applicable, by treatment and dosing regimen. PK time-concentration data may be pooled with data from other studies for PPK analysis, which will be presented in a separate report.

10.3.4 Immunogenicity

Endpoint	Statistical Analysis Methods
• Incidence of ADA to BMS-986258 • [redacted] 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 BMS-986258 baseline ADA-positive participants and ADA-positive participants after initiation of the monotherapy and combination treatment [redacted]

Abbreviations: ADA, anti-drug antibody.

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

[redacted]

[redacted]

10.3.7 Other Analyses

Other exploratory analyses will be described in detail in the Statistical Analysis Plan finalized before database lock. Summary of OS rate [redacted] will be analyzed similarly to PFS rate.

10.3.8 Interim Analyses

The expansion phase of this study employs a 2-stage design framework. Therefore, there will be an interim analysis planned when an adequate number of treated participants have available tumor data. Additional interim analyses may also be performed for administrative purposes or publications. No formal inferences requiring any adjustment to statistical significance level will be performed.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ADA	anti-drug antibody
[redacted]	
AE	adverse event
AI	accumulation index
AI_AUC	AUC accumulation index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve (exposure)
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
BA	bioavailability
BCR	B-cell receptor
BLRM	Bayesian Logistic Regression Model
BMS	Bristol-Myers Squibb
BOR	best overall response
BTLA	B and T-lymphocyte attenuator
C	cycle
Cav-gss	steady-state exposures
CD8	cluster of differentiation 8
CD28	cluster of differentiation 28
[redacted]	

Term	Definition
CHO-OKT3	Chinese hamster ovary cells stably expressing a single-chain variable fragment of anti-CD3 antibody
CI	confidence interval
CLT	total body clearance
[redacted]	[redacted]
Cmax	maximum observed concentration
Cmaxss	steady-state peak concentrations
Cminss	steady-state trough concentrations
CMV	cytomegalovirus
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CRF	case report form
Css-avg	average steady-state concentration
CT	computed tomography
CTLA-4	cytotoxic T lymphocyte–associated antigen 4
Ctau	concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
[redacted]	
CTC	common terminology criteria
CTCAE	common terminology criteria for adverse events
CYP	cytochrome P450
DC	dendritic cells
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
EC50	half-maximal effective concentration
EC90	90% maximal effective concentration
[redacted]	[redacted]

Term	Definition
[redacted]	[redacted]
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor 2
EOI	end of infusion
EOT	end of treatment
ER	exposure response
EWOC	escalation with overdose control
[redacted]	[redacted]
Fc	fraction crystallizable
[redacted]	
FDA	Food and Drug Administration
[redacted]	[redacted]
FIH	first in human
FSH	follicle stimulating hormone
GLP	Good Laboratory Practices
GMR	geometric mean ratio
GPVE	Global Pharmacovigilance and Epidemiology
[redacted]	[redacted]
HAVCR2	hepatitis A virus cellular receptor 2
hERG	human ether-a-go-go-related gene
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HPV	human papillomavirus
HR	hazard ratio
IB	investigator's brochure
ICF	informed consent form
ICOS	inducible costimulator
IFN-γ	interferon gamma
Ig	immunoglobulin

Term	Definition
IgG	immunoglobulin G
[redacted]	[redacted]
IL	interleukin
IMAEs	immune-mediated AEs
IMP	Investigational Medicinal Product
I-O	immuno-oncology
IP	investigational product
irAE	immune-related adverse event
IRT	interactive response technology
IV	intravenous
[redacted]	[redacted]
mAb	monoclonal antibody
MAAD	maximum administered dose
mDOR	median duration of response
MDS	myelodysplastic syndrome
MLR	mixed lymphocyte reaction
MMR	mismatch repair
MMR-D	mismatch repair-deficient
MRI	magnetic resonance imaging
MRSD	maximum recommended starting dose
MSI-H	microsatellite instability high
MSS	microsatellite stable
MST	Medical Surveillance Team
MTD	maximum tolerated dose
[redacted]	[redacted]
N	number of subjects or observations
NCI	National Cancer Institute
NK	natural killer
NOAEL	non-observed-adverse-effect
NSCLC	non-small cell lung cancer

Term	Definition
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	pharmacodynamics
PD-1	programmed cell death 1
PD-L1	programmed death ligand 1
PD-L2	programmed death ligand 2
[redacted]	[redacted]
PET	positron emission tomography
PFS	progression-free survival
PID	patient identification number
PK	pharmacokinetics
PPK	population pharmacokinetic
PR	partial response
PS	phosphatidylserine
PT	preferred term
Q2W	every 2 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks
[redacted]	[redacted]
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
RCC	renal cell carcinoma
RECIST	response evaluation criteria in solid tumors
[redacted]	[redacted]
RO	receptor occupancy
RP2D	recommended Phase 2 dose
rHuPH20	recombinant human hyaluronidase Ph20
RT-PCR	reverse transcription polymerase chain reaction

Term	Definition
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
[redacted]	
T-HALF	apparent elimination half-life
T-HALFeff_AUC	effective elimination half-life that explains the degree of accumulation observed
TIL	tumor-infiltrating lymphocyte
TIM-3	T-cell immunoglobulin and mucin domain-3
Tmax, TMAX	time of maximum observed concentration
[redacted]	
TNBC	triple negative breast cancer
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
[redacted]	
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

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

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

All potential serious breaches must be reported to Sponsor or designee immediately. A serious breach is a breach of the conditions and principles of GCP (occurring in any country) in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of 1 or more subjects of the study or the scientific value of the study.

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if

applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects.

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

- IRB/IEC 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 currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.

- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

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

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

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

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

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

SOURCE DOCUMENTS

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

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

STUDY TREATMENT RECORDS

Records for study 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 • non-study disposition (e.g., lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy.

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

CASE REPORT FORMS

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

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

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

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

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

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

MONITORING

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

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

Certain CRF pages and/or electronic files may serve as the source documents:

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

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

RECORDS RETENTION

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

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

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

RETURN OF STUDY TREATMENT

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

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

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

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

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

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

DISSEMINATION OF CLINICAL STUDY DATA

In order to benefit potential study participants, patients, healthcare providers and researchers, and to help BMS honor its commitments to study participants, BMS will make information about clinical research studies and a summary of their results available to the public as per regulatory and BMS requirements. BMS will post study information on local, national or regional databases in compliance with national and international standards for disclosure. BMS may also voluntarily disclose information to applicable databases.

CLINICAL STUDY REPORT AND PUBLICATIONS

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

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

- Participant recruitment (eg, among the top quartile of enrollers)
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set

forth in the clinical trial agreement (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.

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).

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

EVALUATING AES AND SAES

Assessment of Causality

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

Follow-up of AEs and SAEs

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

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

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

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

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

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

End of Relevant Systemic Exposure

End of relevant systemic exposure is the time point where the IMP or any active major metabolites has decreased to a concentration that is no longer considered to be relevant for human

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

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

Any birth control method used must be highly effective with a failure rate less than 1% per year. WOCBP must use an adequate method(s) to avoid pregnancy for the duration of this study and for up to 5 months after the last dose of study drugs. Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Methods of Contraception	Progestogen only hormonal contraception associated with inhibition of ovulation
	Hormonal methods of contraception including oral contraceptive pills (combination of estrogen and progesterone), vaginal ring, injectables, implants, transdermal and intrauterine hormone-releasing system (IUS)
	Bilateral tubal ligation
	Vasectomized Partner
	Intrauterine devices (IUD)
	Complete abstinence
Unacceptable Methods for Contraception	Vaginal sponge with spermicide
	Progestin only pills
	Cervical cap with spermicide
	Diaphragm with spermicide
	Periodic abstinence (calendar, symptothermal, post-ovulation methods)
	Withdrawal (coitus interruptus)
	Spermicide only
	Lactation amenorrhea method (LAM)
	Male condoms with or without spermicide for partners of female subjects, as the only method of contraception
	Female condoms
	A male and a female condom must not be used together

COLLECTION OF PREGNANCY INFORMATION

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

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

1 EVALUATION OF LESIONS

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

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

1.1 Measurable

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

- 10 mm by CT/MRI scan (scan slice thickness no greater than 5 mm), or ≥ 2x slice thickness if greater than 5mm.

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

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

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

1.2 Non-Measurable

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

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

1.3 Special Considerations Regarding Lesion Measurability

1.3.1 Bone Lesions

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

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

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

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

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

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

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

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

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

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

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

2.1.1.2 Target lesions that become 'too small to measure'

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

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

2.1.1.3 Lesions that split or coalesce on treatment

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

2.2 Evaluation of Non-Target Lesions

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

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

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

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

2.2.1.1 When the patient also has measurable disease

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

2.2.1.2 When the patient has only non-measurable disease

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

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

2.2.2 New Lesions

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

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

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

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

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

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

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

2.3.2 Time Point Response

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

Table 2.3.2-1: Time Point Response

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		
Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR, complete response, PD, progressive disease and NE, inevaluable		

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

2.3.3 Best Overall Response

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

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

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

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

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	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.

APPENDIX 6 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 7 NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Heart failure is usually classified according to the severity of the patient's symptoms. The table below describes the most commonly used classification system, the New York Heart Association (NYHA) functional classification. It places patients in 1 of 4 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, or dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, or 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 8 MANAGEMENT ALGORITHMS

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

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

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

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

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

GI Adverse Event Management Algorithm

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

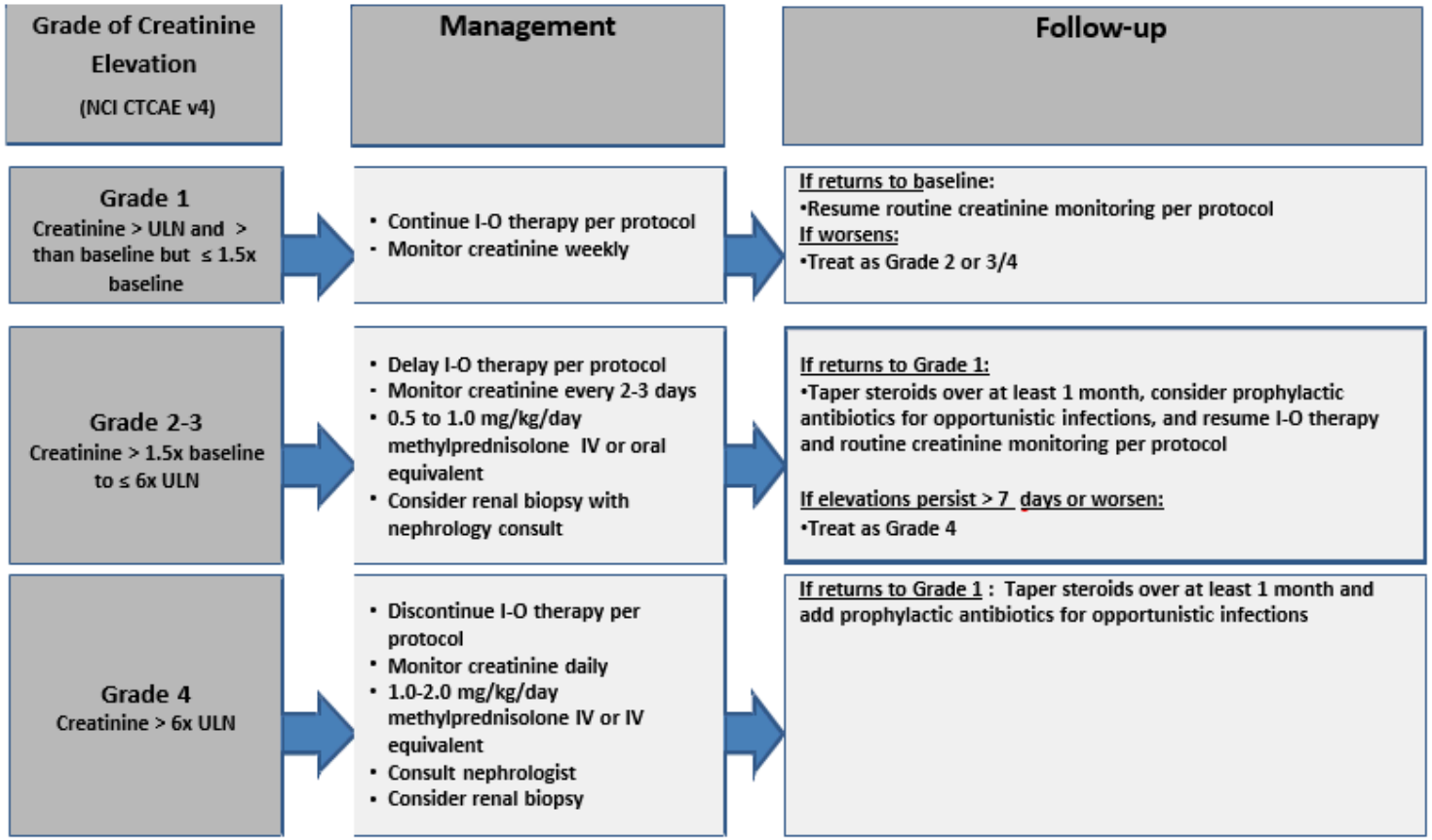
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (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.

