Official Title of Study:

A Randomized, Double-blind, Phase 2 Study of BMS-986315 and Nivolumab in Combination with Chemotherapy versus Nivolumab in Combination with Chemotherapy as First-line Treatment for Participants with Stage IV or Recurrent Non-small Cell Lung Cancer (NSCLC)

NCT Number: NCT06094296

Document Date (Date in which document was last revised): 21 Jun 2023

CLINICAL PROTOCOL CA0471009

A Randomized, Double-blind, Phase 2 Study of BMS-986315 and Nivolumab in Combination with Chemotherapy versus Nivolumab in Combination with Chemotherapy as First-line Treatment for Participants with Stage IV or Recurrent Non-small Cell Lung Cancer (NSCLC)

Compound: BMS-986315

Brief Title: A Phase 2 Study of BMS-986315 and Nivolumab in Combination with Chemotherapy in Participants with First-line Stage IV or Recurrent NSCLC

Medical Monitor Name and Contact Information:

[redacted]
Clinical Trial Physician – Medical Monitor
Bristol-Myers Squibb Company
3551 Lawrenceville Rd
Princeton, NJ 08540
Phone: [redacted]
email: [redacted]

24-hr Emergency Telephone Number
USA: [redacted]
International: [redacted]

Sponsor Name and Legal Registered Address:

Bristol-Myers Squibb Company
Route 206 & Province Line Road
Lawrenceville, NJ 08543

Bristol-Myers Squibb Services Unlimited Company
Plaza 254, Blanchardstown Corporate Park 2, Dublin 15, D15 T867, Ireland

REGULATORY AGENCY IDENTIFIER NUMBER(S)

IND: 145,968
EudraCT/EU Trial Number: 2022-503007-22-00
UTN: U1111-1282-5699

DOCUMENT HISTORY

Document	Date of Issue	Summary of Changes
Original Protocol	21-Jun-2023	Not applicable.

TABLE OF CONTENTS

TITLE PAGE 1
DOCUMENT HISTORY 3
TABLE OF CONTENTS 4
1 PROTOCOL SUMMARY 7
2 SCHEDULE OF ACTIVITIES 14
3 INTRODUCTION 22
3.1 Study Rationale 22
3.2 Background 23
3.2.1 First-line Immunotherapy(ies) in Combination with Chemotherapy in NSCLC 23
3.2.2 Preclinical Activity of BMS-986315 in Combination with Nivolumab 24
3.2.3 BMS-986315 Preliminary Clinical Activity and Safety 25
3.3 Benefit/Risk Assessment 25
3.3.1 Risk Assessment 26
3.3.2 Benefit Assessment 27
3.3.3 Overall Benefit/Risk Conclusion 28
4 OBJECTIVES AND ENDPOINTS 29
5 STUDY DESIGN 32
5.1 Overall Design 32
5.1.1 Data Monitoring Committee and Other Committees 36
5.2 Number of Participants 37
5.3 End of Study Definition 37
5.4 Scientific Rationale for Study Design 38
5.4.1 Rationale for Choice of Control Arm 38
5.4.2 Rationale for ORR as a Primary Endpoint in Part 2 39
5.4.3 Rationale for 2-year Duration of Treatment 39
5.5 Justification for Immunotherapy Dose(s) 40
5.5.1 Nivolumab 41
5.5.2 BMS-986315 41
5.6 Rationale for Exploratory Biomarker Research 42
5.7 Rationale for Optional Future Research 43
6 STUDY POPULATION 43
6.1 Inclusion Criteria 44
6.2 Exclusion Criteria 46
6.3 Lifestyle Restrictions 50
6.4 Screen Failures 50
6.4.1 Re-testing During Screening or Lead-in Period 50
7 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY 51
7.1 Study Interventions Administered 51
7.1.1 Immunotherapy Dosing 53
7.1.2 Chemotherapy Dosing 54
7.1.2.1 Paclitaxel and Carboplatin 55
7.1.2.2 Pemetrexed and Cisplatin 55
7.1.2.3 Pemetrexed and Carboplatin 56
7.1.2.4 Optional Continuation Maintenance 57

7.2 Assignment to Study Intervention 57
7.3 Blinding 58
7.4 Dosage Modification 59
7.4.1 Dose Modification Criteria for Immunotherapy 60
7.4.2 Dose Delay Criteria for Chemotherapy 67
7.4.3 Dose Reductions 68
7.4.3.1 Dose Reduction for Immunotherapy 68
7.4.3.2 Dose Reduction for Chemotherapy 68
7.4.3.3 Chemotherapy: Dose Reductions for Hematologic Toxicity 68
7.4.3.4 Chemotherapy: Dose Reductions for Non-hematologic Toxicities 69
7.4.4 Criteria to Resume Dosing 71
7.4.4.1 Criteria to Resume Treatment with Immunotherapy 71
7.4.4.2 Criteria to Resume Treatment with Chemotherapy 71
7.4.5 Management Algorithms for Immuno-Oncology Agents 72
7.4.6 Dose-limiting Toxicities 72
7.4.7 Treatment of Immunotherapy Infusion Reactions 74
7.5 Preparation/Handling/Storage/Accountability 75
7.5.1 Retained Samples for Bioavailability/Bioequivalence/Biocomparability 76
7.6 Study Intervention Compliance 76
7.7 Concomitant Therapy 77
7.7.1 Prohibited and/or Restricted Treatments 77
7.7.2 Other Restrictions and Precautions 77
7.7.2.1 Imaging Restrictions and Precautions 78
7.7.3 Permitted Therapy 78
7.7.3.1 Palliative Local Therapy 78
7.8 Continued Access to Study Intervention After the End of the Study 79
8 DISCONTINUATION CRITERIA 79
8.1 Discontinuation of Study Intervention 79
8.1.1 Immunotherapy Treatment Beyond Disease Progression 80
8.1.2 Post-study Intervention Study Follow-up 81
8.2 Discontinuation From the Study 81
8.2.1 Individual Discontinuation Criteria 82
8.3 Lost to Follow-up 82
9 STUDY ASSESSMENTS AND PROCEDURES 83
9.1 Efficacy Assessments 83
9.1.1 Imaging Assessment for the Study 83
9.1.1.1 Methods of Measurement 84
9.1.1.2 Imaging and Clinical Assessment 85
9.1.1.3 BICR Confirmation of Progression or Recurrence 85
9.2 Adverse Events 85
9.2.1 Period and Frequency for Collecting AE and SAE Information 86
9.2.2 Method of Detecting AEs and SAEs 86
9.2.3 Follow-up of AEs and SAEs 87
9.2.4 Regulatory Reporting Requirements for SAEs 87
9.2.5 Pregnancy 87
9.2.6 Laboratory Test Result Abnormalities 88

9.2.7 Potential Drug-induced Liver Injury 89
9.2.8 Other Safety Considerations 89
9.2.9 AEs of Special Interest 89
9.3 Overdose 89
9.4 Safety 89
9.4.1 Physical Examinations 89
9.4.2 Vital Signs and Oxygen Saturation 90
9.4.3 Electrocardiograms 90
9.4.4 Clinical Safety Laboratory Assessments 90
9.4.5 Imaging Safety Assessment 91
9.5 Pharmacokinetics and Immunogenicity 91
9.5.1 Pharmacokinetic Sample Collection Windows 93
9.6 Immunogenicity Assessments 93
9.7 Biomarkers 94
9.7.1 Biomarker Assessments in Tumor 94
9.7.2 Biomarker Assessments in Peripheral Blood 95
9.7.2.1 Whole Blood for Immunophenotyping 95
9.7.2.2 Exploratory Serum Biomarkers 95
9.7.2.3 Plasma for Circulating Tumor DNA 95
9.7.2.4 Whole Blood DNA/RNA Analysis 95
9.7.2.5 Peripheral Blood Mononuclear Cells (PBMCs) 96
10 STATISTICAL CONSIDERATIONS 96
10.1 Statistical Hypotheses 96
10.2 Sample Size Determination 96
10.3 Analysis Sets 97
10.4 Statistical Analyses 97
10.4.1 Efficacy Endpoint(s) 98
10.4.2 Safety Endpoint(s) 99
10.4.3 Other Analyses 100
10.5 Interim Analyses for Part 2 100
11 REFERENCES 103
12 APPENDICES 106
APPENDIX 1 LIST OF ABBREVIATIONS 107
APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS 112
APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING 123
APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION 127
APPENDIX 5 ECOG PERFORMANCE STATUS 131
APPENDIX 6 IMAE MANAGEMENT ALGORITHMS 132
APPENDIX 7 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) WITH BMS MODIFICATIONS 141

1 PROTOCOL SUMMARY

Protocol Title:

A Randomized, Double-blind, Phase 2 Study of BMS-986315 and Nivolumab in Combination with Chemotherapy Versus Nivolumab in Combination with Chemotherapy as First-line Treatment for Participants with Stage IV or Recurrent Non-small Cell Lung Cancer (NSCLC)

Brief Title:

A Phase 2 Study of BMS-986315 and Nivolumab in Combination with Chemotherapy in Participants with First-line Stage IV or Recurrent NSCLC

Rationale:

This study aims to assess the clinical efficacy and to establish the safety of combination therapy of BMS-986315, nivolumab, and platinum doublet chemotherapy versus nivolumab and platinum-based doublet chemotherapy in the first-line treatment of Stage IV or recurrent NSCLC.