25-Jun-2019

Renal Adverse Event Management Algorithm

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

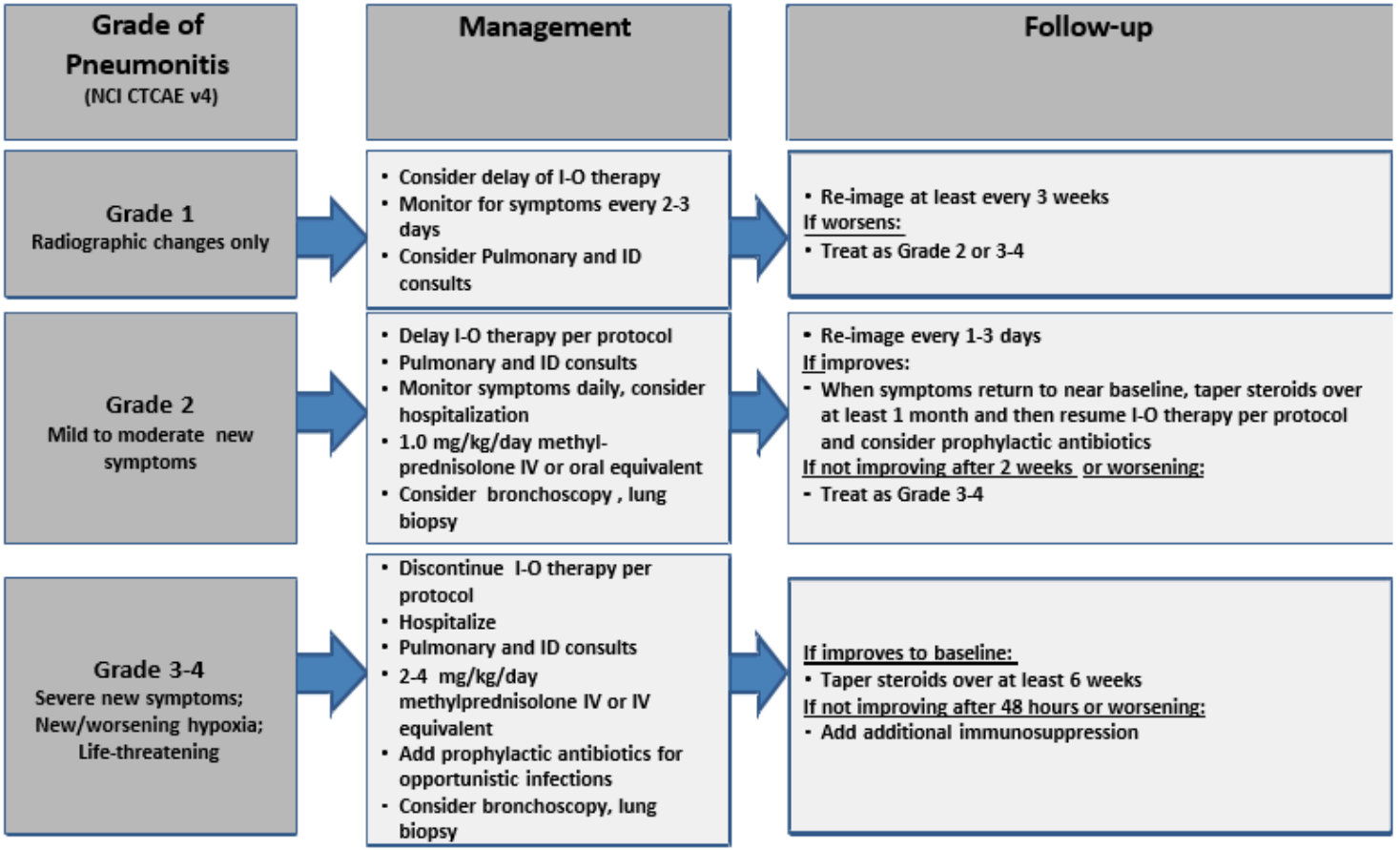


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

25-Jun-2019

Pulmonary Adverse Event Management Algorithm

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

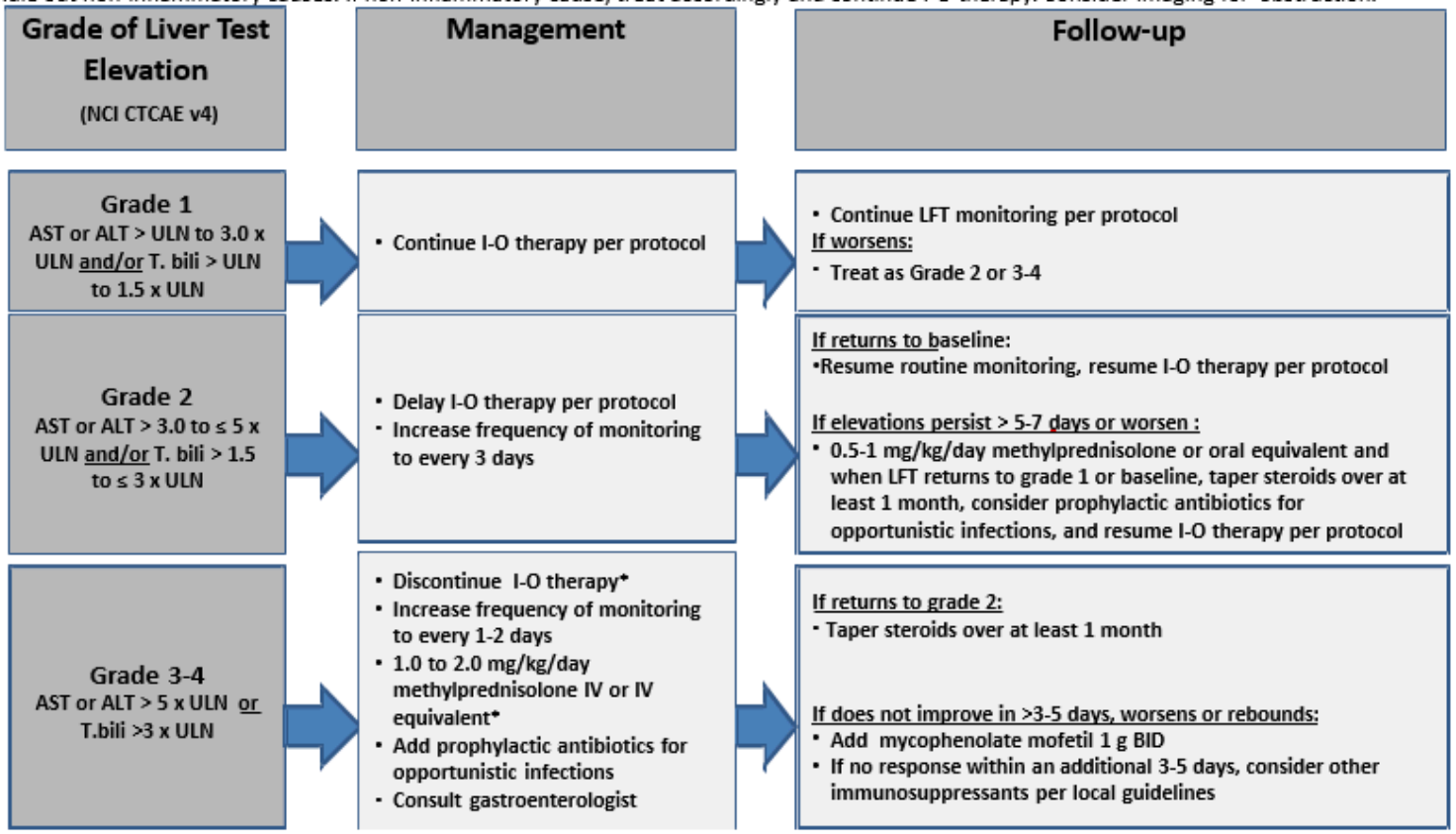


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

25-Jun-2019

Hepatic Adverse Event Management Algorithm

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



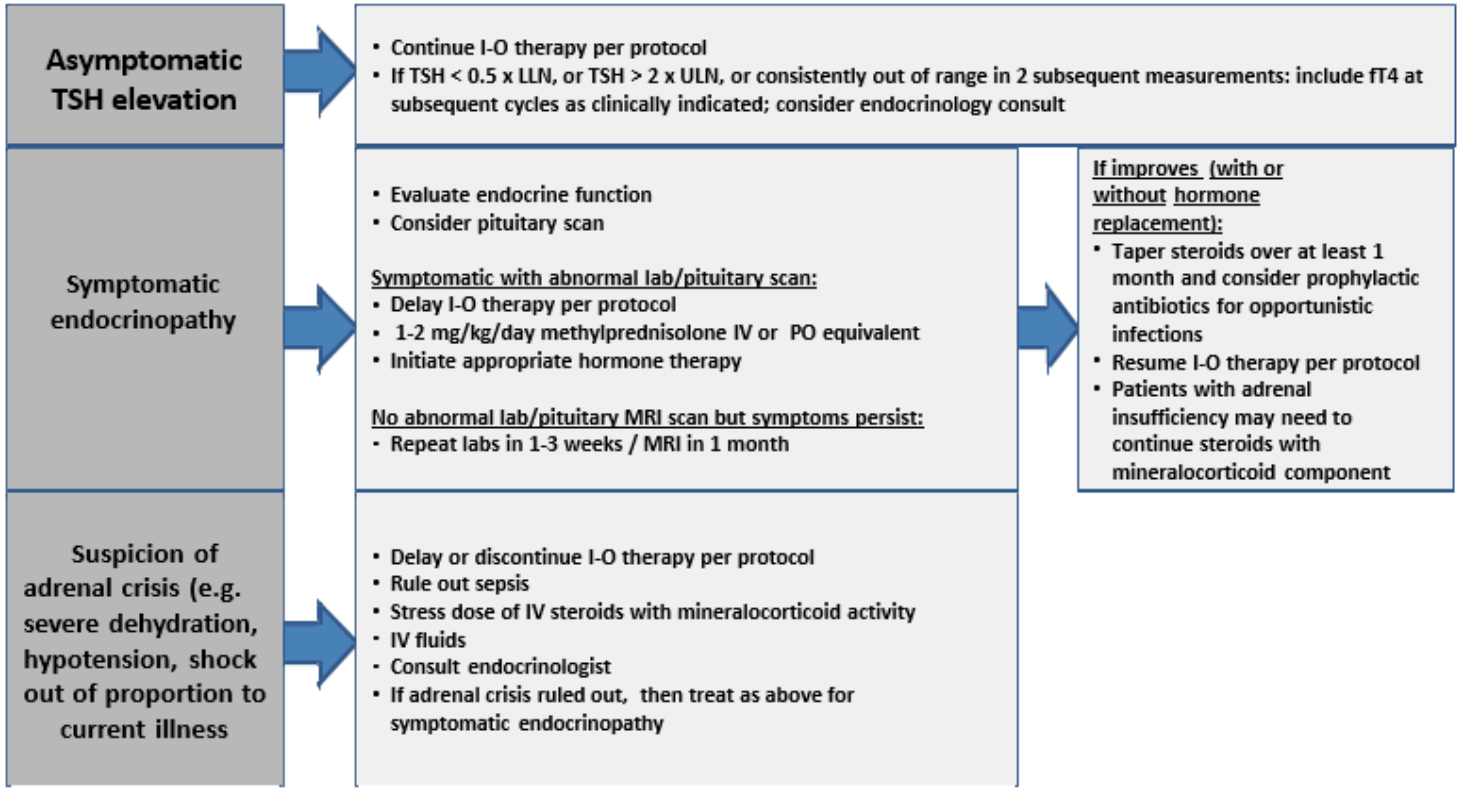
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

25-Jun-2019

Endocrinopathy Adverse Event Management Algorithm

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

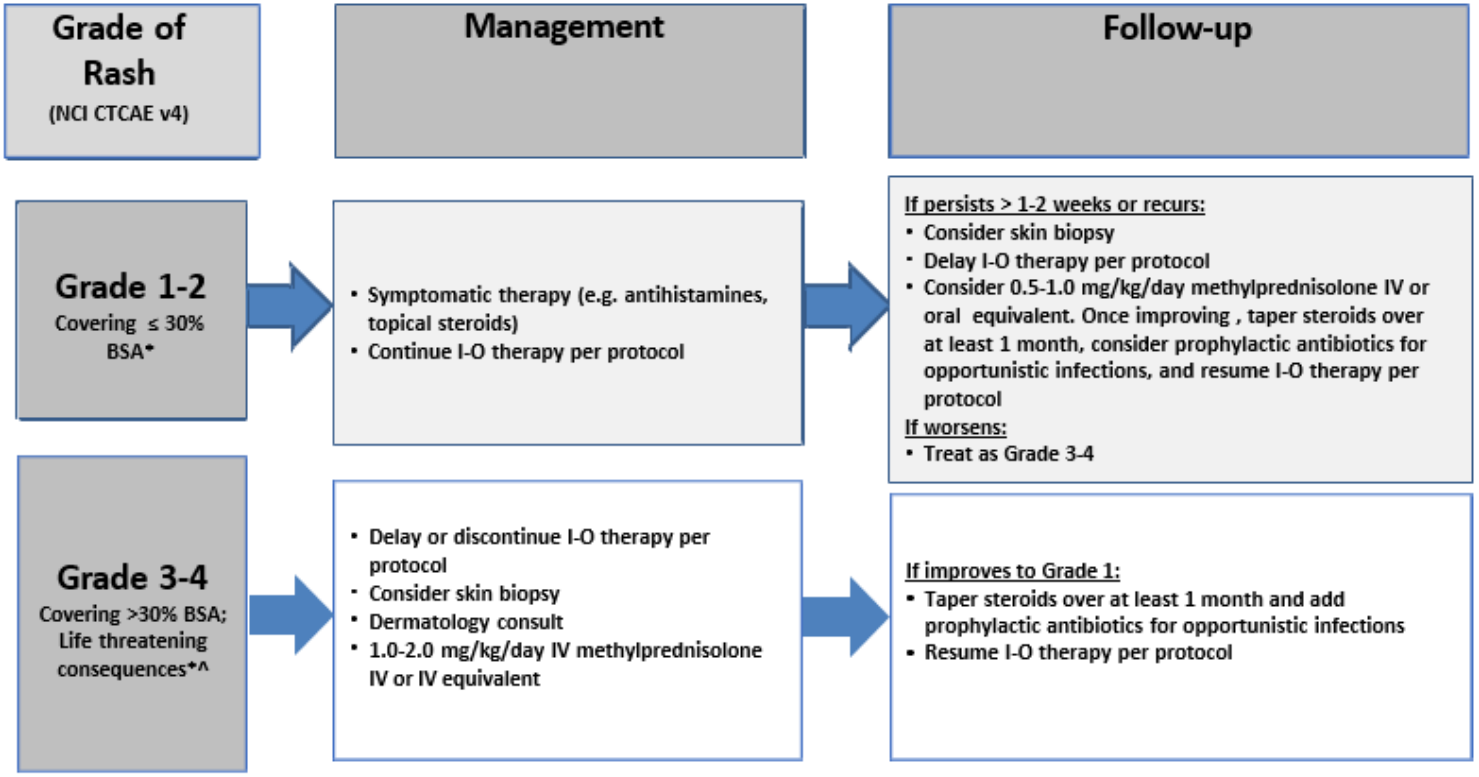


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

25-Jun-2019

Skin Adverse Event Management Algorithm

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



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

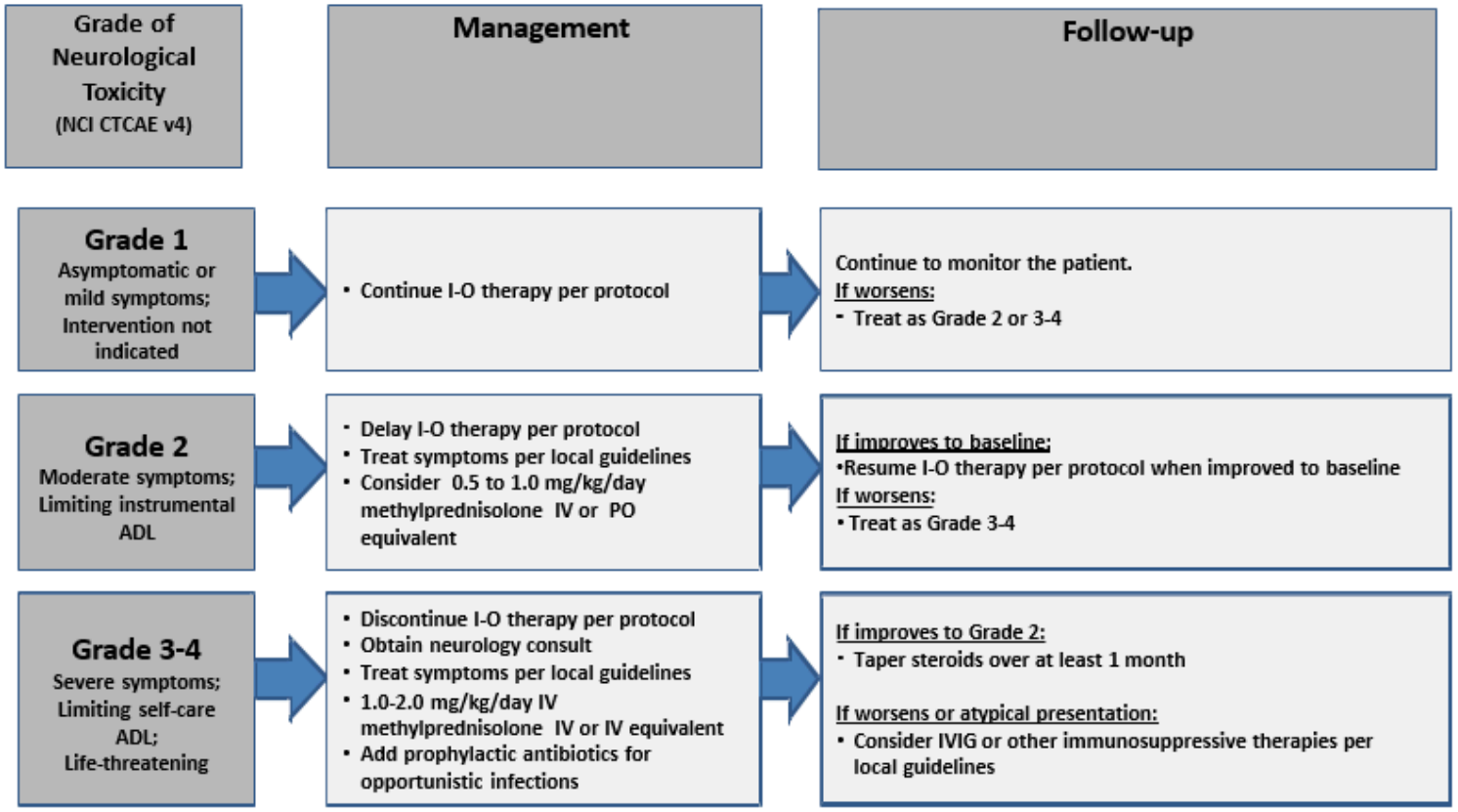
*Refer to NCI CTCAE v4 for term-specific grading criteria.