Despite the success of therapeutic approaches targeting the checkpoint pathways in NSCLC, many patients do not benefit, potentially due to other immune resistance mechanisms. One such resistance mechanism stems from the interaction between the inhibitory receptor natural killer group 2 member A (NKG2A) and its ligand, MHC class I antigen E (HLA-E). CD94/NKG2 is a family of C-type lectin receptors that may stimulate or inhibit the cytotoxic activity of natural killer (NK) cells through recognition of nonclassical major histocompatibility complex (MHC) glycoproteins class I. NKG2A, commonly linked with CD94, is an inhibitory receptor that contains 2 immunoreceptor tyrosine-based inhibitory motif domains that recruit src homology 2 domain-containing protein tyrosine phosphatase 1 (SHP-1) and SHP-2, leading to the dephosphorylation of tyrosine kinase substrates, which results in the inhibition of NK and T-cell responses. NKG2A expression is specific to cytotoxic immune cells (effector/memory cluster of differentiation 8+ [CD8+], NK, NKT, and γδT cells), and it is increased in tumor-infiltrating CD8+ T and NK cells. HLA-E is physiologically expressed in most human tissues at low levels, and overexpression of HLA-E has been correlated to worse prognosis in several tumor types. In parallel, NKG2A expression is higher in NK cells found in breast cancer and NSCLC as compared to normal tissue. As for T-cells, NKG2A expression has been correlated with worse survival in patients with colorectal cancer. NKG2A null NK cells had higher cytotoxicity against HLA-E-expressing tumor cells compared to NKG2A+ cells, highlighting the inhibitory capacity of NKG2A.

Thus, an NKG2A antagonistic antibody, such as BMS-986315, [redacted] could have a unique advantage of restoring both T and NK cell responses. Since NKG2A levels on tumor-infiltrating CD8+ T-cells are associated with high PD-1 expression, the combination of BMS-986315 and anti-PD-1 may overcome anti-PD-1 resistance in patients with advanced solid tumors that express HLA-E.

In the ongoing Phase 1 study CA047004, [redacted], BMS-986315 monotherapy and in combination with nivolumab showed a tolerable safety profile with no dose-limiting toxicities (DLTs) observed [redacted]

[redacted] Recent data from COAST, a Phase 2 study, showed that an anti-NKG2A mAb, monalizumab, in combination with durvalumab (anti-PD-L1 monoclonal antibody) is safe and showed preliminary efficacy in locally advanced NSCLC post-concurrent chemoradiation. Nivolumab, BMS-986315, and chemotherapy each have non-overlapping anti-cancer mechanisms and may have synergistic and/or additive activity as combination therapy, with few overlapping toxicities. [redacted]

Objectives and Endpoints:

Table 1: Objectives and Endpoints

Objectives	Endpoints
Part 1: Safety Lead-in	
• To assess the safety and tolerability of BMS-986315 administered in combination with nivolumab and platinum-based doublet chemotherapy in participants with histologically confirmed Stage IV or recurrent NSCLC in first-line setting.	• Incidence of AEs, TRAEs, SAEs (per CTCAE v5), AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and death.
Part 2: Primary	
• To compare the objective response rate (ORR) of BMS-986315 and nivolumab in combination with platinum-based doublet chemotherapy versus nivolumab and platinum-based doublet chemotherapy in participants with histologically confirmed Stage IV or recurrent NSCLC in first-line setting.	• ORR assessed by blinded independent central review (BICR) is defined as the proportion of participants who achieve a best response of CR or PR using the RECIST 1.1 criteria.
Part 2: Secondary	
• To evaluate the progression-free survival (PFS) of BMS-986315 and nivolumab in combination with platinum-based doublet chemotherapy compared to nivolumab and platinum-based doublet chemotherapy.	• PFS assessed by BICR is defined as the time between the date of randomization and the first date of documented progression, per RECIST 1.1 criteria or death due to any cause, whichever occurs first.
• To assess the safety and tolerability of BMS-986315 and nivolumab in combination with platinum-based doublet chemotherapy compared to nivolumab and platinum-based doublet chemotherapy.	• Incidence of AEs, TRAEs, SAEs (per CTCAE v5), AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and death.
• To evaluate other efficacy endpoints including duration of response (DoR), time to objective response (TTR), and disease control rate (DCR) of BMS-986315 and nivolumab in combination	• DoR assessed by BICR is defined as the time between the date of first documented response (CR or PR) to the date of the first documented progression as determined by RECIST 1.1 criteria or death due to any cause, whichever occurs first.

Table 1: Objectives and Endpoints

Objectives	Endpoints
with chemotherapy compared to nivolumab and chemotherapy	• TTR assessed by BICR is defined as the time between the date of randomization and the first confirmed documented response (CR or PR) per RECIST 1.1 criteria. • DCR assessed by BICR is defined as the proportion of participants who achieve a best response of CR, PR, or SD using the RECIST 1.1 criteria.
• To characterize the PK of BMS-986315 in combination with nivolumab and chemotherapy. • To characterize the immunogenicity of BMS-986315 in combination with nivolumab and chemotherapy.	• Summary of PK parameters: Cmax, Tmax, AUC(0-T), and other parameters as appropriate • Incidence of anti-drug antibodies to BMS-986315 when in combination with nivolumab and chemotherapy.

Abbreviations: AUC(0-T), Area under the serum concentration-time curve from time zero to time of last quantifiable concentration; AE, adverse event; BICR, blinded independent central review; Cmax, Maximum observed serum concentration; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DLT, dose-limiting toxicity; DoR, duration of response; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression free survival; PK, pharmacokinetics; PR, partial response, RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; SD, stable disease; Tmax, Time of maximum observed serum concentration; TRAE, treatment-related adverse event; TTR, time to response.

Overall Design:

This study is composed of 2 parts: Part 1: Safety Lead-in for 2 dose levels of BMS-986315 administered in combination with nivolumab and platinum-based doublet chemotherapy, and Part 2: randomization to BMS-986315 in combination with nivolumab and platinum-based doublet chemotherapy, or the control arm of nivolumab and platinum-based doublet chemotherapy. The study design schema is shown in Figure 1.

Part 1: Safety Lead-in

BMS-986315 450 mg [redacted] or 900 mg [redacted] and nivolumab 360 mg in combination with histology-based platinum doublet chemotherapy will be administered intravenously at Day 1 of every 3 week cycle for 4 cycles, followed by BMS-986315 and nivolumab combination for up to 2 years. This Safety Lead-in will be evaluated for safety and tolerability in a dose-escalation sequence based on dose-limiting toxicities (DLTs), using Bayesian optimal interval (BOIN) design to guide escalation decisions, and the overall assessment of available safety, pharmacokinetic (PK), and pharmacodynamic data. The Part 2 randomization phase will be initiated upon the safety evaluation of the protocol-defined DLT and overall safety assessment of Part 1.

Part 2

[redacted]

Part 2 of the study will start with randomization [redacted]

Arm A: Nivolumab 360 mg every 3 weeks (Q3W) + 4 cycles of histology-based platinum doublet chemotherapy

Arm B: BMS-986315 900 mg Q3W + nivolumab 360 mg Q3W + 4 cycles of histology-based platinum doublet chemotherapy

Arm C: BMS-986315 450 mg Q3W + nivolumab 360 mg Q3W + 4 cycles of histology-based platinum doublet chemotherapy

Histology-based platinum doublet chemotherapy will be as follows:

- Squamous histology: Carboplatin area under the concentration-time curve (AUC) 6 + paclitaxel 200 mg/m^2 Q3W
- Non-squamous histology: Carboplatin AUC 5 or 6 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 Q3W (optional maintenance therapy with 500 mg/m^2 Q3W pemetrexed alone).

Treatment will continue until disease progression, unacceptable toxicity, or other reasons as specified in the protocol, and the maximum duration of treatment for nivolumab and BMS-986315 will be 2 years (24 months) from first dose for BMS-986315 and nivolumab, whichever comes first.

[redacted]

[redacted]

Number of Participants:

Part 1: Safety Lead-in

[redacted] participants will be enrolled in the safety Lead-in phase. [redacted]

Part 2:

[redacted] participants will be randomized [redacted]

Study Population:

Key Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

- Ages 18 or older
- Participants must have a life expectancy of at least 3 months
- Participants must have histologically confirmed NSCLC per the 8th International Association for the Study of Lung Cancer classification of squamous or non-squamous histology with Stage IV or recurrent disease following multimodal therapy for locally advanced disease.
- No prior systemic anti-cancer treatment (including tyrosine kinase inhibitors) given as primary therapy for advanced or metastatic disease. Prior adjuvant or neoadjuvant chemotherapy for early-stage lung cancer is permitted if completed at least 6 months prior to initiating study treatment.
- Eastern Cooperative Oncology Group Performance Status of 0 or 1.
- Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Key Exclusion Criteria

- Participants with central nervous system metastases as the only disease site will be excluded.
- Participants with known epidermal growth factor receptor (EGFR) mutation, ALK receptor tyrosine kinase (ALK) translocation, and ROS proto-oncogene 1 (ROS1) fusion which are

sensitive to available targeted inhibitor therapy are excluded. [redacted].

- Participants with known gene mutations including neurotrophic tyrosine receptor kinase (NTRK) fusion, mesenchymal epithelial transition (MET) exon 14 skipping mutation, B-Raf proto-oncogene (BRAF) V600E mutation, or RET proto-oncogene (RET) rearrangement, which are sensitive to available targeted inhibitor therapy are excluded. If the test status is unknown or indeterminate for these 4 genes, the participants are eligible.
- [redacted]

Study Intervention for CA0471009		
Intervention Name	**Unit Dose Strength(s)**	**IP/IMP/Non-IP/ Non-IMP/AxMP**
BMS-986315 Concentrate for Solution for Infusion	[redacted] mg/mL	IMP, Open-label (Part 1) IMP, Blinded (Part 2)
Nivolumab (BMS-936558) Solution for Injection	10 mg/mL	IMP, Open label
Pemetrexed Powder for Concentrate for Solution for Infusion[a]	500 mg per vial	IMP, Open label
Cisplatin Concentrate for Solution for Infusion[a]	1 mg/mL	IMP, Open label
Carboplatin Concentrate for Solution for Infusion[a]	10 mg/mL	IMP, Open label
Paclitaxel Concentrate for Solution for Infusion[a]	6 mg/mL	IMP, Open label

Abbreviations: AxMP, Auxiliary Medicinal Product; IMP, Investigational Medicinal Product; IP, Investigational Product; Non-IMP and Non-IP, Non-investigational Medicinal Product.

[a] These products may be obtained by the investigational sites as local commercial product in certain countries if allowed by local regulations. In these cases, products may be a different pack size/potency than listed in the table. These products should be prepared/stored/administered in accordance with the package insert or summary of product characteristics (SmPC).

Statistical Methods:

It is expected that the objective response rate (ORR) with first-line Stage IV or recurrent NSCLC randomized to BMS-986315 with nivolumab in combination with chemotherapy will be improved as compared to participants receiving nivolumab in combination with chemotherapy.

In Part 1, the dose escalation will utilize the BOIN method to guide dose-escalation decisions. Changes in tumor measurements will be assessed by blinded independent central review (BICR), and tumor responses determined using RECIST v1.1 criteria.

[redacted]

A detailed description of the statistical analyses will be described in the statistical analysis plan.

Data Monitoring Committee: Yes

An internal, independent Data Assessment Committee will be used in this study.

Other Committee: Yes

A BICR committee will be used in this study.

Brief Summary:

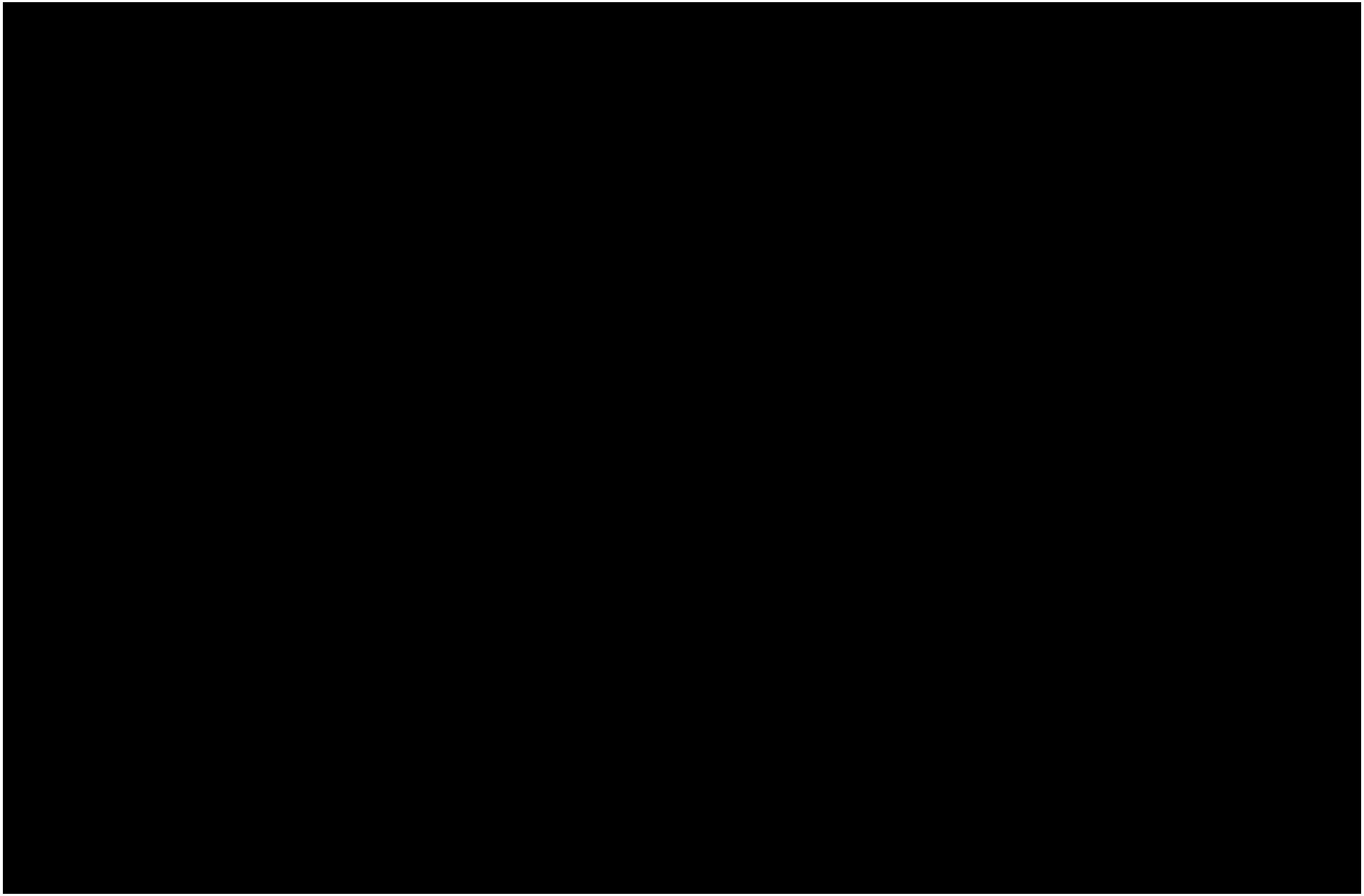
Study Intervention Duration: Each dosing cycle lasts 3 weeks (21 days). Study intervention is administered on Day 1 ± 3 days, and the maximum duration of treatment for nivolumab and BMS-986315 will be up to 2 years.

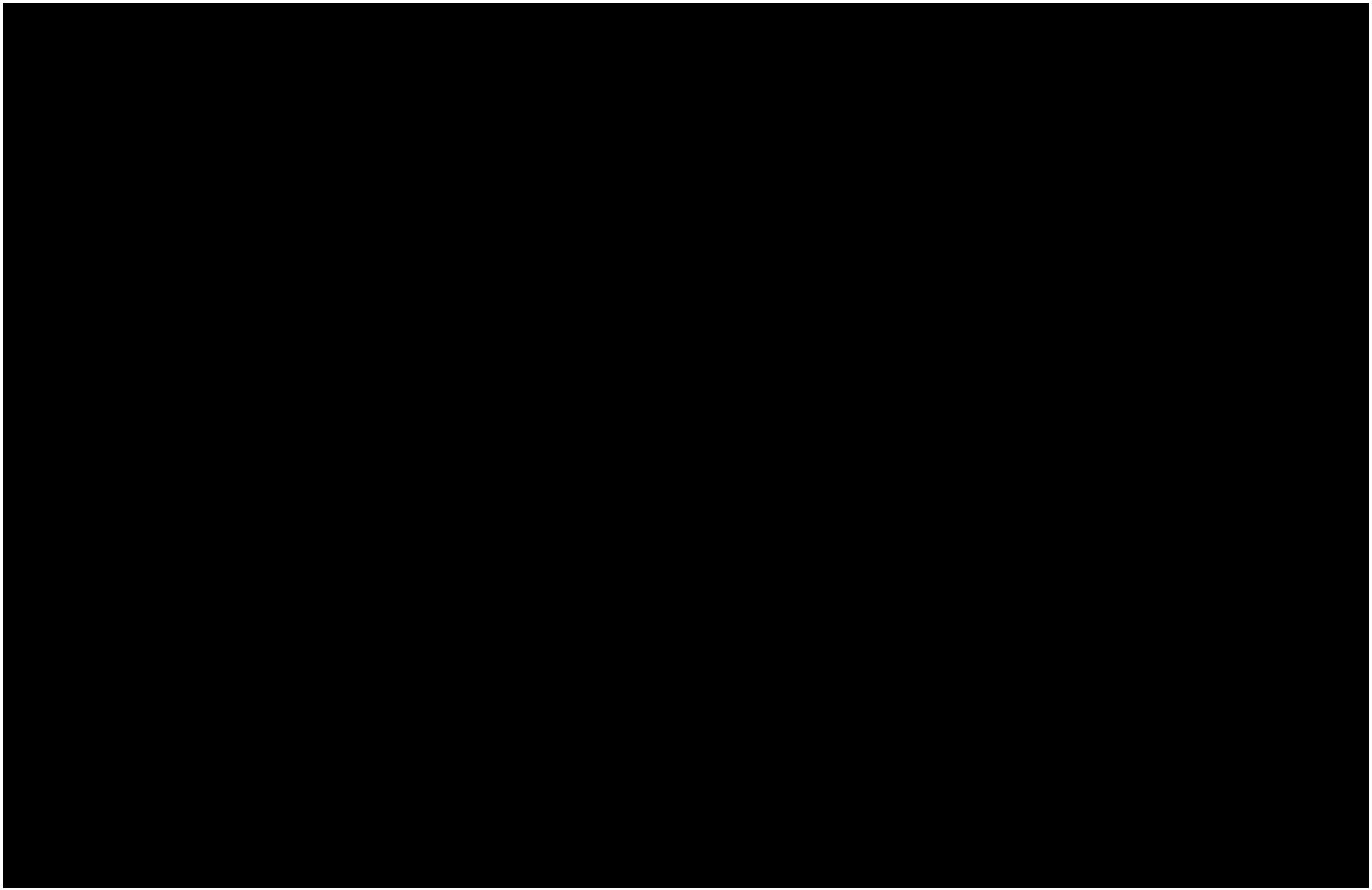
Study Visit Frequency: Study intervention will be given Q3W. [redacted]