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

25-Jun-2019

Neurological Adverse Event Management Algorithm

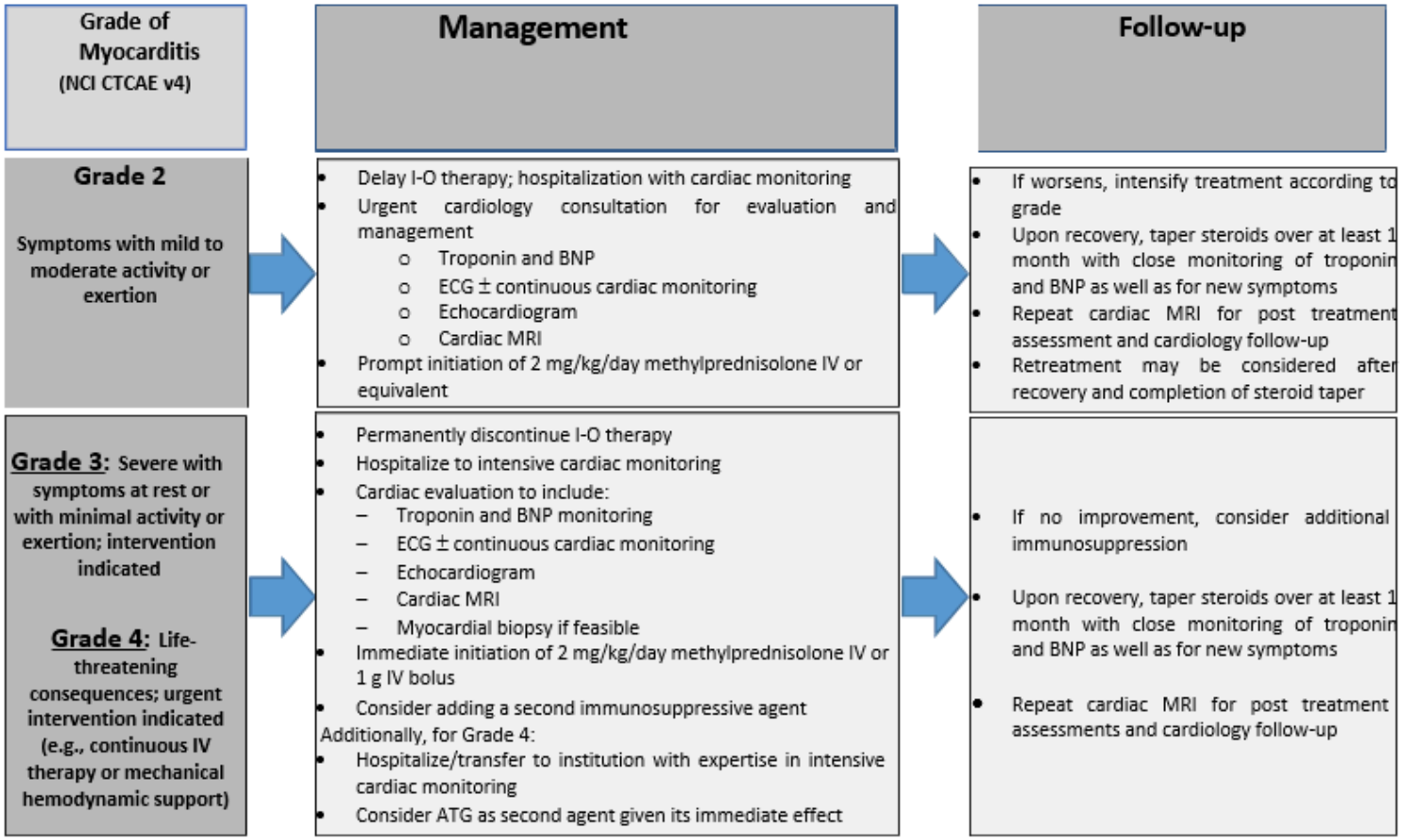
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

25-Jun-2019

Myocarditis Adverse Event Management Algorithm

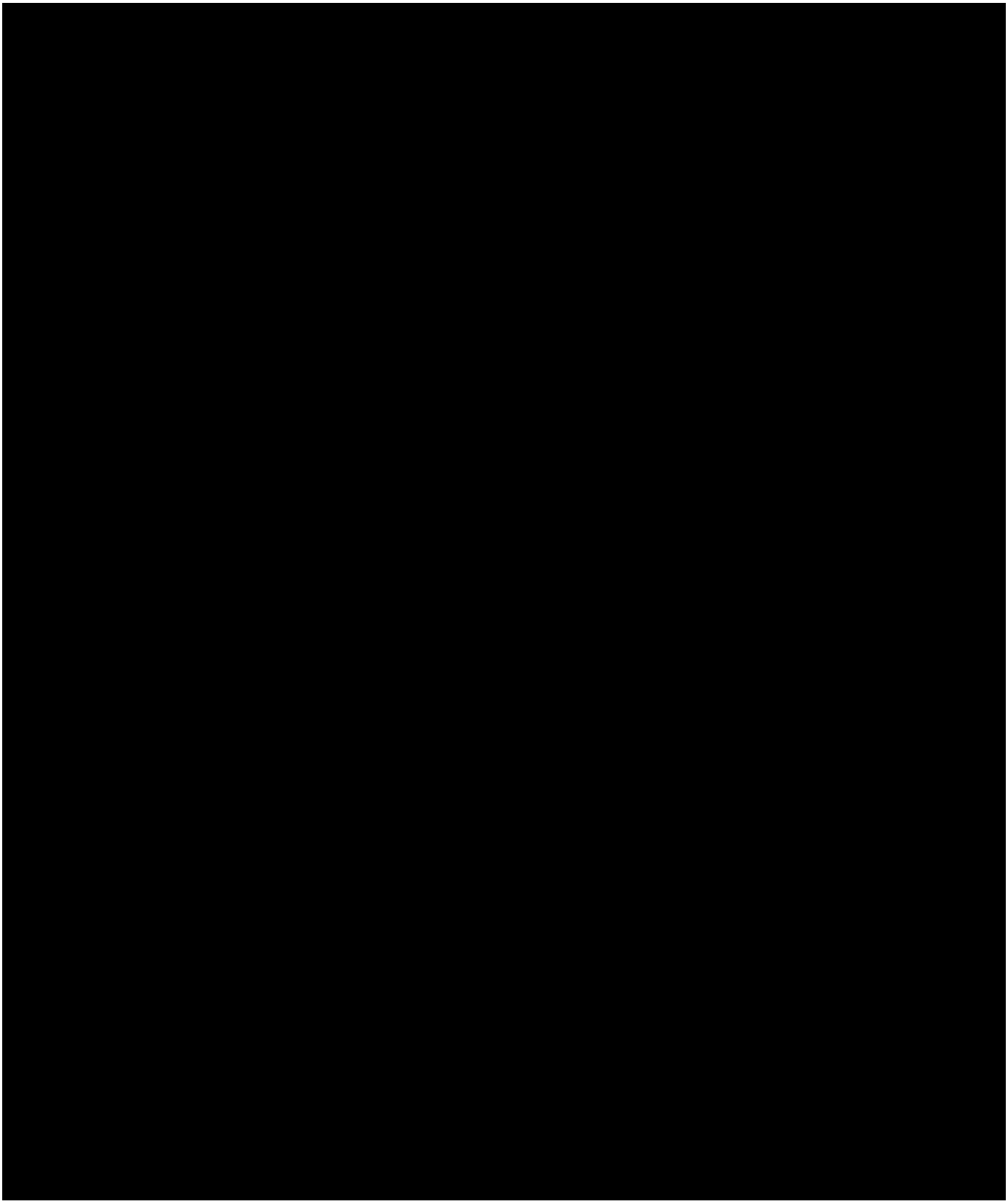


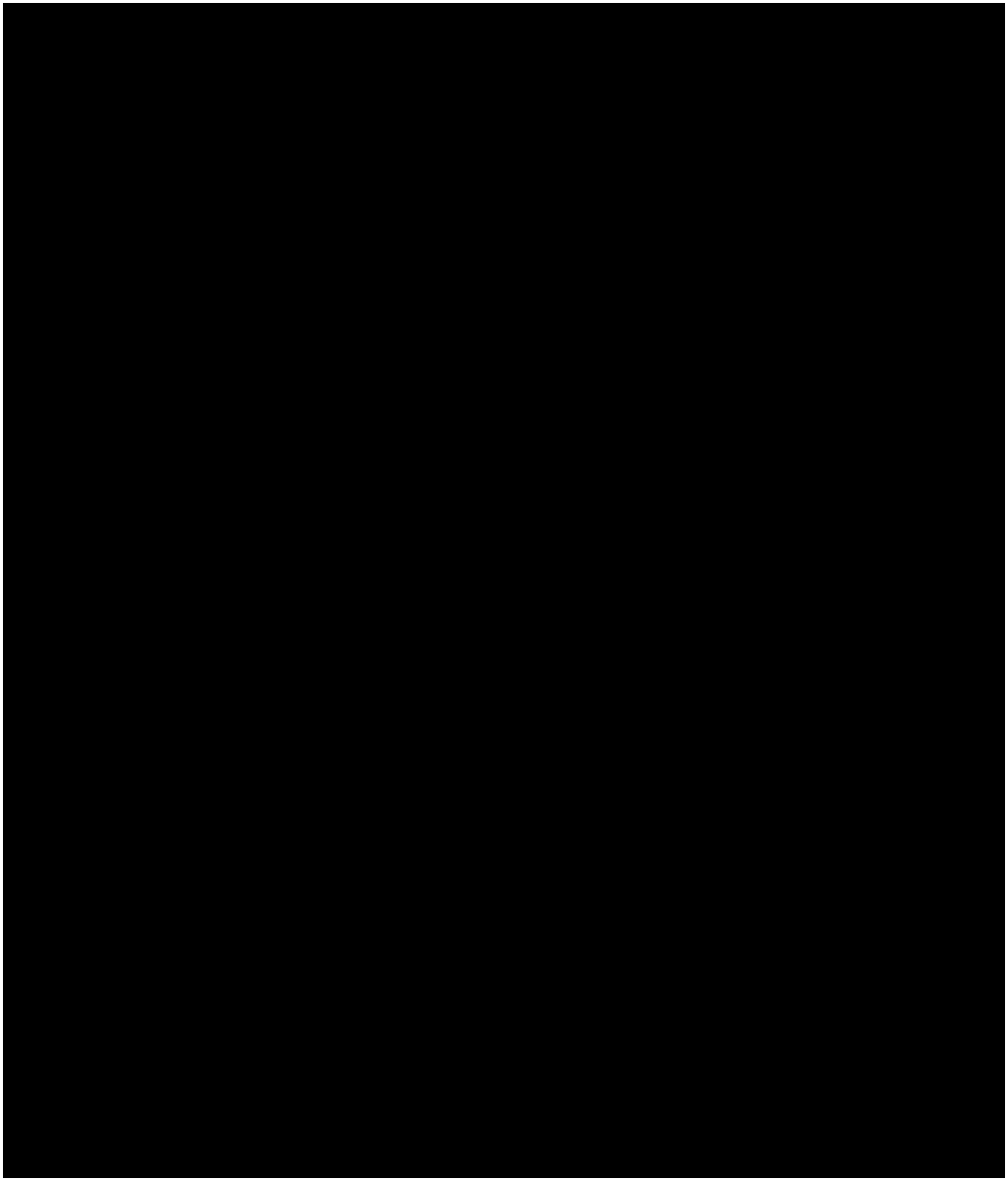
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

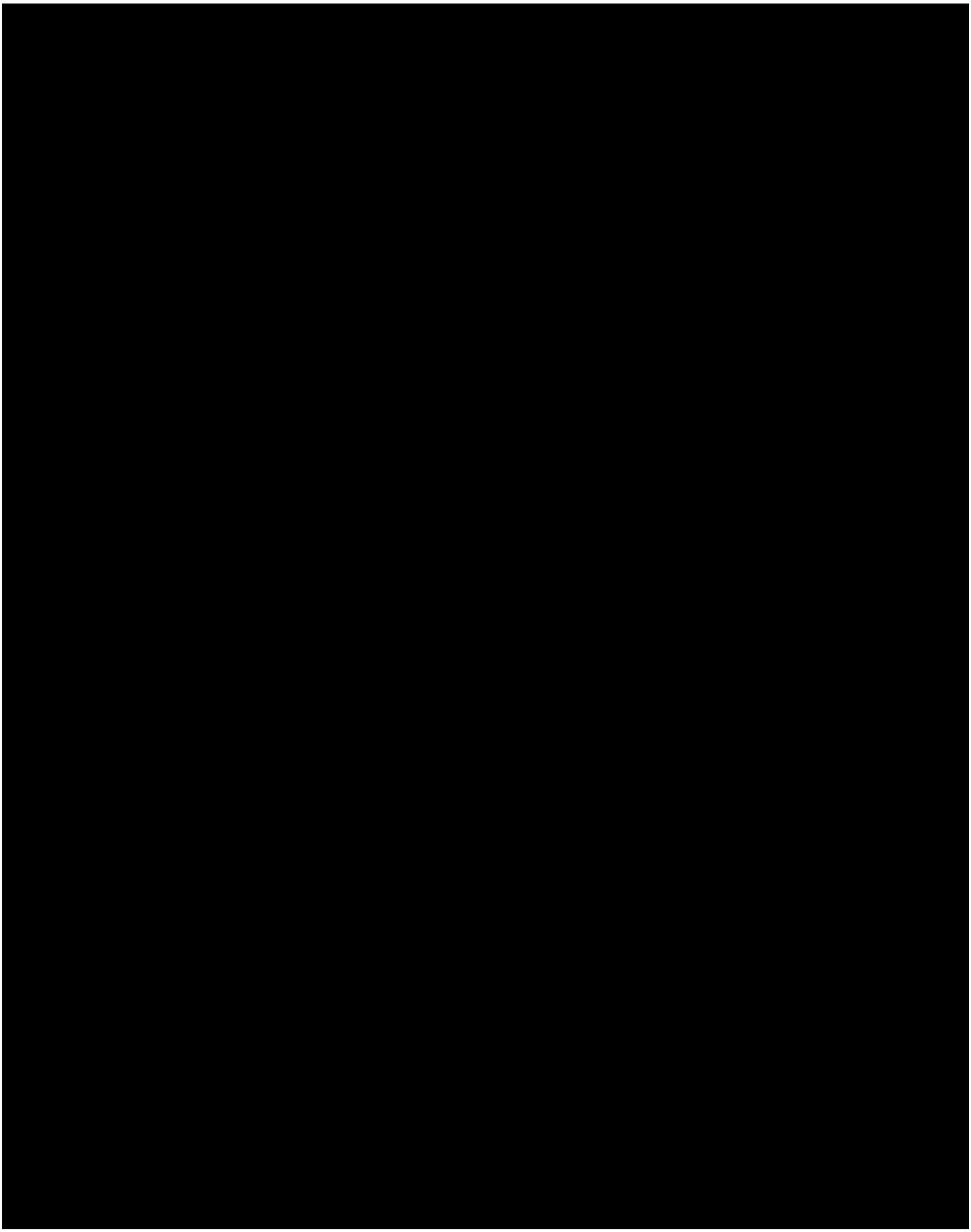
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