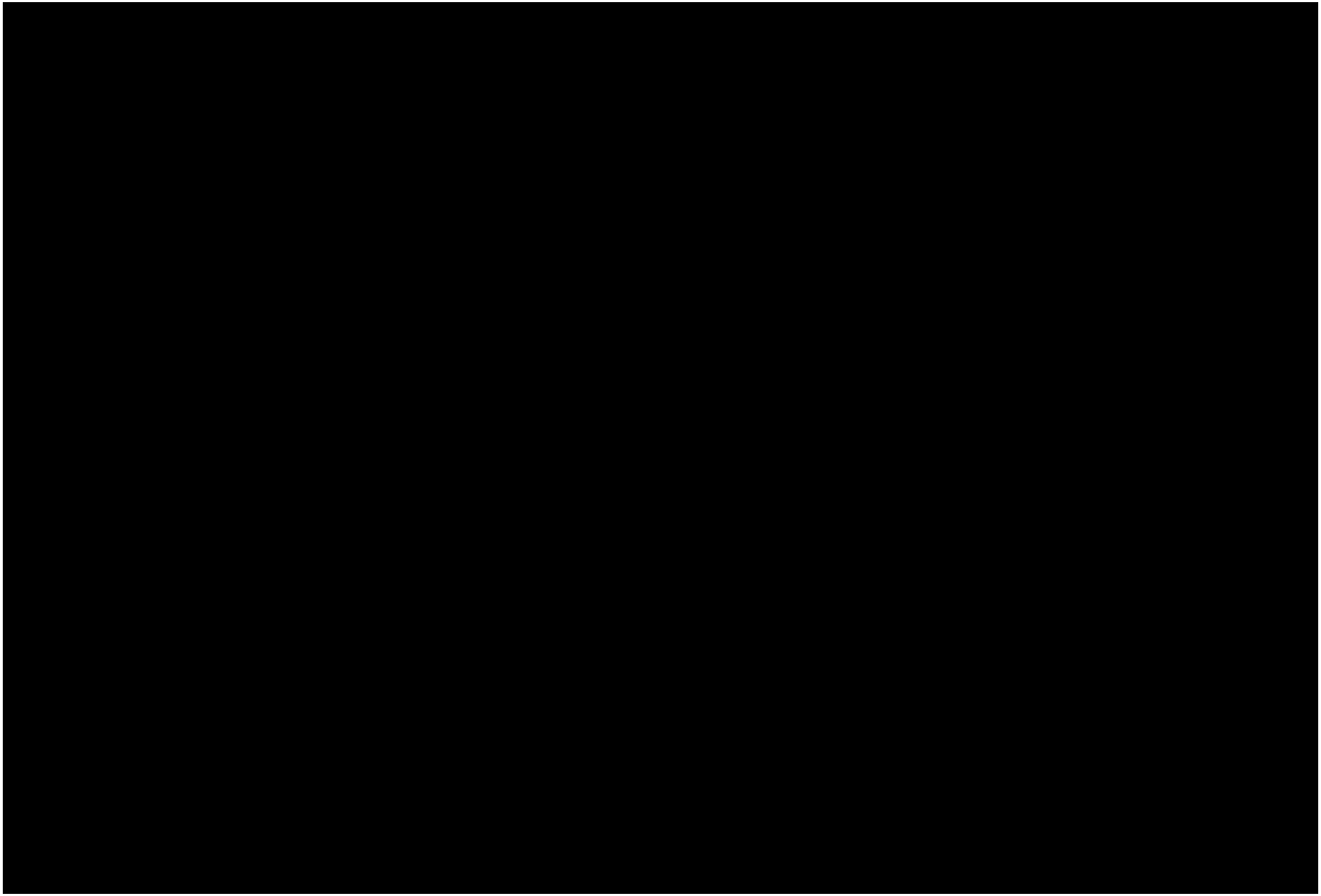
2 SCHEDULE OF ACTIVITIES

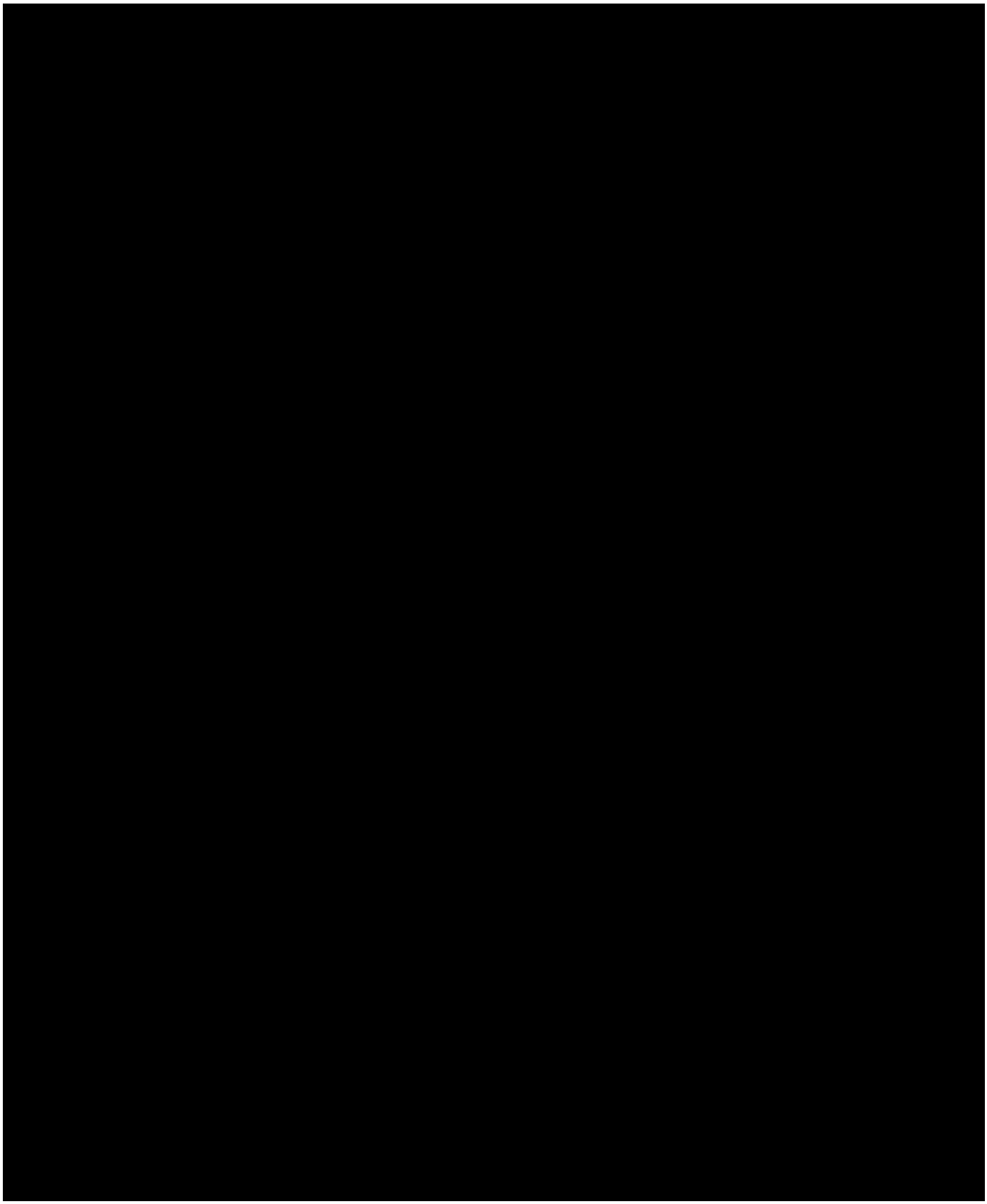
Study assessments and procedures are presented in [redacted]

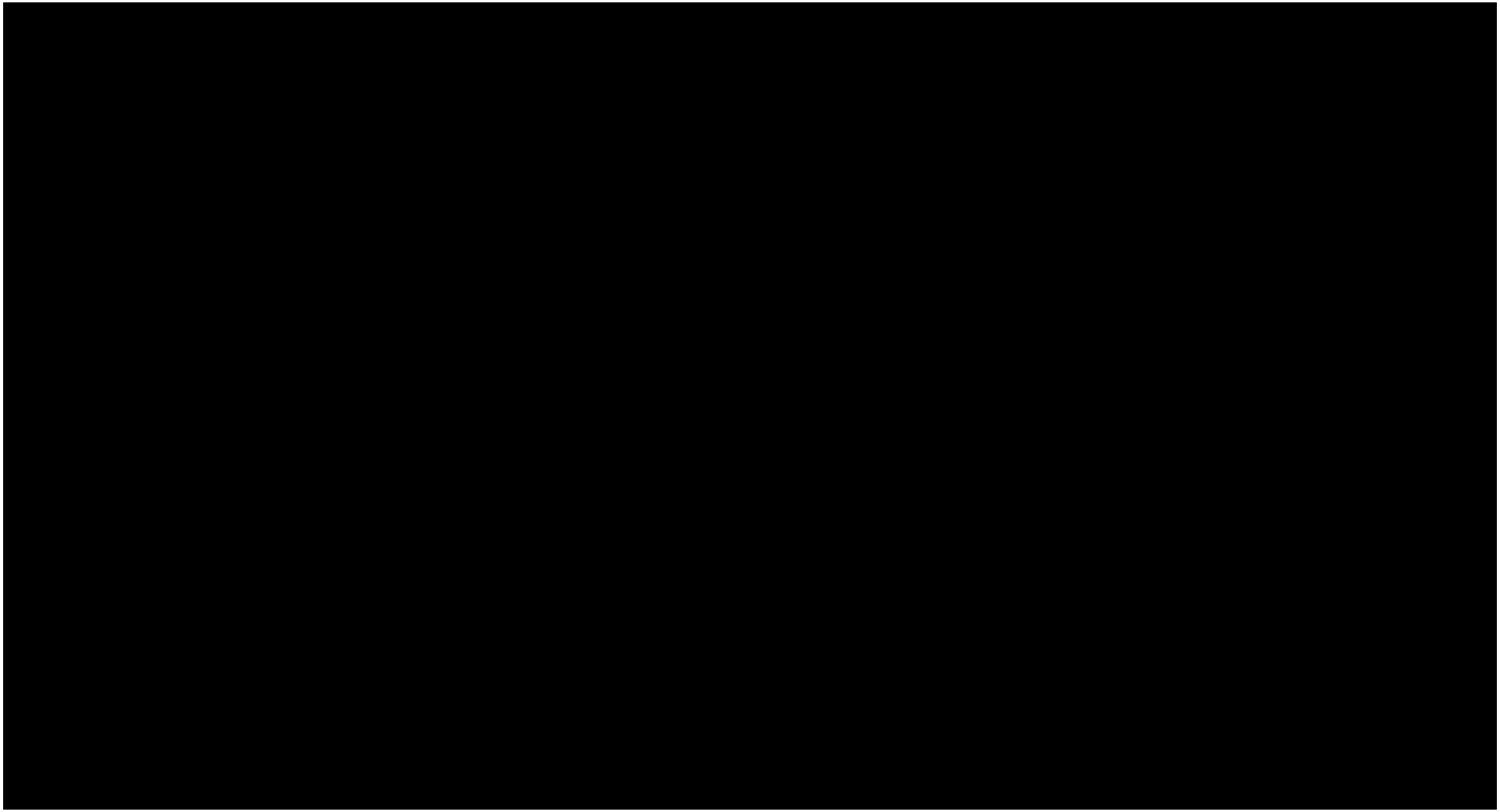
In the event that multiple procedures are required at a single time point, the electrocardiogram (ECG) may be obtained up to 15 minutes earlier, vital signs may be obtained up to 10 minutes earlier or later, and clinical laboratory samples may be obtained up to 5 minutes earlier than the nominal time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











3 INTRODUCTION

Study CA0471009 is a randomized, double-blind, Phase 2 study of BMS-986315 and nivolumab in combination with chemotherapy versus nivolumab in combination with chemotherapy as first-line treatment for participants with Stage IV or recurrent non-small cell lung cancer (NSCLC). BMS-986315 is a fully human immunoglobulin G1.3 (IgG1.3) monoclonal antibody (mAb) that binds [redacted] to human natural killer group 2 member A (NKG2A) [redacted]

This study aims to provide preliminary evidence of clinical efficacy and to establish the safety of combination therapy of BMS-986315, nivolumab, and histology-based platinum doublet chemotherapy (PDCT) in the first-line treatment of Stage IV or recurrent NSCLC via a 2-part design: a safety lead-in for 2 dose levels of BMS-986315 administered in combination with nivolumab and PDCT (Part 1), and a randomization part for 2 dose levels of BMS-986315 in combination with nivolumab and PDCT, and the control arm of nivolumab and PDCT (Part 2).

3.1 Study Rationale

The most extensively studied immune-modulating molecules are agents blocking checkpoint molecules, such as programmed cell death 1 (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. In first-line therapy of programmed death-ligand 1 (PD-L1) expressing metastatic NSCLC patients, monotherapy of pembrolizumab, an anti-PD-1 monoclonal antibody (mAb), or a combination of nivolumab and ipilimumab, the PD-1 and CTLA-4 dual blockade respectively, provided clinical evidence of improvement in overall survival (OS) in Phase 3 trials Keynote 042 [1] and CheckMate 227.[2] In metastatic NSCLC, regardless of PD-L1 expression level, pembrolizumab plus chemotherapy, or nivolumab plus ipilimumab plus 2 cycles of chemotherapy have been approved to improve overall survival in all comers with acceptable and manageable safety profiles in Phase 3 trials Keynote 189,[3] Keynote 407,[4] and CheckMate 9LA.[5]

Despite the above success of therapeutic approaches targeting the checkpoint pathways in NSCLC, many patients do not benefit, potentially due to other immune resistance mechanisms. One such resistance mechanism stems from the interaction between the inhibitory receptor natural killer group 2 member A (NKG2A) receptor and its ligand, HLA-E. CD94/NKG2 is a family of C-type lectin receptors that may stimulate or inhibit the cytotoxic activity of NK cells through recognition of nonclassical major histocompatibility complex (MHC) glycoproteins class I. NKG2A, commonly linked with CD94, is an inhibitory receptor that contains 2 immunoreceptor tyrosine-based inhibitory motif (ITIM) domains that recruit SHP-1 and SHP-2, leading to the dephosphorylation of tyrosine kinase substrates, which results in the inhibition of NK and T-cell responses. NKG2A expression is specific to cytotoxic immune cells (effector/memory CD8+, NK, NKT, and γδT cells), and it is increased in tumor-infiltrating CD8+T and NK cells. HLA-E is physiologically expressed in most human tissues at low levels, and overexpression of HLA-E has

been correlated to worse prognosis in several tumor types. In parallel, NKG2A expression is higher in NK cells found in breast cancer and NSCLC as compared to normal tissue. As for T cells, NKG2A expression has been correlated with worse survival in patients with colorectal cancer. NKG2A null NK cells had higher cytotoxicity against HLA-E-expressing tumor cells compared to NKG2A+ cells, highlighting the inhibitory capacity of NKG2A.

Thus, an NKG2A antagonistic antibody, such as BMS-986315, [redacted] could have a unique advantage of restoring both T and NK cell responses. Since NKG2A levels on tumor-infiltrating CD8+ T cells are associated with PD-1 high expression, the combination of BMS-986315 and anti-PD-1 may overcome anti-PD-1 resistance in patients with advanced solid tumors that express HLA-E.

In the ongoing Phase 1 study, CA047004, [redacted],[8] BMS-986315 monotherapy cohort and in combination with nivolumab showed a tolerable safety profile with no dose-limiting toxicities (DLTs) [redacted] Recent data from COAST,[6] a Phase 2 study, showed that an anti-NKG2A mAb, monalizumab, in combination with durvalumab is safe and showed preliminary efficacy in locally advanced NSCLC post-concurrent chemoradiation. Nivolumab, BMS-986315, and chemotherapy each have non-overlapping anti-cancer mechanisms and may have synergistic and/or additive activity as combination therapy, with few overlapping toxicities. [redacted]. The inclusion/exclusion criteria (Section 6.1, Section 6.2) in this study recapitulate a participant population who would typically be eligible to receive anti-PD-1 and chemotherapy-based combination treatment.

3.2 Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of BMS-986315 is provided in the Investigator's Brochure (IB)[8] and information for nivolumab is provided in the nivolumab IB. For prescribing information and administration instructions on pemetrexed, paclitaxel, cisplatin, and carboplatin, please refer to the current label and package insert that is applicable to the applicable geographic region.

3.2.1 First-line Immunotherapy(ies) in Combination with Chemotherapy in NSCLC

NSCLC remains the leading cause of cancer-related mortality worldwide, accounting for approximately 18% of all cancer deaths.[7] Until recently, the treatment of patients with advanced NSCLC whose tumors did not have a targetable genetic alteration was cytotoxic chemotherapy alone. The introduction of immune checkpoint inhibitors targeting the PD-1 signaling pathway in the treatment of patient with NSCLC has had a significant effect on participant survival. Pembrolizumab combined with chemotherapy has been approved by the US Food and Drug Administration (FDA) in the front-line setting and has demonstrated an improvement in OS in

NSCLC participants as compared to chemotherapy alone.[1] Although not approved by the FDA for use in the front-line setting for NSCLC, nivolumab in combination with histology-based PDCT was recently studied in Part 2 of the Phase 3 trial.[1] A summary of the efficacy results was presented at the European Society for Medical Oncology (ESMO) Immuno-Oncology (I-O) in 2019. Across all randomized, squamous (SQ), and non-squamous (NSQ) populations, there were clinically meaningful improvements with nivolumab + chemotherapy in OS, objective response rate (ORR), and progression-free survival (PFS) although in the primary endpoint population (NSQ), the results were not statistically significant. Specifically, OS results favored the nivolumab + chemotherapy arm in all randomized participants with median OS 18.3 m versus 14.7 m, OS hazard ratio (HR) 0.81 (95% confidence interval [CI], 0.67–0.97), and participants with SQ NSCLC with median OS 18.3 m vs 12.0 m, HR 0.69 (95% CI, 0.50–0.97). However, despite these advances, many patients do not benefit, potentially due to other immune resistance mechanisms.