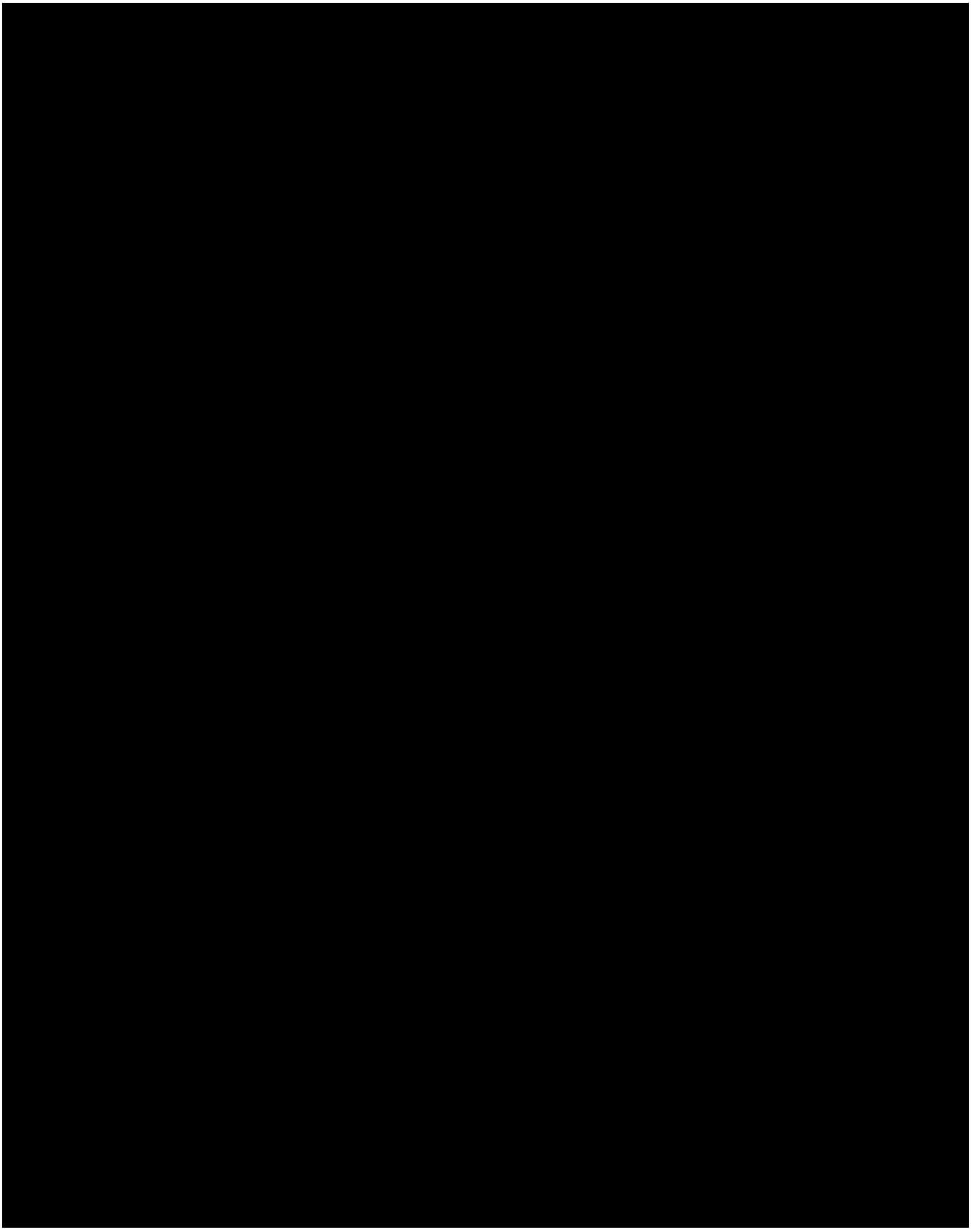
ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

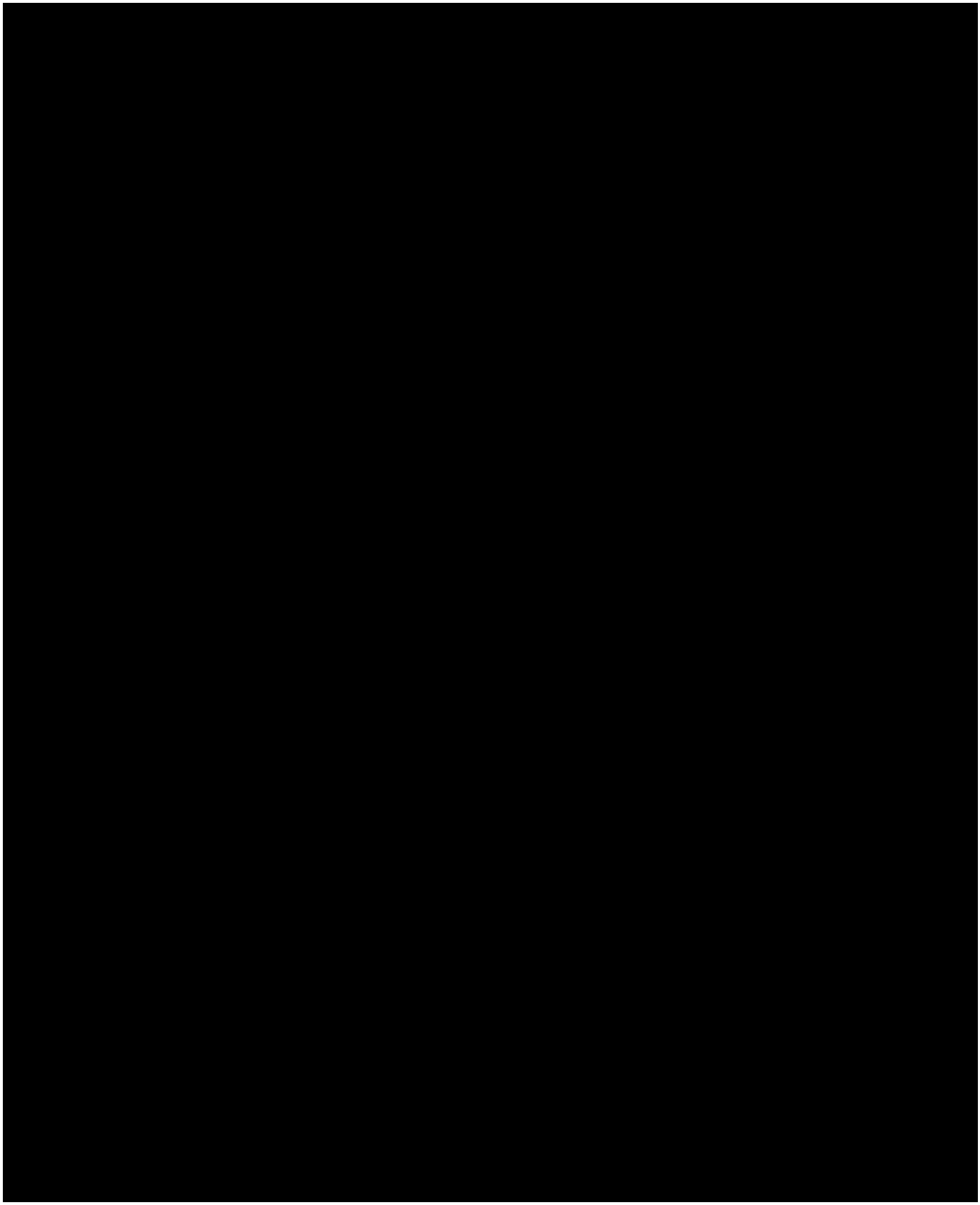
25-Jun-2019

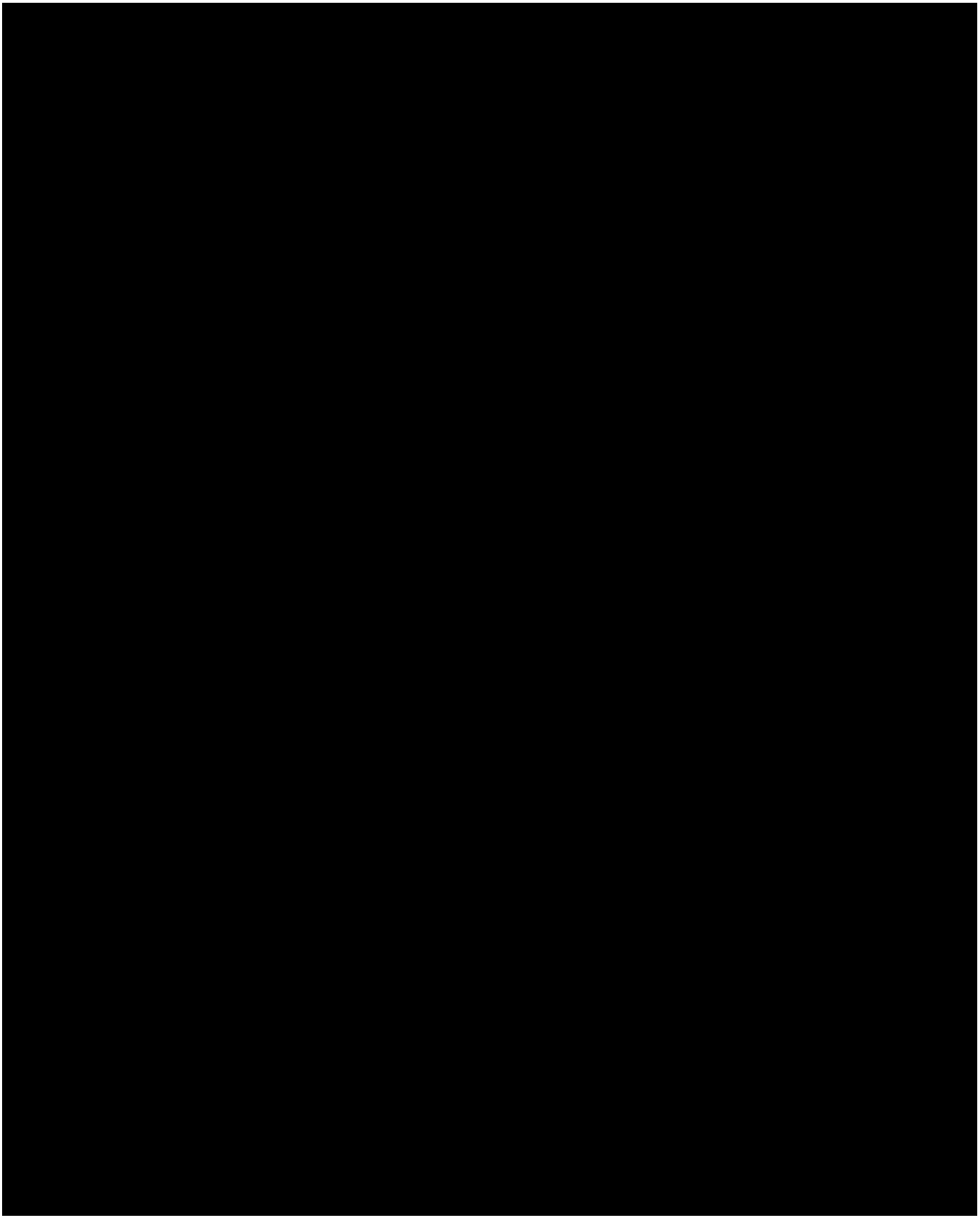


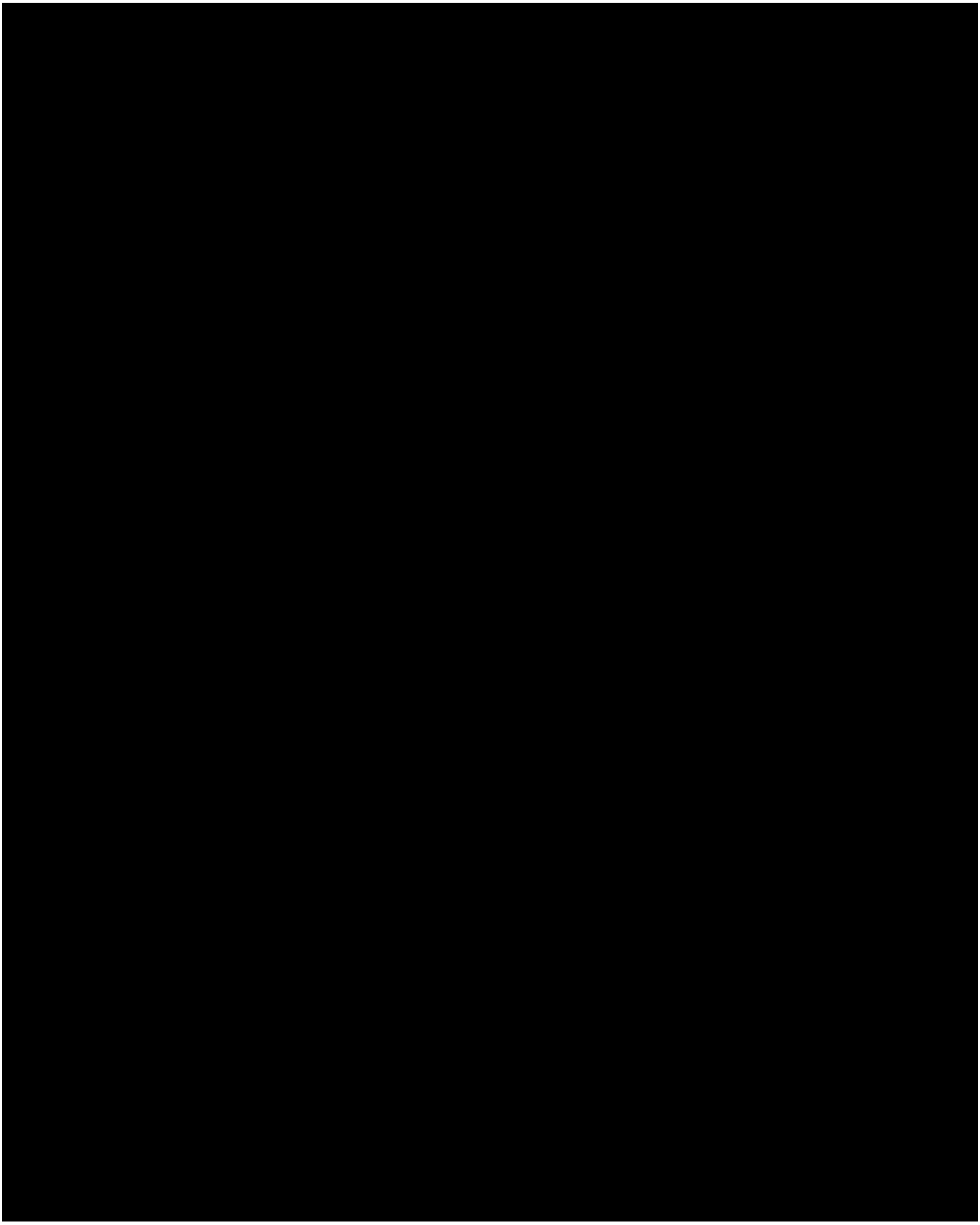


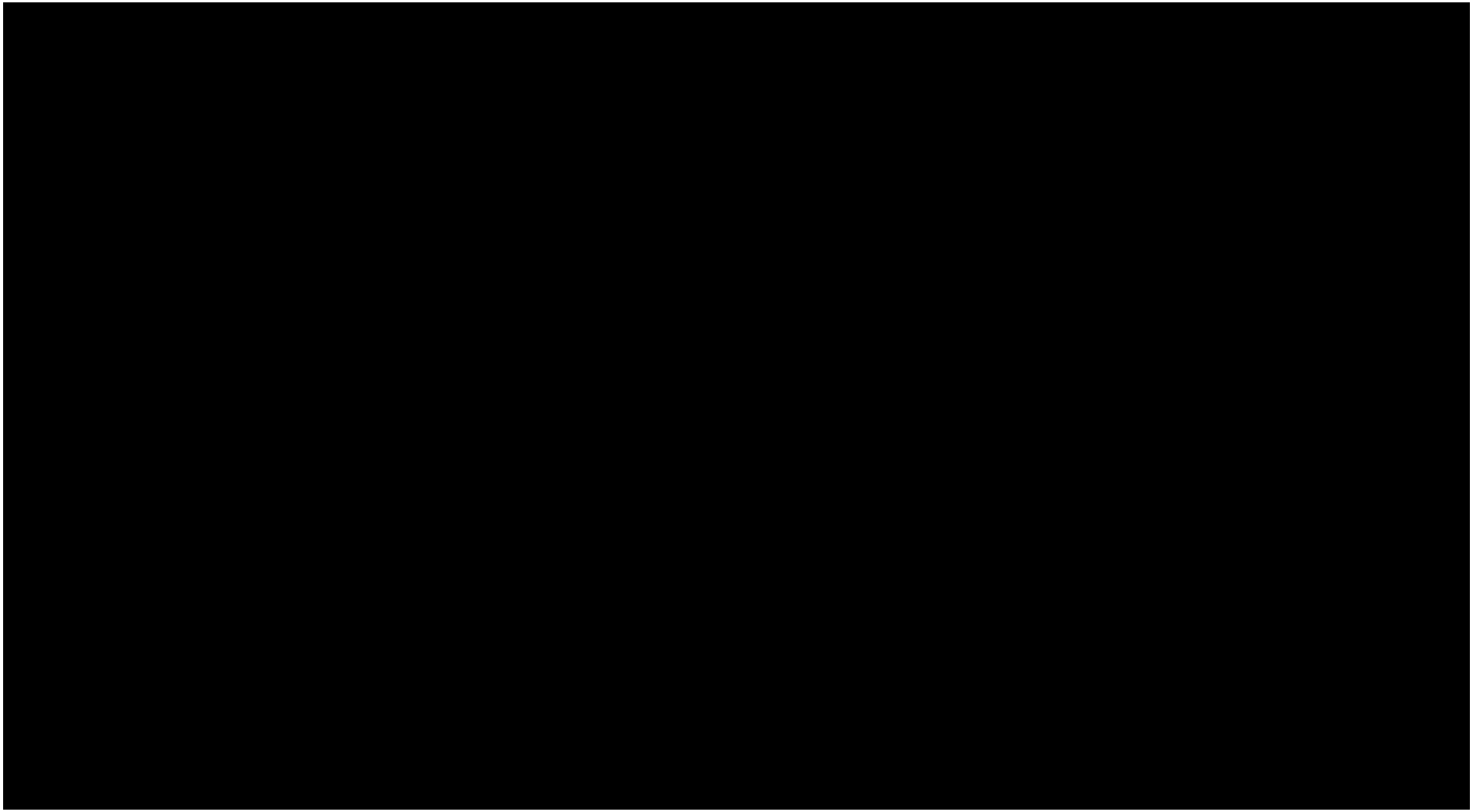


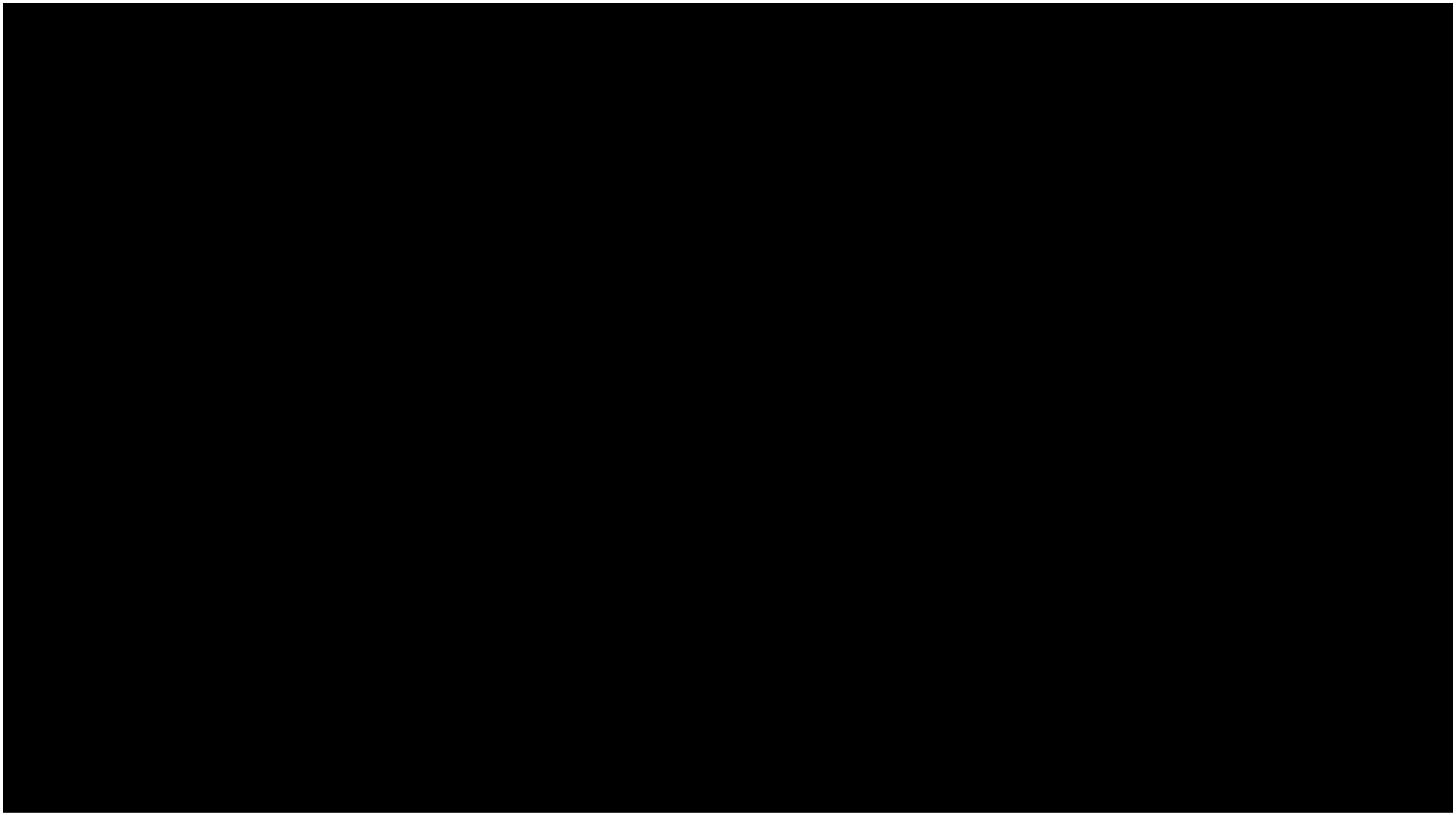


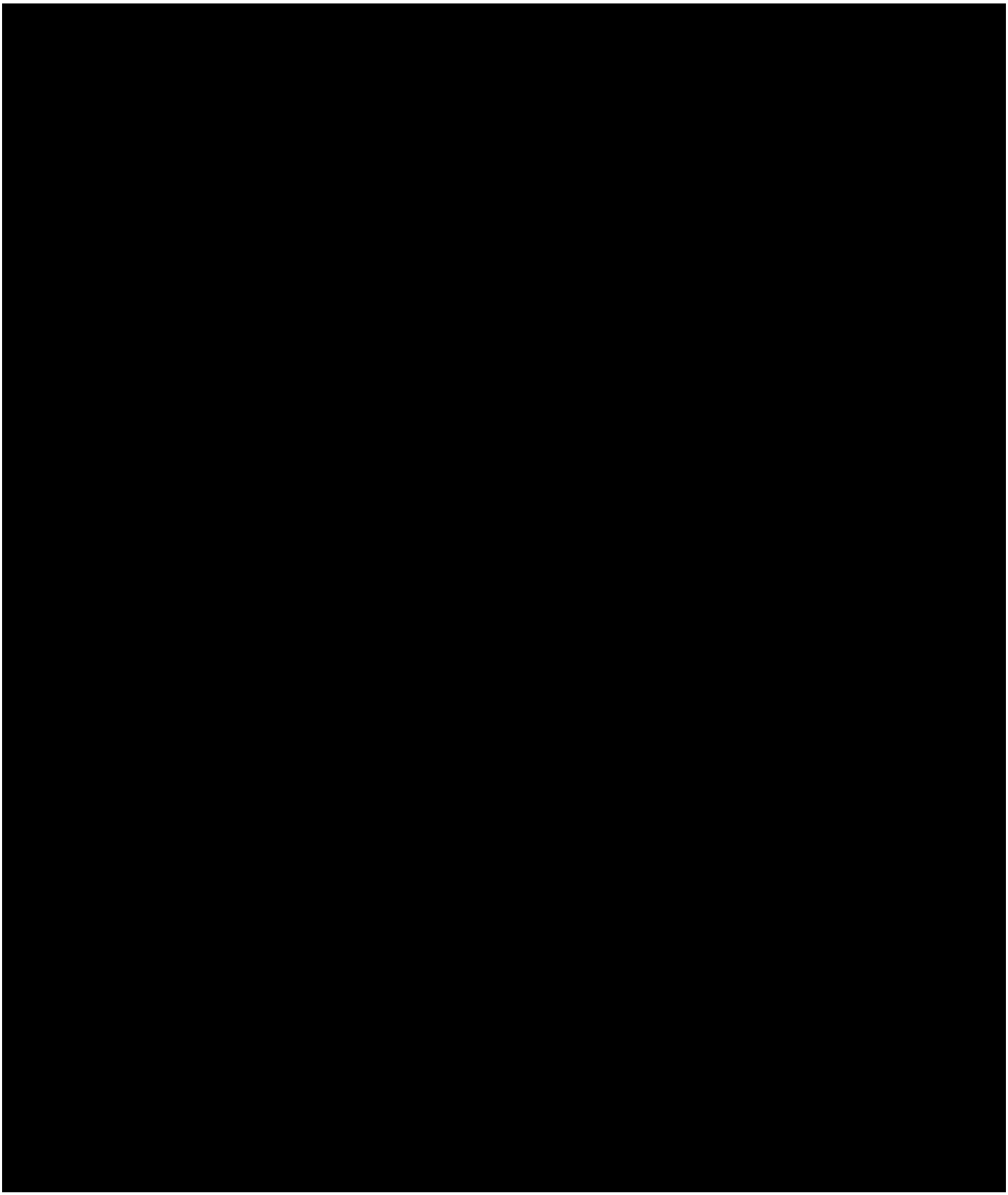