To this end, dual immunotherapies in combination with histology-based chemotherapy have been developed and shown to improve efficacy outcomes with a manageable safety profile. Study CA2099LA[5] which evaluated nivolumab plus ipilimumab in combination with PDCT vs PDCT in a similar population of first-line NSCLC participants, reported a hazard ratio (HR) for OS of 0.66 (95% CI, 0.55-0.80). Similarly, the current Phase 2 CA0471009 study evaluates BMS-986315, a novel antagonistic antibody to NKG2A, in combination with nivolumab plus PDCT in NSCLC in the first-line setting.

3.2.2 Preclinical Activity of BMS-986315 in Combination with Nivolumab

The mechanism of action and preclinical functional activity of BMS-986315 are detailed in the IB[8]. Briefly, BMS-986315 is a fully human IgG1.3 mAb that binds [redacted] to human NKG2A [redacted] The antitumor therapeutic activity of anti-NKG2A mAb was also studied using an anti-mouse NKG2A (mNKG2A) mAb. [redacted]

3.2.3 BMS-986315 Preliminary Clinical Activity and Safety

BMS-986315 is currently being evaluated in the first-in-human study, CA047004. [redacted], Part 1A and 1B of Study CA047004 were open and evaluating the dose escalation of BMS-986315 as monotherapy (Part 1A) and in combination with nivolumab (Part 1B). The dose-escalation Phase in combination with cetuximab (Part 1C) is not open to enrollment[8].

[redacted]

In Part 1A BMS-986315 monotherapy, [redacted] The majority of AEs reported were Grade 1 or 2. [redacted] There were no reported treatment-related serious AEs. [redacted]

In Part 1B BMS-986315 in combination with nivolumab, [redacted] no DLTs reported. [redacted]

At this time, no formal clinical efficacy evaluations have been conducted.

3.3 Benefit/Risk Assessment

Extensive details on the safety profile of BMS-986315, nivolumab, and chemotherapy agents (pemetrexed, paclitaxel, cisplatin, and carboplatin) are available in the IBs, and/or the current label and package insert that is applicable for the investigator's geographic region and, will not be repeated herein.

3.3.1 Risk Assessment

As described in Section 3.2.3, BMS-986315 showed a tolerable safety profile with no dose-limiting toxicities (DLTs) [redacted]

Nivolumab, BMS-986315, and PDCT each have non-overlapping anti-cancer mechanisms with few overlapping toxicities. Based on available safety data for BMS-986315 as monotherapy and in combination with nivolumab [8,9]as well as the known safety profile of nivolumab plus PDCT [10,11], the BMS-986315 + nivolumab + PDCT triplet therapy is expected to have manageable toxicity with no new serious AE categories expected, and [redacted]

In combination therapy, BMS-986315 may potentiate immune-mediated adverse events (IMAEs) caused by nivolumab. The safety profile of nivolumab is characterized by immune-related toxicities such as diarrhea, rash, pneumonitis, liver toxicity and endocrinopathies. The frequency and types of IMAEs associated with nivolumab are similar across multiple tumor types and are further described in the Reference Safety Information in the IB (BMS-986315 Investigator Brochure v2).

Participants who develop IMAEs may require prolonged treatment with high-dose corticosteroids and other immunosuppressive agents. This could increase the risk of opportunistic infections. IMAE management algorithms in the protocol recommend antibiotic prophylaxis against opportunistic infections in such situations (see Appendix 6). Due to the potential risk of exaggerated inflammatory response, participants with auto-immune disorders, who are at risk for flare of autoimmunity, will be excluded.

Whether nivolumab, PDCT, and/or BMS-986315 administration increases the risk for contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or increases the severity or duration of symptoms is currently unknown. This unknown risk must be considered when enrolling a participant. No additional safety monitoring or routine screening tests will be required due to the SARS-CoV-2 pandemic. Participants with recent or acute infections will be excluded or delay start of treatment. If a participant has a confirmed SARS-CoV-2 infection while on study intervention, dose delay or interruption of study intervention is required to meet the criteria for resuming study intervention. (see Section 7.4.4)

[redacted]

[redacted]

3.3.2 Benefit Assessment

There remains a need to improve long-term outcomes in participants with first-line Stage IV NSCLC. As described in the BMS-986315 Investigator's Brochure,[9] preclinical studies demonstrated that combination blockade of PD-1 and NKG2A had improved antitumor activity than either reagent alone. In the ongoing Phase 1 study, CA047004, BMS-986315 monotherapy and in combination with nivolumab, showed a tolerable safety profile with no DLTs observed [redacted].[8] Recent data from COAST[6] a Phase 2 study, showed that an anti-NKG2A mAb, monalizumab, in combination with durvalumab is safe and showed preliminary efficacy in locally advanced NSCLC post-concurrent chemoradiation.[6] Nivolumab, BMS-986315, and PDCT each have non-overlapping anti-cancer mechanisms and may have synergistic and/or

additive activity as combination therapy, with few overlapping toxicities. [redacted].

3.3.3 Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with combination therapy of BMS-986315 with nivolumab plus PDCT are justified by the anticipated benefits that may be afforded to participants with first-line Stage IV NSCLC.

An independent, internal Data Assessment Committee (DAC) (see Section 5.1.1) will evaluate safety based on all available data with particular attention to: (i) AEs or other safety trends whose character, severity, and/or frequency suggest that participants would be exposed to an unreasonable and significant risk of illness or injury; (ii) new non-clinical data suggesting unreasonable and significant risk of illness or injury. In addition to the DAC, the Bristol-Myers Squibb Company (BMS) Safety Management Team (SMT) routinely monitors for actual or potential issues related to participant safety, including clinical trial data, information from literature, and non-clinical toxicology reports, which could result in a change in the medical risk-benefit balance associated with study treatment. In this study, the SMT will also use quantitative approaches for continuous safety monitoring of specific AE signals (eg, Grade 3 to Grade 4 treatment-related AEs). If a safety signal is detected by the SMT, then an ad hoc DAC meeting may occur to assess the risk/benefit and make recommendations about the safety.

If such evaluation suggests that the benefit/risk profile of the study has become unfavorable to participants, the Sponsor will pause enrollment and/or treatment until further evaluation of data, and interaction with the appropriate Health Authority(ies) can take place on potential actions. Such actions may include (but are not limited to) study continuation, substantial amendment, or termination of the study.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints [Estimands]

Objectives	Endpoints
Part 1: Safety Lead-in • To assess the safety and tolerability of BMS-986315 administered in combination with nivolumab and platinum-based doublet chemotherapy, in participants with histologically confirmed Stage IV or recurrent NSCLC in first-line setting.	• Incidence of AEs, TRAEs, SAEs (as per CTCAE v5), AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and death.
Main Estimand for the Primary Objective • Treatment: BMS-986315 450 mg Q3W + nivolumab 360 mg Q3W+ histology-based chemotherapy Q3W [redacted] and BMS-986315 900 mg Q3W + Nivolumab 360 mg Q3W + Histology-based Chemotherapy Q3W • Population: Participants with Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC) • Variable: Occurrence of AEs, TRAEs, SAEs (as per CTCAE v5), AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and death. • Intercurrent events (strategy): AEs meeting protocol-defined DLT criteria (principal stratum strategy). Occurrence of AEs, TRAEs, SAEs (as per CTCAE v5), AEs leading to discontinuation, and death (while on treatment). • Population-level summary: Adverse event (AE) incidence rate	
Part 2: Primary	
• To compare the objective response rate (ORR) of BMS-986315 and nivolumab in combination with platinum-based doublet chemotherapy versus nivolumab and platinum-based doublet chemotherapy in participants with histologically confirmed Stage IV or recurrent NSCLC in first-line setting.	• ORR assessed by blinded independent central review (BICR) is defined as the proportion of participants who achieve a best response of CR or PR using the RECIST 1.1 criteria.

Table 4-1: Objectives and Endpoints [Estimands]

Objectives	Endpoints
Main Estimand for the Primary Objective • Treatment: Nivolumab 360 mg Q3W + Histology-based Chemotherapy Q3W (Arm A), and BMS-986315 900 mg Q3W + Nivolumab 360 mg Q3W + Histology-based Chemotherapy Q3W (Arm B), and BMS-986315 450 mg Q3W + Nivolumab 360 mg Q3W + Histology-based Chemotherapy Q3W (Arm C) • Population: Participants with Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC) • Variable: Best overall response (BOR), defined as the best response, as determined by BICR recorded between the date of randomization and the date of first objectively documented progression per RECIST 1.1 • Intercurrent events (strategy): Early discontinuation of study treatment (treatment policy); initiation of subsequent anti-cancer therapy (excluding allowed palliative radiotherapy/surgery to non-target/non-thoracic sites) (treatment policy) • Population-level summary: ORR, defined as the number of randomized participants who achieve a BOR of confirmed complete response (CR) or confirmed partial response (PR) based on BICR assessments (using RECIST 1.1) divided by the number of all randomized participants in each treatment group, will be provided with a 95% exact confidence interval (CI). For the difference of ORR between arms, a 2-sided 90% exact CI will be provided for Arm A vs. Arm B. For ORR differences between Arm A vs. Arm C or between Arm B vs. Arm C a 95% CI will be provided.	
Part 2: Secondary	
• To evaluate the progression-free survival (PFS) of BMS-986315 and nivolumab in combination with platinum-based doublet chemotherapy compared to nivolumab and platinum-based doublet chemotherapy	• PFS assessed by BICR is defined as the time between the date of randomization and the first date of documented progression, as per RECIST 1.1 criteria or death due to any cause, whichever occurs first.
Main Estimand for the Key Secondary Objective • Treatment: Nivolumab 360 mg Q3W + Histology-based Chemotherapy Q3W (Arm A), and BMS-986315 900 mg Q3W + Nivolumab 360 mg Q3W + Histology-based Chemotherapy Q3W (Arm B), and BMS-986315 450 mg Q3W + Nivolumab 360 mg Q3W + Histology-based Chemotherapy Q3W (Arm C) • Population: Participants with Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC) • Variable: PFS, defined as the time between the date of randomization and the first date of documented progression, determined by BICR assessments (using RECIST 1.1), or death due to any cause, whichever occurs first • Intercurrent events (strategy): Early discontinuation of study treatment (treatment policy); initiation of subsequent anti-cancer therapy (excluding allowed palliative radiotherapy/surgery to non-target/non-thoracic sites) prior to progressive disease or death (hypothetical strategy) • Population-level summary: Kaplan Meier (KM) estimated HR, median survival time and landmark survival rate of PFS	
• To assess the safety and tolerability of BMS-986315 and nivolumab in combination with platinum-based doublet chemotherapy compared to nivolumab and platinum-based doublet chemotherapy.	• Incidence of AEs, TRAEs, SAEs (as per CTCAE v5), AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and death

Table 4-1: Objectives and Endpoints [Estimands]

Objectives	Endpoints
Main Estimand for the Secondary Objective • Treatment: Nivolumab 360 mg Q3W + Histology-based Chemotherapy Q3W (Arm A), and BMS-986315 900 mg Q3W + Nivolumab 360 mg Q3W + Histology-based Chemotherapy Q3W (Arm B), and BMS-986315 450 mg Q3W + Nivolumab 360 mg Q3W + Histology-based Chemotherapy Q3W (Arm C) • Population: Participants with Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC) • Variable: Incidence of AEs, TRAEs, SAEs (as per CTCAE v5), AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and death • Intercurrent events (strategy): Early discontinuation of study treatment (while on treatment) • Population-level summary: Adverse event (AE) incidence rate	
• To evaluate other efficacy endpoints including duration of response (DoR), time to objective response (TTR), and disease control rate (DCR) of BMS-986315 and nivolumab in combination with chemotherapy compared to nivolumab and chemotherapy	• DoR assessed by BICR is defined as the time between the date of first documented response (CR or PR) to the date of the first documented progression as determined by RECIST 1.1 criteria or death due to any cause, whichever occurs first. • TTR assessed by BICR is defined as the time between the date of randomization and the first confirmed documented response (CR or PR) per RECIST 1.1 criteria. • DCR assessed by BICR is defined as the proportion of participants who achieve a best response of CR, PR, or SD using the RECIST 1.1 criteria.
• To characterize the PK of BMS-986315 in combination with nivolumab and chemotherapy • To characterize the immunogenicity of BMS-986315 in combination with nivolumab and chemotherapy	• Summary of PK parameters: Cmax, Tmax, AUC(0-T), and other parameters as appropriate • Incidence of anti-drug antibodies to BMS-986315 when in combination with nivolumab and chemotherapy
• **Part 2: Exploratory**	
• To characterize the PK and immunogenicity of nivolumab in combination with BMS-986315 and chemotherapy.	• Summary measure of trough nivolumab concentrations • Incidence of anti-drug antibodies to nivolumab
• To explore the pharmacodynamic (PD) activity of BMS-986315 and nivolumab in combination with chemotherapy via assessment of translational biomarkers	• Summary of measures of change (or % change) from baseline for tumor and peripheral biomarkers of immune activation and associations with antitumor activity
• To explore potential associations between antitumor activity and select biomarker measures in the tumor and peripheral blood prior to treatment	• Summary of associations between baseline levels of select biomarkers and antitumor activity such as, but not limited to, tumoral PD-L1 [redacted] • ORR, PFS, DoR, TTR, OS in randomized participants defined by tumor PD-L1 expression [redacted] based on RECIST v1.1 by BICR and investigator's assessment

Table 4-1: Objectives and Endpoints [Estimands]

Objectives	Endpoints
• To explore the relationship between BMS-986315 and select biomarkers in tumor and peripheral blood	• Associations between BMS-986315 concentrations and tumor and peripheral biomarkers
• To evaluate the overall survival (OS) of BMS-986315 and nivolumab in combination with chemotherapy compared to nivolumab and chemotherapy	• OS in all randomized participants • 1-year OS rate is defined as the percentage of randomized participants still alive at one year from first dose
• To explore potential associations between image-based features, including, but not limited to, heterogeneity, shape, and/or volumetric changes, and antitumor activity	• Summary of measures of image-based feature changes, including, but not limited to, heterogeneity, shape and/or volume, from baseline for every timepoint until progression or study treatment discontinuation, whichever occurs later, or withdrawal consent of tumor assessment, or death.

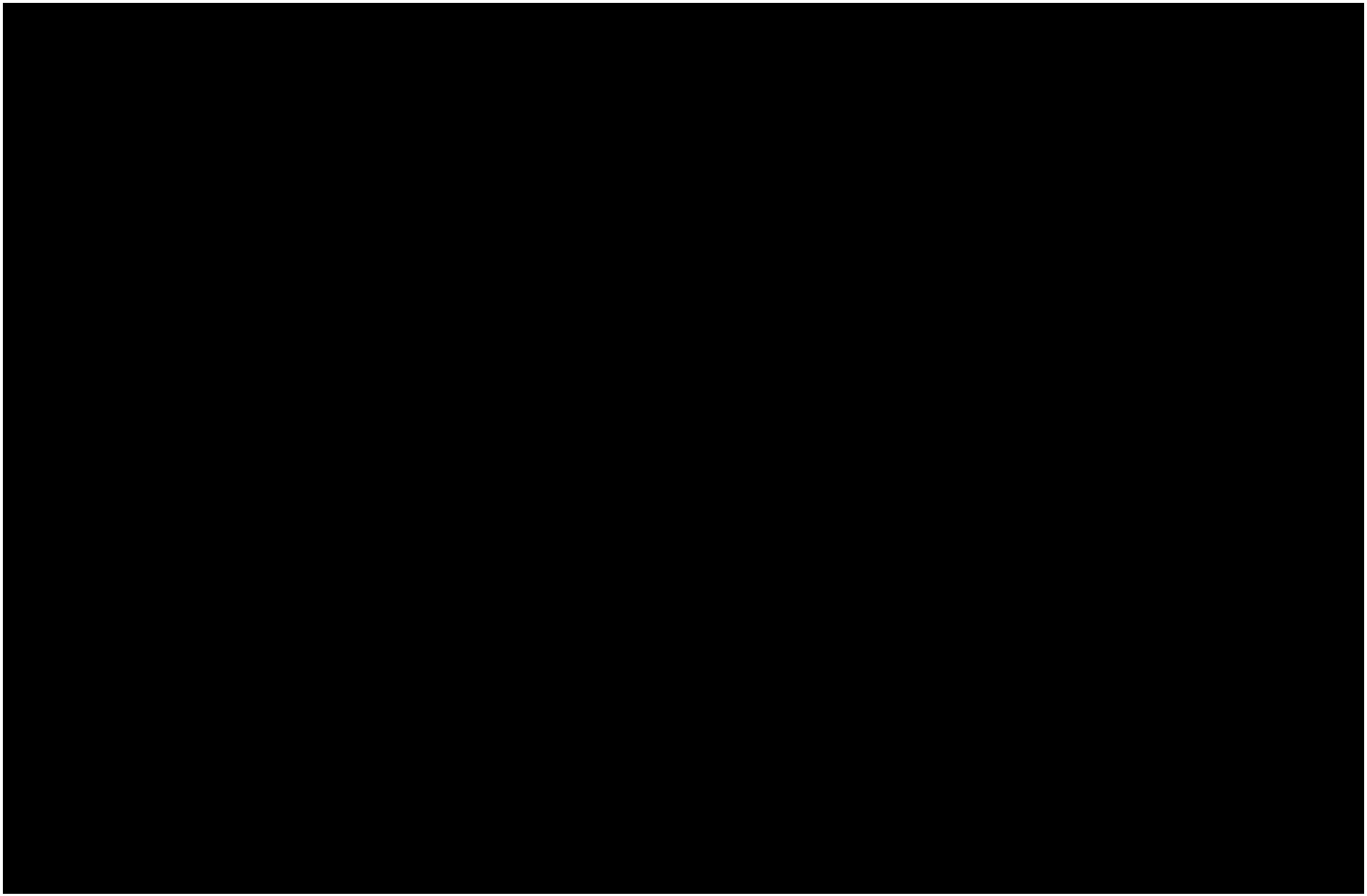
Abbreviations: AUC(0-T), Area under the serum concentration-time curve from time zero to time of last quantifiable concentration; AE, adverse event; BICR, blinded independent central review; BOR, best overall response; CI, confidence interval; [redacted]; Cmax, Maximum observed serum concentration; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DF, Degree of fluctuation; DLT, dose-limiting toxicity; DoR, duration of response; [redacted]; HR, hazard ratio; [redacted]; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, pharmacodynamic; PD-L1, programmed-death ligand 1; PFS, progression free survival; PK, pharmacokinetics; PR, partial response, Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; SD, stable disease; Tmax, Time of maximum observed serum concentration; TRAE, treatment-related adverse event; TTR, time to response.

5 STUDY DESIGN

5.1 Overall Design

This multi-center, randomized trial will evaluate the efficacy and safety of the combination of BMS-986315 plus nivolumab and PDCT vs nivolumab and PDCT in adults with untreated Stage IV or recurrent non-small cell lung cancer (NSCLC). This study will be carried out in 2 parts: Part 1: Safety lead-in for 2 dose levels of BMS-986315 administered in combination with nivolumab and chemotherapy, and Part 2: randomization to BMS-986315 in combination with nivolumab and PDCT or the control arm of nivolumab and PDCT.