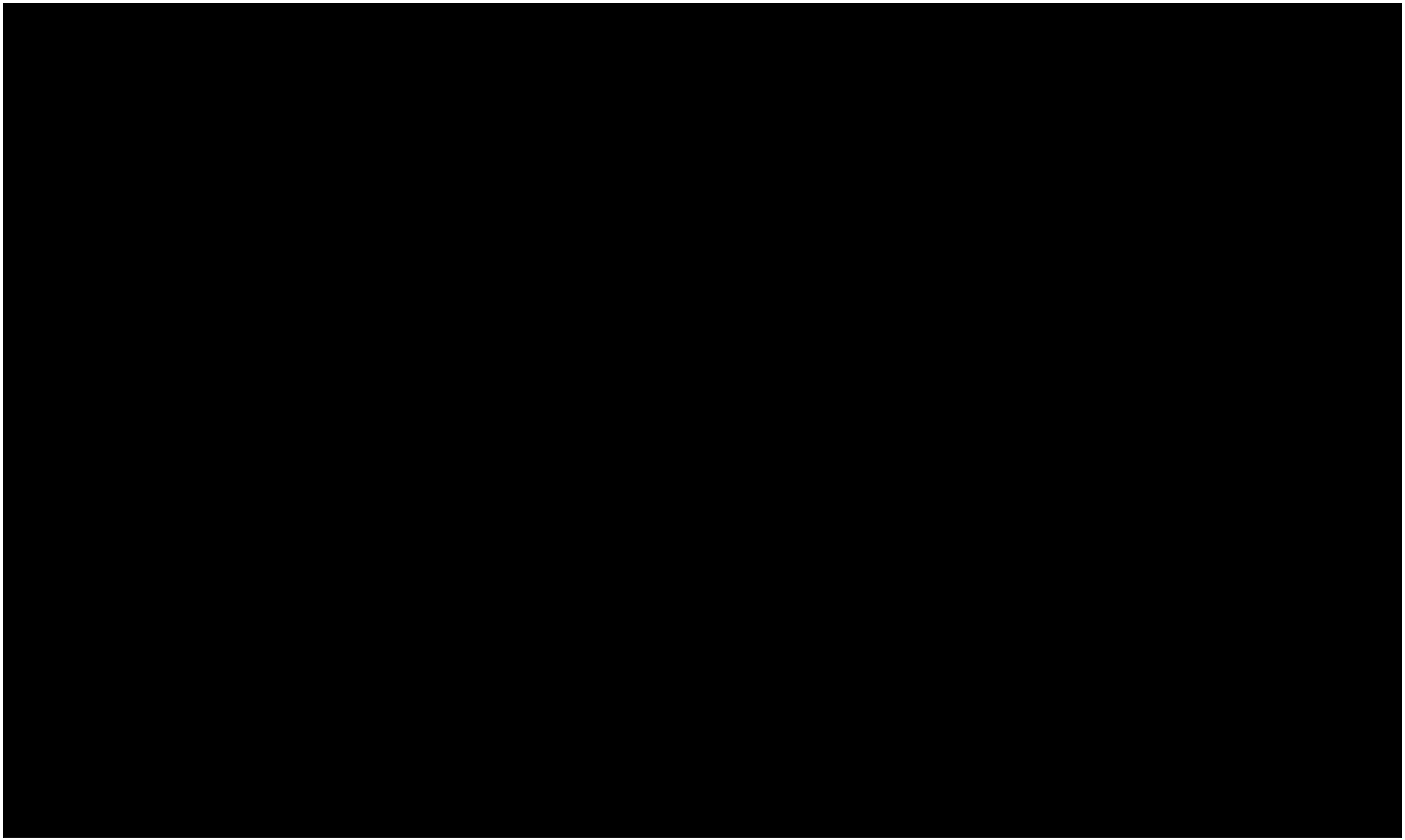












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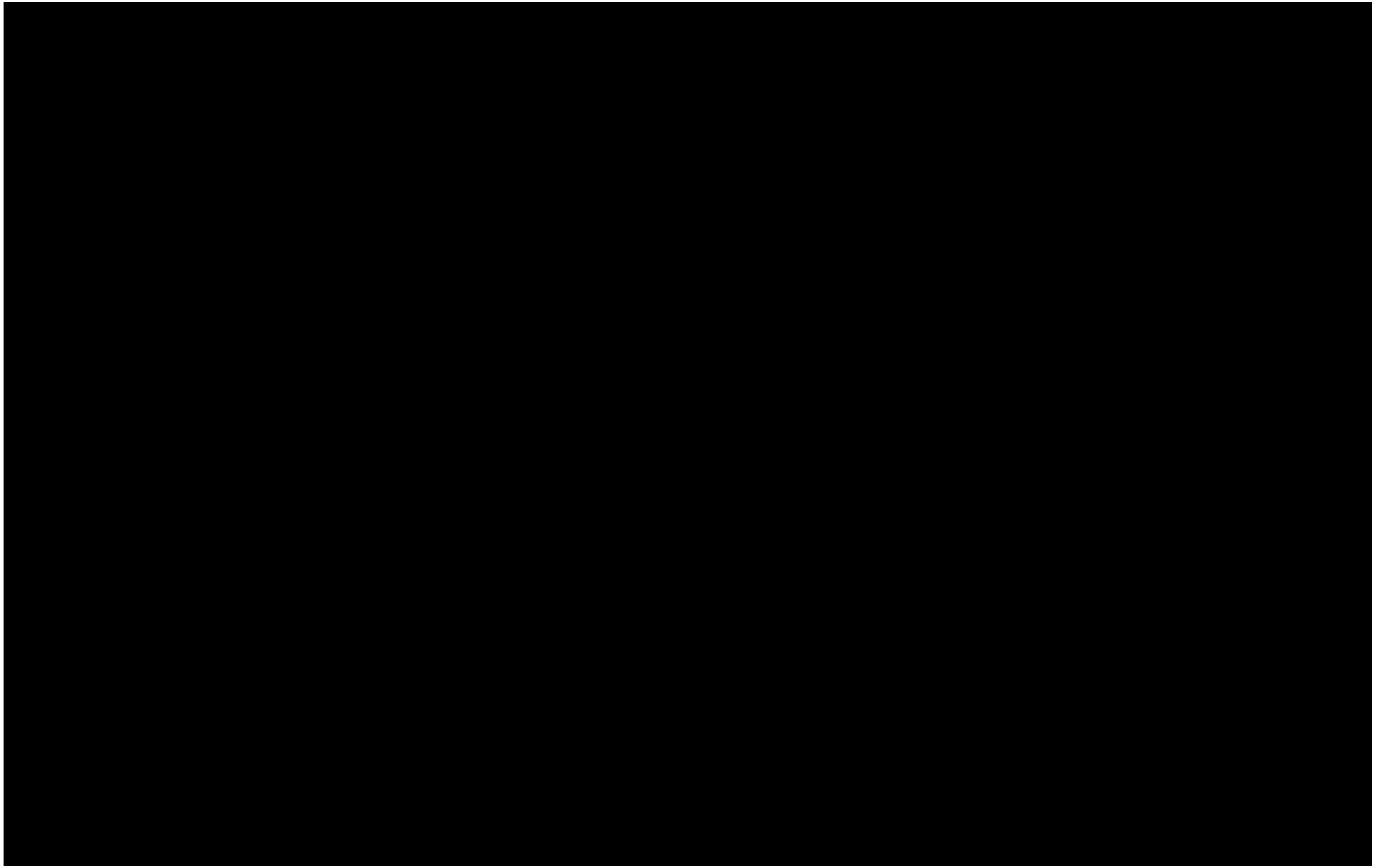
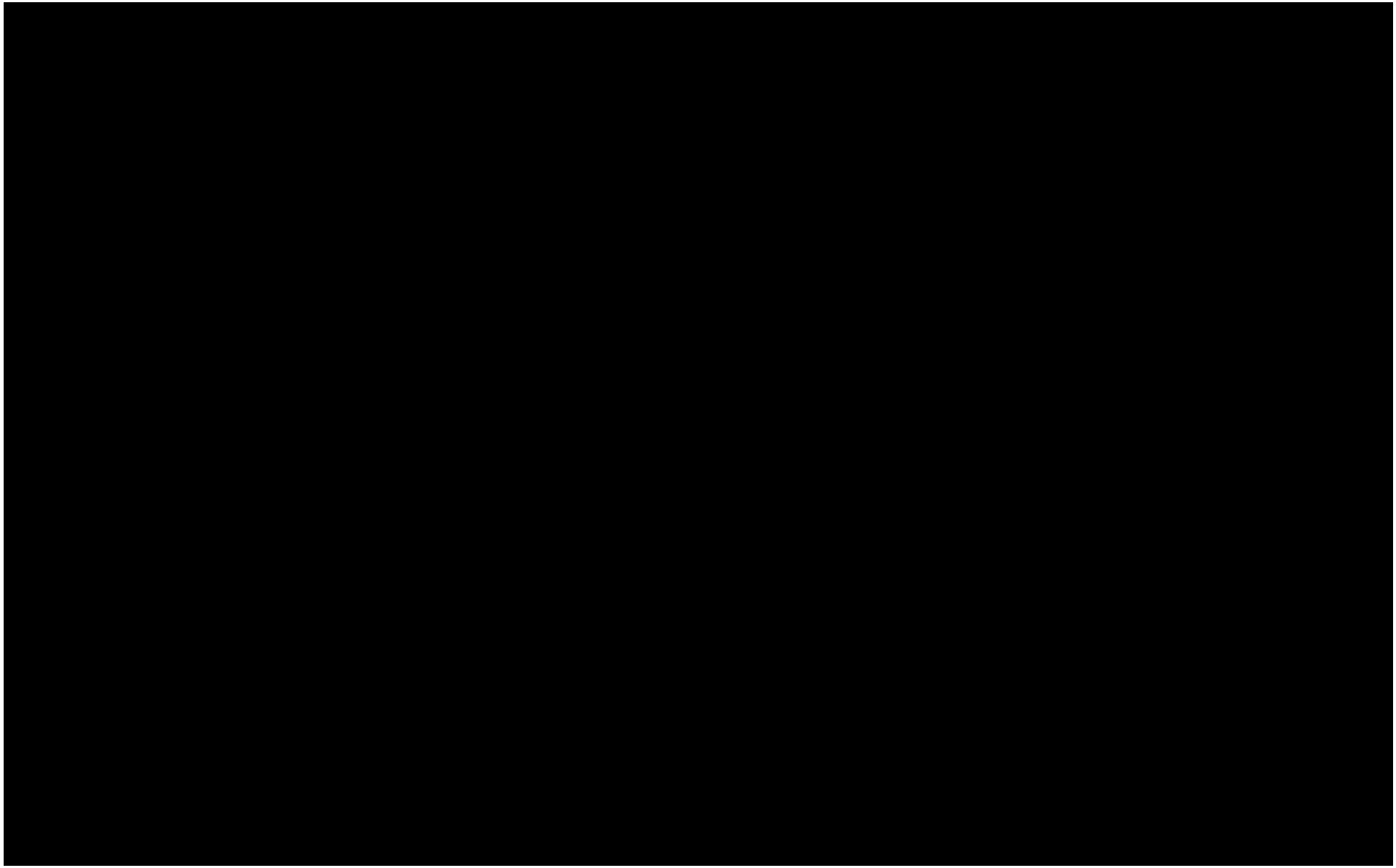
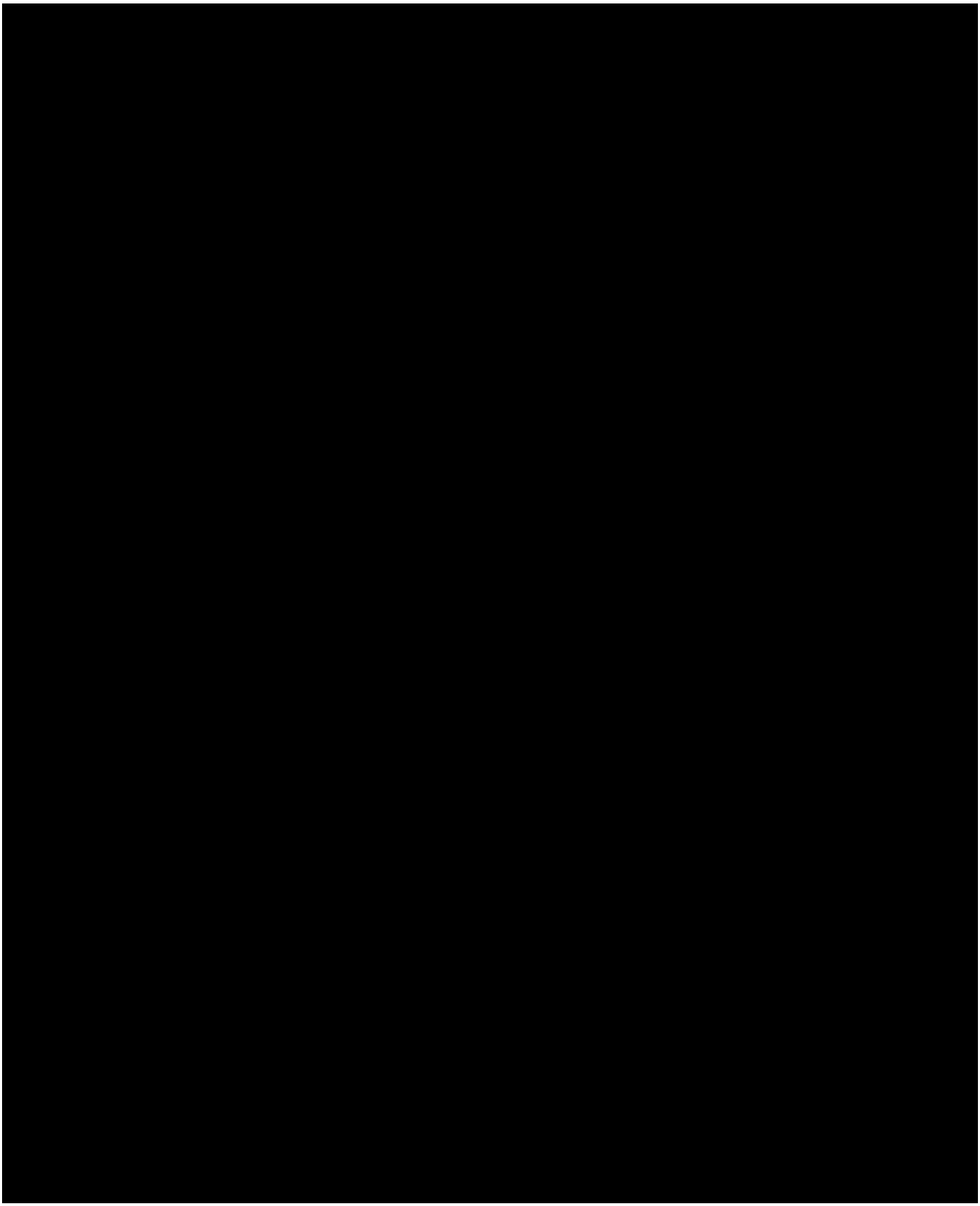
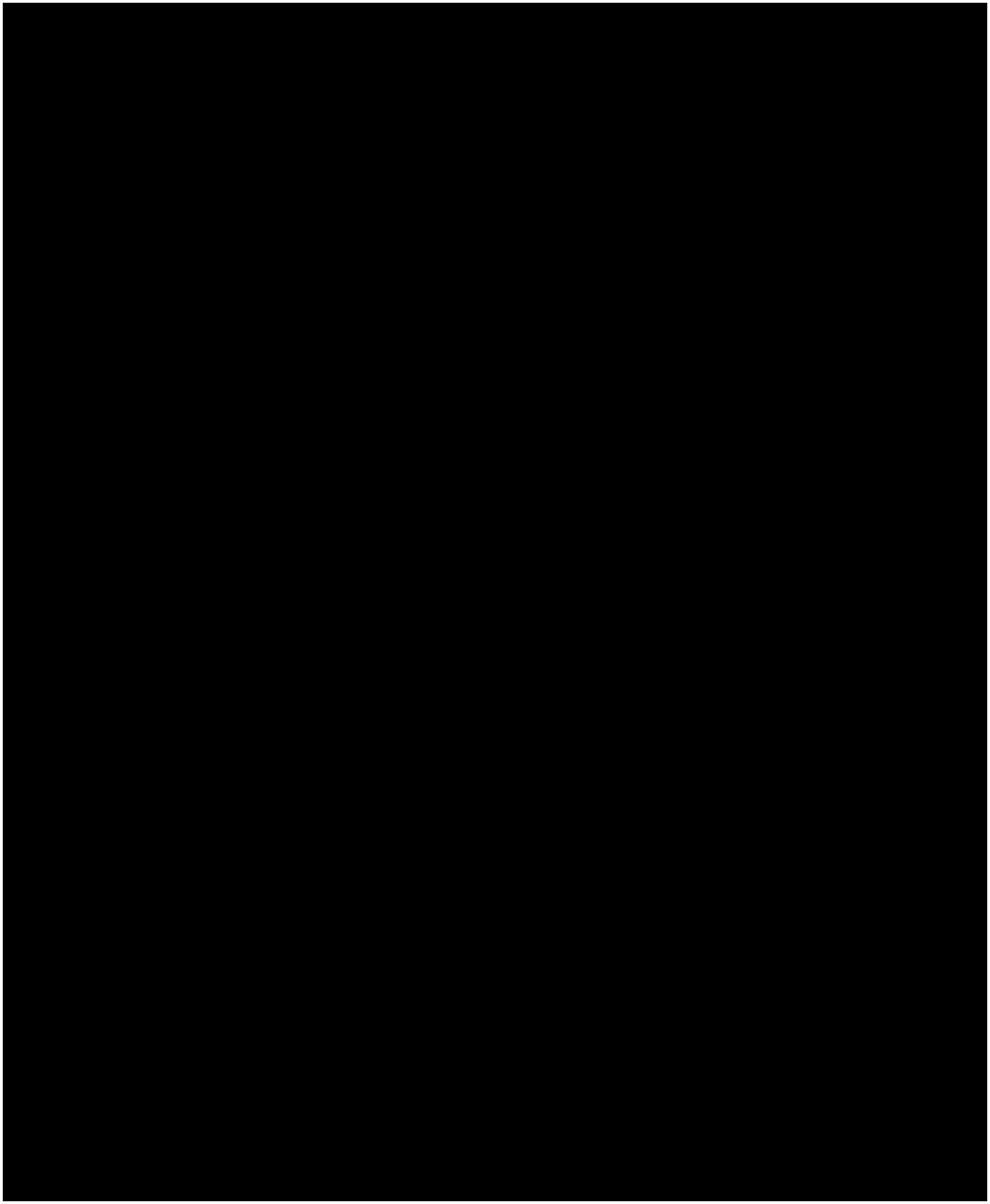
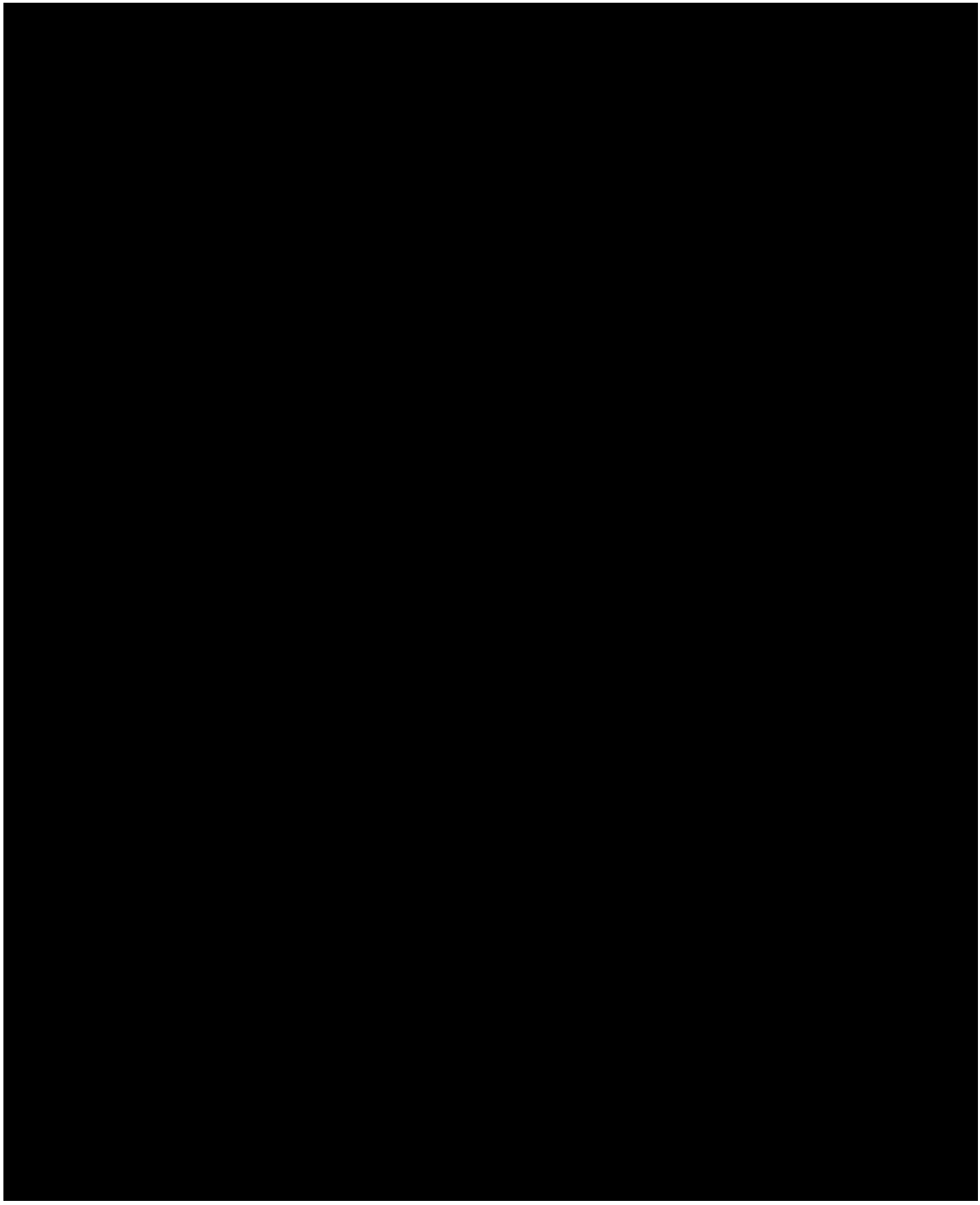


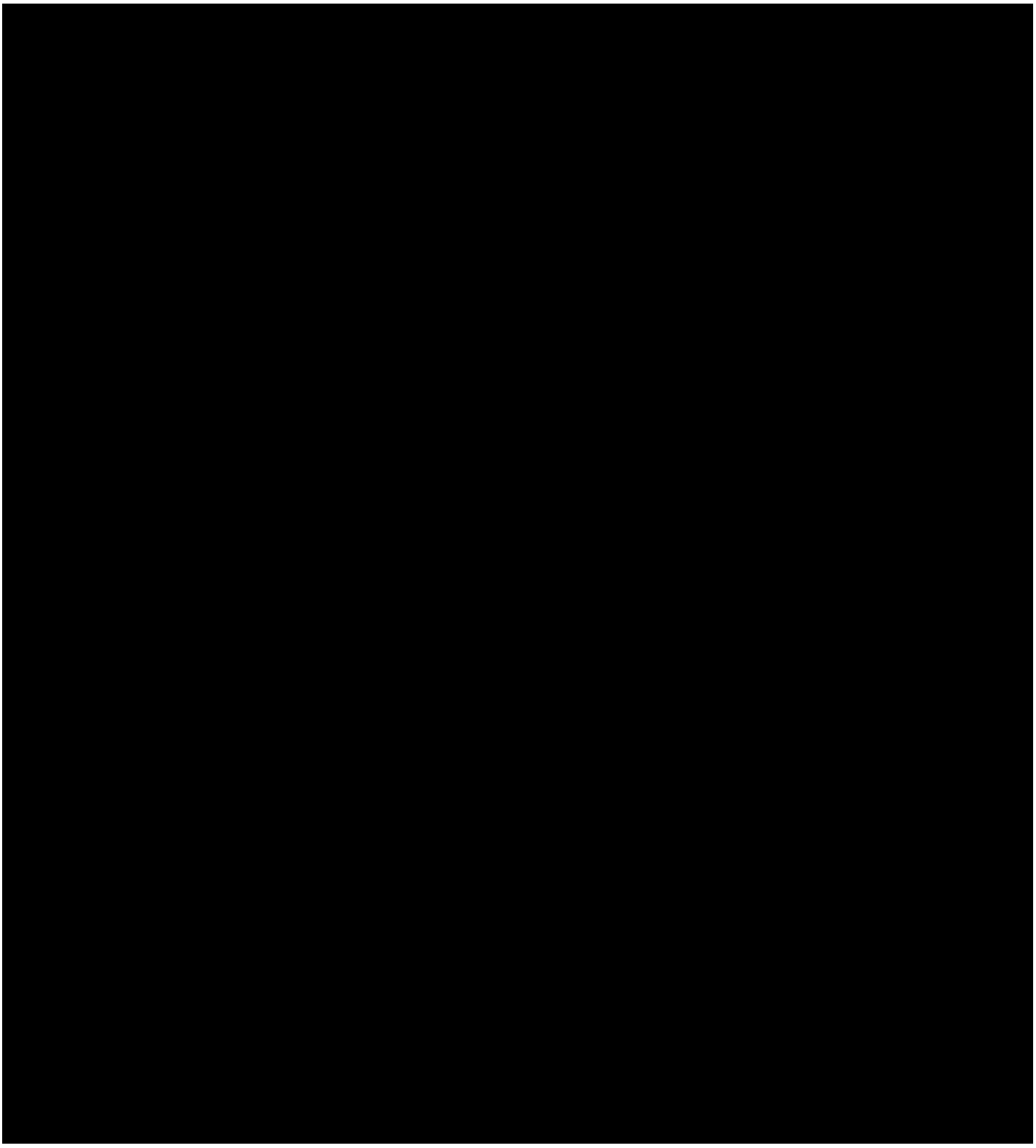


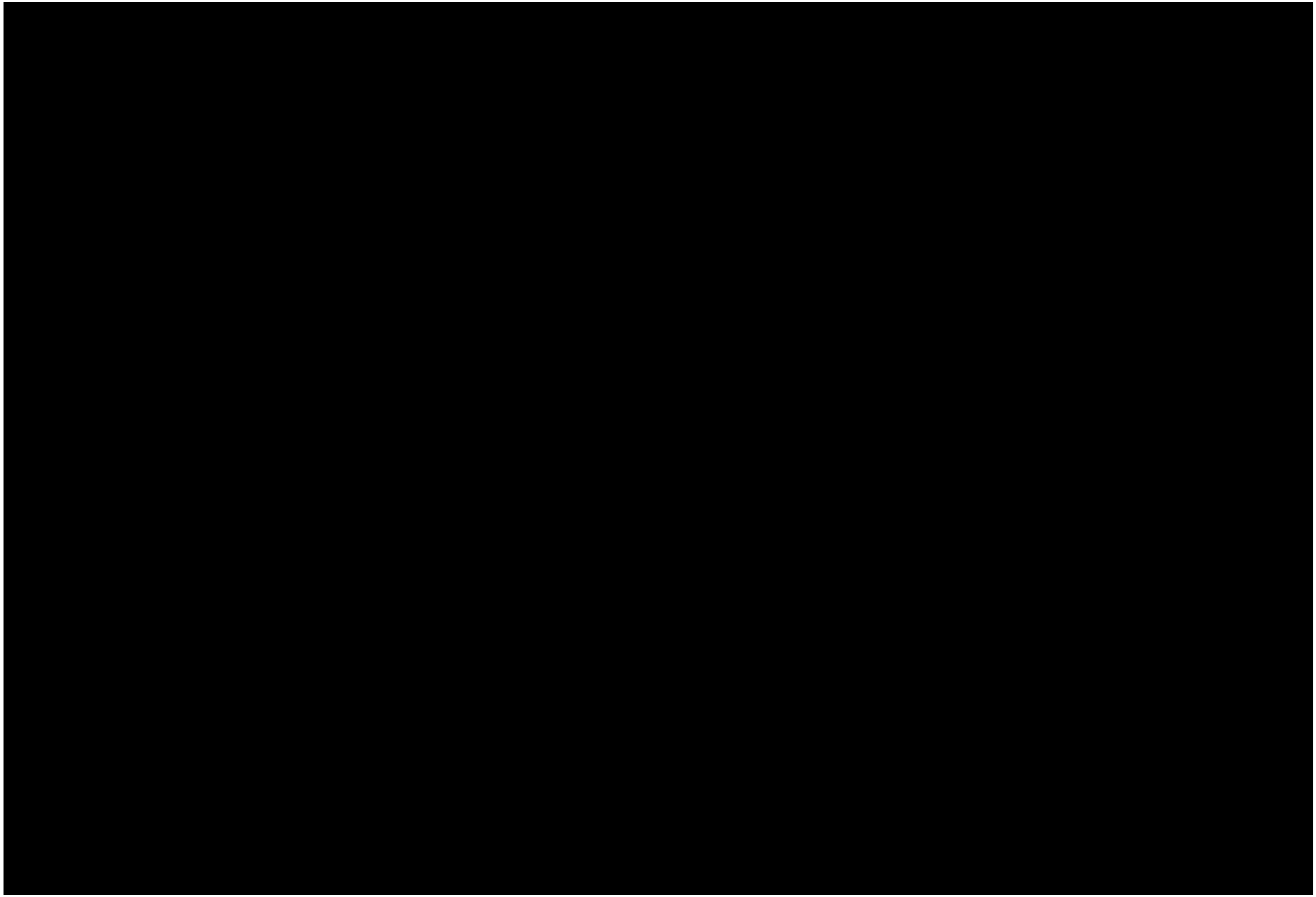




[redacted]







APPENDIX 11 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 06, 23-Dec-2020

The rationale for this amendment was to include:

- New BMS-986258 formulation [redacted].
- Additional corrections in numbering of exclusion criterion 3, male contraception, and in the [redacted] were included.
- [redacted].
- [redacted] for inclusion in NSCLC PD cohorts. Candidates to NSCLC PD cohorts will be allowed to be enrolled in dose escalation cohorts (Part A and B) if the [redacted] is not fulfilled.

BMS document titling nomenclature has been updated to align with Transcelerate guidance, therefore Revised Protocols are now titled as Amendments.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Added Clinical Scientist contact detail information	Editorial change
Section 1-Synopsis	The synopsis has been modified to incorporate all changes described below.	Updated to align with study protocol changes.
[redacted]		
Section 5-Study Design	Reduced the [redacted]	To facilitate the recruitment in the in Parts A and B NSCLC PD cohorts
Section 5.1.1-Pre-screening for PD Cohorts only (NSCLC)	Reduced the [redacted] Allowed participants to be enrolled in dose escalation cohorts (Part A and B) if not eligible for NSCLC PD cohorts, and therefore, continue with screening procedures while waiting for [redacted] result	To facilitate the recruitment in the in Parts A and B NSCLC PD cohorts and in dose escalation (Part A and B) cohorts
Section 5.4.4-Rationale for Design of the NSCLC Pharmacodynamic Cohorts in	Reduced the [redacted]	To align it with the current [redacted]

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Parts A and B and for Patient Selection Strategy		
Section 6.1-Inclusion Criteria	Updated inclusion 1)b, 2)a, [redacted] Inclusion criterion 4)e is not applicable	To align with the current [redacted] and with the current [redacted] Monoclonal antibodies are not genotoxic and do not concentrate in seminal fluid at concentrations sufficient to cause fetal toxicity. For these reasons, in studies involving monoclonal antibodies, there are no contraception requirements for male participants or WOCBP partners of male participants.
Section 6.2-Exclusion Criteria	Renumbered Exclusion criterion 3	To align exclusion criteria numbering with the previous protocol version.
Section 7-Treatment	Included additional formulation and strength of BMS-986258 in Table 7-1 Study Treatments	Added to provide most current formulation for BMS-986258
Section 8.1-Discontinuation from Study Treatment	Removed sentence concerning pregnancy in the partner of male participant	Monoclonal antibodies are not genotoxic and do not concentrate in seminal fluid at concentrations sufficient to cause fetal toxicity. For these reasons, in studies involving monoclonal antibodies, there are no contraception requirements for male participants or WOCBP partners of male participants
Section 9.2.5-Pregnancy	Removed information related to female partner's pregnancy of a male study participant	Monoclonal antibodies are not genotoxic and do not concentrate in seminal fluid at concentrations sufficient to cause fetal toxicity. For these reasons, in studies involving monoclonal antibodies, there are no contraception requirements for male participants or WOCBP partners of male participants.
[redacted]		

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Appendix 4-Women of childbearing potential definitions and methods of contraception	Updated contraception guidance for female participants of childbearing potential table and removed information related to contraception guidance for male participants with partner(s) of childbearing potential	Monoclonal antibodies are not genotoxic and do not concentrate in seminal fluid at concentrations sufficient to cause fetal toxicity. For these reasons, in studies involving monoclonal antibodies, there are no contraception requirements for male participants or WOCBP partners of male participants.
[redacted]		
Entire document	Additional editorial or formatting changes, where appropriate.	Added to provide clarity.

Overall Rationale for Revised Protocol 05, 22-Oct-2020

The rationale for this revision was to define dose for subcutaneous (SC) administration so that Part A1, SC investigation, of the study could be opened.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated name and address of Medical Monitor/Study Director.	Editorial change.
Section 1-Synopsis	The synopsis has been modified to incorporate all applicable changes described below.	Updated to align with study protocol changes.
[redacted]		
[redacted], 3.2.2-Nivolumab	Added additional paragraph on nonclinical toxicology and updated nivolumab background.	Updated to reflect updated latest version of the Nivolumab IB.
Section 3.3.3-BMS-986258 Starting Dose for Part A1 (Monotherapy SC)	Added additional paragraph for starting dose and treatment for Part A1.	Added to include the rationale for the starting dose of BMS-986258

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
		monotherapy, administered subcutaneously.
Section 3.3.6-Safety Monitoring	Added additional paragraph on SARS-CoV-2 safety monitoring.	Added to clarify information of safety monitoring regarding SARS-CoV-2 infection.
[redacted]		
Section 5.1-Overall design	Updated [redacted] to include new dose. Added [redacted] for Part A1.	Added to align with study protocol changes and to subcutaneous administration.
Section 5.4.2- Rationale for Subcutaneous Administration of BMS-986258 (Part A1)	Added paragraph on rHuPH20 rationale for subcutaneous administration and additional safety information. Added paragraph on detailed dosing and timing information for rHuPH20.	Added to provide additional background information on rHuPH20 characteristics, mechanism of action and results of its combination with other compounds.
Section 6.1-Inclusion criteria	Updated inclusion criteria 2) f) iii); [redacted] 3) a) i) ii) and iii); and 4) a), b), c), e) with additional language. Removed inclusion criteria 4)f). Added inclusion criteria 4)g),h), i), and j). modified language in paragraph below 4)j).	Changes added to provide clarity about targeted treatments that the participants must have received prior to the clinical trial, according to mutations related to their disease and to align with EPE v6.
Section 6.2-Exclusion criteria	Added new exclusion criteria 2) f); 3) a) b), g) xiii) and xiv). Updated language in 3)g)iii). Updated numbering.	Added to align with EPEv6 updates and SARS-CoV-2 language and to provide clarity.
Section 6.4.1-Restesting During Screening or Lead-In Period	Added language for SARS-CoV-2 infection.	To allow participants to be rescreened if they present suspected or confirmed SARS-CoV-2 infection.
Section 7.1-Treatments Administered	Updated Table 7.1-1 to include new BMS-986258 dose and rHuPH20 dose and infusion times. Added additional paragraphs on both IV and SC dosing requirements. Removed additional detail on nivolumab infusion procedures.	Added to provide additional information on IV and SC BMS-986258 administration aligned with study protocol changes and to provide clarity.
Section 7.4.1-Dose Delays Due to Toxicity	Added confirmed SARS-CoV-2 infection as AE requiring study drug(s) withheld.	Addition of standard language for BMS protocol with respect to SARS-CoV-2.
Section 7.4.2-Criteria to Resume Treatment	Added guidance for resuming treatment after SARS-CoV-2 infection.	Addition of standard language for BMS protocol with respect to SARS-CoV-2.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.7.1 Prohibited and/or Restricted Treatments	Added language for SARS-CoV-2 infections and vaccines.	Addition of standard language for BMS protocol with respect to SARS-CoV-2.
Section 9.2.1- Time Period and Frequency for Collecting AE and SAE Information, Section 9.2.3-Follow-up of AEs and SAEs	Added language for SARS-CoV-2 AE collection and AE monitoring.	Addition of standard language for BMS protocol with respect to SARS-CoV-2.
Section 9.5-Pharmacokinetic Parameters	Updated Table 9.5-1 definition headings. Updated table footnote b definition and timing for EOI in Table 9.5-2. Updated table footnote b definition and timing for EOI in Table 9.5-3 [redacted]	Added to clarify PK and immunogenicity sampling BMS-986258 Q4W in dose escalation.
[redacted]		
Section 10.3.3-Pharmacokinetic Analyses for BMS-986258 and Nivolumab	Added additional information on the parameters and posts under endpoints and statistical analysis methods. Added clarification language.	Added to provide clarity.
Appendix 4-Women of childbearing potential definitions and methods of contraception	Updated language under contraception guidance.	Updated to align with EPEv6 updates.
[redacted]		
Entire document	Additional editorial or formatting changes, where appropriate.	Added to provide clarity.

Overall Rationale for Revised Protocol 04, 27-Apr-2020

Because no safety signals were identified at the maximal dose level (1200 mg) and the available PK and PD data are supportive, the decision was made to further escalate doses of BMS-986258 by defining [redacted] dose levels (1600 mg and 2400 mg) in Part A (monotherapy) and [redacted] dose level (1600 mg) in Part B (combination with nivolumab 480 mg). This decision was based on the assessment of clinical safety for [redacted] participants who have been treated in this study (CA031002) with either BMS-986258 monotherapy up to 1200 mg IV every 4 weeks (Q4W) or BMS-986258 480 mg IV Q4W in combination with nivolumab 480 mg IV Q4W as of the data cutoff of [redacted] and non-clinical toxicity data that supports the proposed maximum IV dose of 2400 mg Q4W.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Global	Removed reference to "Part B (all participants)" in regards to prospective selection based on [redacted] in screening biopsies.	Only participants in Part A and Part B NSCLC PD cohorts will be prospectively selected for [redacted] in screening biopsies. Participants enrolled in escalation cohorts in Part B will not be prospectively selected.
Global	Added new proposed doses to be tested: 1600 mg (Part A and B) and 2400 mg (Part A).	Safety data supports dose escalation up to 2400 mg (see overall rationale above).

[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
3.1.1, Rationale for Subcutaneous Administration of BMS-986258	Deleted section.	Rationale added to Section 5.4.2.
[redacted]		
3.3, Benefit/Risk Assessment	Updated section with initial safety data observed for BMS-986258 in the current study, nivolumab-related safety data from the Investigator Brochure, and the safety data reported by other companies for other TIM-3 inhibitors.	Inform evaluation of benefit-risk for this study.
3.3.4, BMS-986258 Starting Dose for Pat B (Combination with Nivolumab)	Updated section text as starting dose for Part B was selected to be 480 mg BMS-986258 Q4W in combination with 480 mg nivolumab Q4W.	Data from Part A and preliminary PK and biomarker data supports initiation at 480 mg BMS-986258 Q4W in combination with 480 mg nivolumab Q4W.
3.3.6, Safety Monitoring on Study Therapy	• Updated pretreatment tumor biopsy participant eligibility language. • Added text highlighting there were no infusion-related reactions in monotherapy doses of 8 to 1200 mg.	• Updated language for clarity. • Text provides supporting information for the addition of new dose levels to Part A and Part B.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
5.1.3, Treatment Period	Updated the infusion time to read "up to approximately [redacted]."	Dose increases to 1600 and 2400 mg will use longer infusion times.
5.1.3.1, BMS-986258 Monotherapy Dose Escalation (Part A) (including NSCLC PD cohorts) and Subcutaneous Dose (Part A1)	Updated number of participants to be treated.	Added 2 new dose levels to Part A.
5.1.3.2, BMS-986258 in Combination with Nivolumab Dose Escalation and PD Cohorts (Part B)	Updated number of participants to be treated.	Added [redacted] and reduced number of NSCLC PD cohorts in Part B.
5.1.3.3, BMS-986258 in Combination with Nivolumab Expansion Cohorts (Part C)	Included RP2D in the following sentence: "Treatment in Part C will be initiated when the RP2D, MTD, or MAD for BMS-986258 in combination with nivolumab..."	Updated language for clarity.
5.1.4.2, Survival Follow up	Updated to be consistent with changes to Survival Follow-up period in [redacted]	Updated language for clarity.
5.2, Number of Participants	Updated number of participants.	Added [redacted] to Part A and Part B and reduced number of NSCLC PD cohorts in Part B.
5.4.2, Rationale for Subcutaneous Administration of BMS-986258 (Part A1)	Replaced previous text with text from Section 3.1.1 and new text has been updated to reflect current data.	Updated text to reduce redundancy of data and to add supporting information.
6.1, Inclusion Criteria; 2) Type of Participant and Target Disease Characteristics; d); v)	Removed inclusion criteria	duplicate of 2), d), iv)
6.1, Inclusion Criteria; 2) Type of Participant and Target Disease Characteristics; i); 4)	Updated text to indicate at screening that the date of and criteria used to determine disease progression should be documented on eCRF. Additionally, submission of available scans to support the information recorded in the eCRF may be required at the Sponsor's discretion.	Updated language for clarity.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
6.1, Inclusion Criteria; 4) Age and Reproductive Status; c)	Added the following sentence: WOCBP participants must agree not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period.	Updated language for clarity.
6.2, Exclusion Criteria; 2) Prior/Concomitant Therapy	Added the following exclusion criterion: e) Treatment with botanical preparations (eg herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment. Refer to Section 7.7.1 for prohibited therapies.	Update to current BMS standards.
6.2, Exclusion Criteria; 5) Other Exclusion Criteria; a)	Updated to be consistent with Section 8.1.	Update for consistency.
6.3, Lifestyle Restrictions 6.4, Screen Failures 6.4.1, Retesting During Screening or Lead-In Period	Text updated to reflect the current BMS required language for each of these sections.	Update to current BMS standards.
7.1, Treatments Administered	Added subsection for nivolumab dosing and infusion information	Updated to current nivolumab standards.
Table 7.1-1: Selection and Timing of Dose	Updated doses for BMS-986258 to include 1600 and 2400 mg and updated rHuPH20 dose to [redacted].	Added [redacted] dose levels to Part A and Part B.
7.1.2, Management Algorithms for Immuno-Oncology Agents	Myocarditis added to list of Management Algorithms. Algorithm was added to Appendix 8.	Update to current nivolumab standards.
7.4.1, Dose Delays Due to Toxicity	Added the following Dose Delay criteria: [redacted]	Update to current nivolumab standards.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
7.7.1, Prohibited and/or Restricted Treatments	Added the following: Any botanical preparation (eg herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.	Update to current BMS standards.
8.1, Discontinuation from Study Treatment	Added the following: 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.	Update to current BMS standards.
8.1.3, Treatment Beyond Progression	Added definition of further progression for participants who continue nivolumab study therapy beyond progression.	Update to current nivolumab standards.
9.1.1, Imaging Assessment for the Study	Updated text to reflect that all images will be submitted to a central imaging vendor and scans may undergo blinded independent central review at the Sponsor's discretion. Added the following paragraph: Unscheduled CT/MRI should be submitted to central imaging vendor. X-rays and bone scans that clearly demonstrate interval progression of disease, for example most commonly as unequivocal lesions that are unmistakably new since the prior CT/MRI, should be submitted to central imaging vendor. Otherwise, they do not need to be submitted centrally.	Updated language for clarity.
9.1.1.1, Methods of Assessment	Added the following paragraph: MRI of brain (without and with contrast) should be acquired as outlined in [redacted] (Schedule of Activities). CT of the brain (without and with contrast) can be performed if MRI is contraindicated.	Updated language for clarity.
9.1.1.2, Imaging and Clinical Assessment	Replaced text.	Update to current BMS standards.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
9.2.1, Time Period and Frequency for Collecting AE and SAE Information	• Clarified that SAEs will be collected for 30 days for participants assigned to treatment but never treated after the main ICF is signed. • Added timing for collection of all nonserious adverse events. • Added text stating that Investigators must assess all adverse events as to whether it is considered immune-mediated.	Updated language for clarity and to current BMS standards.
9.2.2, Method of Detecting AEs and SAEs	Text updated to reflect the current BMS required language.	Update to current BMS standards.
9.2.5, Pregnancy	For cases where study drug can be present in seminal fluid, updated text to read that if sexual activity has occurred between a male participant and a pregnant partner without the use of a condom during or for at least 5 half-lives of study treatments plus 90 days (duration of sperm turnover) defined as 220 days after the end of treatment in the male participant, then it should be reported even if male participant has had a vasectomy.	Update to current BMS standards.
9.2.7, Potential Drug Induced Liver Injury (DILI)	Deleted paragraph stating specific criteria for identifying potential DILI have not been identified.	DILI is defined in text.
9.3, Overdose	Change the following sentence to say "study drug" instead of "BMS-986258" For this study, any dose of study drug greater than the assigned dose and considered excessive and medically important by the Investigator will be considered an overdose.	To include other treatments received by participants.
9.5, Pharmacokinetics	Updated the infusion time to read "up to approximately [redacted]" in footnote b in Table 9.5-2, Table 9.5-3, Table 9.5-4, and Table 9.5-5.	Dose increases to 1600 and 2400 mg will use longer infusion times.

[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
10.1.1, Dose Escalation	Updated number of participants.	Added [redacted] dose levels to Part A and Part B and reduced number of NSCLC PD cohorts in Part B.
Appendix 4 Women Of Childbearing Potential Definitions And Methods Of Contraception	Added definition for end of relevant systemic exposure Changed the number of days for use of effective methods of contraception for female partners of male participants and for male participants with pregnant or breastfeeding partners from 160 to 220 days.	Update to current BMS standards.
Appendix 8 Management Algorithms	Updated treatment algorithms and added myocarditis algorithm.	Update to current nivolumab standards.
[redacted]		

Overall Rationale for Revised Protocol 03, 14-Mar-2019

The purpose of the revised protocol is to:

[redacted]

Also includes Administrative Letter 01 which removed the unit of dose strength of rHuPH20 from the protocol.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**

[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 3.3 Benefit/Risk Assessment	Added updated information on efficacy and safety data for NSCLC participants that had progressed on or after anti-PD(L)1 treatment and then received dual TIM-3 and PD-1 blockade.	To provide the latest efficacy and safety data.
Section 3.3.6 Safety Monitoring on Study Therapy	Biopsies should be performed at minimal clinical risk and provided requirements for the biopsy.	To ensure participant safety.
[redacted]		
Section 5.1 Overall Study Design and other applicable sub-sections; [redacted]	Added language for PD cohorts, pre-screening period for NSCLC PD cohorts only, and [redacted]	To align the text and study schematics with the addition of the NSCLC PD cohorts.
Section 5.1.1 Pre-screening for PD Cohort only (NSCLC)	Added section describing that participants in PD NSCLC cohorts will be required to pre-screen for [redacted] status	To align the text with the addition of the NSCLC PD cohorts.
Section 5.1.3.1 BMS-986258 Monotherapy Dose Escalation (Part A) (including PD cohorts) and Subcutaneous Dose (Part A1); Section 5.1.3.2 BMS-986258 in Combination with Nivolumab Dose Escalation and PD Cohorts (Part B) Table 7.1-1 Selection and	Planned highest dose level of BMS-986258 for monotherapy and combination therapy are changed from 800 mg to 1200 mg	Doses up to [redacted] QW have been tested in a definitive (GLP-compliant) pre-clinical 1-month IV toxicity study with good tolerance. Escalation up to 1200mg will be based on safety, PK and PD data from the initially proposed cohorts.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Timing of Dose; Section 5.5.2.1 BMS-986258		
Section 5.4 Scientific Rationale for Study Design	Language added for the PD cohorts	To align the text with the addition of the NSCLC PD cohorts.
Section 5.4.4 Rationale for Pharmacodynamic cohorts selected based on [redacted]	Rationale added for the PD cohorts	Previous clinical studies with nivolumab monotherapy have shown that patients with TIM-3 expression on [redacted] may have higher response rates than those with indeterminate expression.
Section 6.1 Inclusion Criteria 1) b) Signed Written Informed Consent	Added text regarding acceptable risk to the participant for the biopsy.	To protects the participant's safety during biopsy procedure.
2) Type of Participant and Target Disease Characteristics	Participants with RCC, CRC, NSCLC, SCCHN: Removed: Anti-PD(L)1 therapy naive participants may be eligible for Part B	To align the inclusion criteria throughout the protocol to be able to better compare data between monotherapy and combination cohorts.
	Participants with NSCLC: added language for PD cohorts and for pre-treatment [redacted] status	To understand the drug effect in a more specific population of participants.
	Guidelines for participants with anti-PD-1/anti-PD-L1 refractory/resistant RCC, CRC, NSCLC, and SCCHN	To more clearly define PD-(L)1 resistant populations.
4) Age and Reproductive Status f) and Section 9.2.5 Pregnancy	Clarified that azoospermic males are exempt from contraceptive requirements unless the potential exists for fetal toxicity due to study drug being present in seminal fluid, even if the participant has undergone a successful vasectomy or if the partner is pregnant.	To align with BMS standards for contraception.
Section 6.2 Exclusion Criteria Medical History e) iv) (4)	Removed pericarditis or significant pericardial effusion as an exclusion criteria	To correct unnecessary exclusion criteria.
Table 7.1-1 Selection and Timing of Dose	Added 1200 mg dosage level for BMS-986258	[redacted]. Escalation up to 1200mg will be based on safety, PK and PD data from the initially proposed cohorts.
Section 7.3 Blinding	Added text to allow randomization codes to be released prior to database lock	To facilitate the bioanalytical analysis of pharmacokinetic and immunogenicity samples.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Appendix 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW UP AND REPORTING	Entire appendix was replaced.	To align with the latest BMS standards.
Appendix 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION	Updated the methods of contraception and requirements for male contraception with partners of childbearing potential.	To align with the latest BMS standards.
[redacted]		

Overall Rationale for Revised Protocol 02, 12-Jun-2018:

The purpose of the revised protocol is to add a cohort (PartA1), to [redacted] subcutaneous (SC) administration of BMS-986258 using ENHANZE® Drug Product (rHuPH20). Both Q4W and (SC) administration offer potential convenience and improved compliance to patients. Revised Protocol 02 adds Part A1 to the study design and seeks to confirm feasibility of Q4W dosing by SC route of administration of BMS-986258. Additionally microbiome analysis has been added to [redacted] the potential influence of the gut microbiome on cancer treatment outcomes. 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**
[redacted]		

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 3.1.1, Rationale for Subcutaneous Administration of BMS-986258 (Part A1)	Added the rationale for adding Part A1 SC dosing of BMS-986258.	SC dosing objective has been added to Part A1 of this study to assess an alternative approach to dosing.
Section 3.3.1, Recombinant Human Hyaluronidase PH-20 rHuPH20	Added information about the pharmacology of new study drug - Recombinant Human Hyaluronidase PH-20 (rHuPH20).	rHuPH20 will be co-administered with BMS-986258 SC
Section 3.3.3, BMS-986258 Starting Dose for Part A1 (Monotherapy SC)	Added Part A1 to the section describing the dose and timing of dosing in relation to the other parts of the study.	SC dosing objective has been added to Part A1 of this study to assess an alternative approach to dosing.
[redacted]		

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1, Overall Design: [redacted] Section 5.1.2, Treatment Period: Section 5.1.2.1, BMS-986258 Monotherapy Dose Escalation (Part A) and Subcutaneous Dose (Part A1); Section 7.1.1, Dose Limiting Toxicities, 7.2, Method of Treatment Assignment	Sections added or modified based on addition of [redacted] relating to BMS-986258 SC dosing in Part A1.	[redacted] has been added as Part A1 of this study to assess an [redacted] to BMS-986258 dosing.
Section 5.2, Number of Participants	Updated to include Part A1 participants; up to approximately [redacted] participants in to evaluate up to two dose levels.	Additional subjects added [redacted].
Section 5.4.2, Rationale for Subcutaneous Dose Cohort (Part A1)	Section added based on [redacted] relating to bioavailability of subcutaneous dosing in Part A1.	[redacted] has been added as Part A1 of this study to assess an alternative approach to dosing.
Section 5.5.2, Rationale for Dose Selection and Dosing Schedule	Added the rationale for subcutaneous administration of BMS-986258.	[redacted] has been added as Part A1 of this study to assess an alternative approach to dosing.
Section 6.1, Inclusion Criteria h) ii)	Included Part A1 where applicable in tumor types. In addition, for SCCHN modified the criteria for previous therapies h), ii) Participants must have received and progressed on or after, or have been intolerant or refractory to, at least 1 standard chemotherapy regimen	Clarified which tumor type inclusion criteria was applicable for Part A1.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	containing anthracycline and taxane; in addition the participant must have received at least 1 regimen for the treatment of metastatic or locally advanced disease.	
Section 7, Treatment: Section	Added ENHANZE® Drug Product (rHuPH20) as study treatment to tables and text and updated treatment assignments based [redacted] for subcutaneous dosing in Part A1.	To support the [redacted] has been added to this study.
Section 7.7.3 Permitted Therapy	Revised the duration of corticosteroid treatment from less than 3 weeks to less than 1 week for prophylaxis or for treatment of non-autoimmune conditions	Correction of original text to align with clinical practice.
[redacted]		
Section 9.1.1.1 Methods of Assessment	For participants with SCCHN, a CT or MRI of the neck is required.	Imaging requirement for SCCHN participants.
Section 9.2.1 Time Period and Frequency for Collecting AE and SAE Information	Text revised to clarify timing of start of SAE and AE collection.	To clarify timing to start collection of SAE from signing of consent and AE collection from the start of study treatment.
Table 9.2.8-1 Preferred Terms Included in Analysis of IMAEs to Support	Removed the table and text listing specific preferred terms for immune mediated adverse events.	The list of immune mediated adverse events is ever changing and it is not practical to provide the list in the protocol.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Warnings and Precautions		
Section 9.3 Overdose	Text revised to clarify that overdoses that meet the regulatory definition of an SAE will be reported.	To align with the updated Appendix #3 "Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow up and Reporting".
Section 9.5, Pharmacokinetics: Table 9.5-3, Pharmacokinetic Sampling Schedule for BMS-986258 Q4W in Monotherapy Subcutaneous PK Sub-study (Part A1)	Table for pharmacokinetic sampling was added to include Part A1.	To support the [redacted] that has been added to this study.
[redacted]		
Section 10.1.1, Dose Escalation: Section 10.3.1 Efficacy Analysis	Section updated to include Part A1 sample size calculation and summary statistics.	To support the [redacted] that has been added to this study.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
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	Defines what AE events meet or do not meet the AE definition. Provides the definition of an SAE. Pregnancy and drug induced liver injury must follow same transmission timing and processes as used for SAEs	Appendix was updated to provide definitions and to align with Transcelerate Protocol Model Document.
Appendix 5 Recist 1.1 Criteria	Appendix was updated. New title is: "Response Evaluation Criteria In Solid Tumors Guidelines (Version 1.1) With BMS Modifications".	To be in alignment with the current RECIST Guidelines and BMS criteria.

Overall Rationale for Revised Protocol 01, 08-Jan-2018:

The revised protocol clarifies some exclusion criteria, dose limiting criteria and criteria for discontinuation as described in the Summary of Key Changes table. Applies to all participants

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.3: Exclusion Criteria	Exclusion criteria 6.2.e.v was updated to state that participants with active interstitial lung disease will be excluded	Not only history of, but active interstitial lung disease represent a potential risk factor for development of pneumonitis with the use of IO drugs
[redacted]		
Section 8.1: Discontinuation from Study Treatment	Clarified that an exception to the discontinuation of BMS-986258 can be made in the case of a nivolumab-related hypersensitivity/infusion reaction.	Because nivolumab is administered first, if a participant presents with a reaction before the administration of BMS-986258 has started, treatment with BMS-986258 may continue after the hypersensitivity or infusion related reactions have been resolved.
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized

APPENDIX 12 REFERENCES

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