The study design schema is presented in [redacted].



Part 1: Safety Lead-in

BMS-986315 450 mg [redacted] or 900 mg [redacted] and nivolumab 360 mg in combination with histology-based PDCT will be administered intravenously (IV) at day 1 of every 3-week (Q3W) schedule for 4 cycles, followed by BMS-986315 and nivolumab combination (and optional pemetrexed maintenance therapy for nonsquamous participants) for up to 2 years. This Safety lead-in part will be evaluated for safety and tolerability in a dose escalation sequence based on dose-limiting toxicities (DLTs) within the [redacted] evaluation period, using Bayesian optimal interval (BOIN) design to guide escalation decisions, and the overall assessment of available safety, PK, and pharmacodynamic data.

[redacted]

During Part 1, approximately 6 participants (and up to 12) will be treated at each dose level. For all dose escalation cohorts, a sentinel participant approach will be used with a 5-day interval between the treatment initiation of the first participant and the treatment of subsequent participants in that dose level. Initially, 3 participants will be enrolled at the start of each dose-escalation cohort, in accordance with the sentinel participant approach above. However, to allow for any unforeseen discontinuations (such as disease progression) before the [redacted] DLT period [redacted] is completed, an extra participant may be enrolled in each dose escalation cohort. Cohort tolerability assessment and subsequent dose recommendation will occur when [redacted] participants within a cohort have completed a [redacted] DLT period or have been sufficiently followed, based on the BOIN design, to make an escalation decision depending on the number of DLTs so far. Dose de-esclation decision may be made as early as [redacted] subjects have completed the DLT period based on totality of data. 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 7.4.6.

Part 2

[redacted]

Part 2 of the study will start with randomization [redacted]

[redacted]

[redacted]

Arm A: Nivolumab 360 mg Q3W + 4 cycles of histology-based PDCT

Arm B: BMS-986315 900 mg Q3W + nivolumab 360 mg Q3W + 4 cycles of histology-based PDCT

Arm C: BMS-986315 450 mg Q3W + nivolumab 360 mg Q3W + 4 cycles of histology-based PDCT

Histology-based platinum doublet chemotherapy will be as follows:

- Squamous histology: Carboplatin under the concentration-time curve (AUC) 6 + paclitaxel 200 mg/m^2
- Non-squamous histology: Carboplatin AUC 5 or 6 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 (optional maintenance therapy with 500 mg/m^2 Q3W pemetrexed)

Planned BMS-986315 dose levels may be modified and intermediate dose levels of BMS-986315 utilized, based upon the totality of the data and outcome of the safety-lead in (Part 1) and continued safety monitoring in Part 2.

If, based on the dose safety data in Part 1, the regimen including BMS-986315 900 mg [redacted] is confirmed to be safe, then this dose level will be evaluated in Part 2 of the trial [redacted]. If, based on the dose safety data, the regimen including BMS-986315 900 mg is not confirmed to be safe, but the regimen including BMS-986315 450 mg [redacted] is confirmed to be safe, an intermediate dose level may be tested. [redacted] (900 mg) would be reduced by 25% or greater. The highest dose level that is confirmed to be safe in the safety lead-in will be evaluated in Part 2.

[redacted]

Treatment will continue until disease progression, or unacceptable toxicity, or other reasons as specified in the protocol, and the maximum duration of treatment for with BMS-986315 and nivolumab will be for up to 2 years (24 months) since the first dose for BMS-986315 and nivolumab, whichever comes first.

The investigator must decide prior to randomization whether the participant with non-squamous histology will receive cisplatin, if eligible. This information will be captured in the study database. Participants with non-squamous histology who have stable disease or response after induction chemotherapy are permitted to receive optional pemetrexed maintenance therapy.

Dose reductions are not permitted for BMS-986315 and nivolumab. All participants will be treated until progression, presence of intolerable toxicities, withdrawal of consent, or study end, whichever comes first. Continuous safety evaluations and tumor assessments will guide the decision to treat a participant with additional cycles of study therapy if the participant has confirmed clinical benefit.

In all study parts, participants with unconfirmed 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:

- Progressive disease defined by Response Evaluation Criteria in Solid Tumors (RECIST v1.1) per investigator assessment, unless participants meet criteria for treatment beyond progression
- Clinical deterioration suggests that no further benefit from treatment is likely
- Intolerability to therapy
- Participant meets criteria for discontinuation of study treatment
-

Efficacy assessments for the antitumor activity of BMS-986315 and nivolumab in combination with chemotherapy will be based on tumor measurements, using RECIST v1.1, with computed tomography (CT) and/or magnetic resonance imaging (MRI), as appropriate. Assessments will be performed [redacted]

[redacted]

Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECGs), and clinical laboratory evaluations will be performed at selected times throughout the dosing interval. Participants will be closely monitored for AEs throughout the study.

5.1.1 Data Monitoring Committee and Other Committees

An independent, internal Data Assessment Committee (DAC) will be used for this study. The DAC will be composed of Sponsor employees who are independent of the CA0471009 study team.

The DAC charter will describe the procedures related to the committee operations in greater detail. The DAC will review data from Part 2 of the study and not the safety lead-in, Part 1.

The DAC will provide general oversight and safety considerations during the study. The DAC will provide advice to the CA0471009 study team regarding actions the committee deems necessary for the continuing protection of participants enrolled in this study. The DAC will be charged with assessing such actions in light of an acceptable benefit-risk profile for BMS-986315, nivolumab, and chemotherapy. The DAC will act in an advisory capacity and will monitor participant safety data of the study.

In addition to the independent DAC, BMS has in place a multi-layered process for ensuring participant safety through close collaboration of study site investigators, the BMS study team, and the BMS Worldwide Patient Safety (WWPS)-led SMT. [redacted]

The minutes of the DAC meetings will be documented in the Trial Master File. The SMT will not share responsibilities with the independent DAC. Decisions on safety, toxicity, and benefit-risk will be solely the responsibility of the BMS CA0471009 study team and therapeutic area leadership and will take account of the totality of the data available and in consideration of any DAC recommendations.

A Blinded Independent Central Review (BICR) is recommended by regulatory agencies in situations where clinical site image interpretation is variable and results of image measurements are important for eligibility determination, safety, and/or efficacy endpoints. Specifically, BICR of scans may mitigate bias regarding endpoint assessment due to the subjectivity involved in lesion measurement and interpretation of tumor response and progression. Sites should submit all images to BICR on a continuing basis. However, should the BICR interpretation be in conflict with the local evaluation, treatment decisions will be based on investigator assessment and not the BICR assessment.

5.2 Number of Participants

Part 1: Safety Lead-in

[redacted] participants will be enrolled in the safety lead-in phase. [redacted]

Part 2:

[redacted] participants will be randomized [redacted].

5.3 End of Study Definition

The start of the study is defined as the first participant's first visit, or first participant screened, or scheduled procedure shown in the Schedule of Activities (see Section 2).

End of trial is defined as the last participant last visit or scheduled procedure shown in the Schedule of Activities (see Section 2) for the last participant, whichever occurs later.

Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected if this is not the same.

A participant is considered to have completed the study if he/she has completed the last procedure shown in the Schedule of Activities.

The primary completion date is defined as the date on which the last data point is collected for the study's primary endpoint. If the study has multiple primary endpoints, the primary completion date is the date on which the last data point is collected for the last primary endpoint. End of study is defined as the last participant's last visit.

5.4 Scientific Rationale for Study Design

Despite the latest success of therapeutic approaches targeting the checkpoint pathways in NSCLC, many patients do not benefit, potentially due to other immune resistance mechanisms. One such resistance mechanism stems from the interaction between inhibitory receptor natural killer group 2 member A (NKG2A) receptor and its ligand, HLA-E. CD94/NKG2 is a family of C-type lectin receptors that may stimulate or inhibit cytotoxic activity of NK cells through recognition of nonclassical major histocompatibility complex (MHC) glycoproteins class I. NKG2A, commonly linked with CD94, is an inhibitory receptor that contains 2 immunoreceptor tyrosine-based inhibitory motif (ITIM) domains that recruit SHP-1 and SHP-2, leading to the dephosphorylation of tyrosine kinase substrates, which results in the inhibition of NK and T cell responses. NKG2A expression is specific to cytotoxic immune cells (effector/memory CD8+, NK, NKT, and γδT cells), and it is increased in tumor-infiltrating CD8+T and NK cells. HLA-E is physiologically expressed in most human tissues at low levels, and overexpression of HLA-E has been correlated to worse prognosis in several tumor types. In parallel, NKG2A expression is higher in NK cells found in breast cancer and NSCLC as compared to normal tissue. As for T cells, NKG2A expression has been correlated with worse survival in patients with colorectal cancer. NKG2A null NK cells had higher cytotoxicity against HLA-E expressing tumor cells compared to NKG2A+ cells, highlighting the inhibitory capacity of NKG2A.

[redacted]

5.4.1 Rationale for Choice of Control Arm

In metastatic NSCLC, regardless of PD-L1 expression level, pembrolizumab plus chemotherapy, or nivolumab plus ipilimumab plus two cycles of chemotherapy have been approved to improve overall survival in all comers with acceptable and manageable safety profiles in Phase 3 trials Keynote 189, Keynote 407, and CheckMate 9LA. In CA209-012 [12], a multi-arm Phase 1 safety study of nivolumab in chemotherapy-naive NSCLC, 56 participants were administered nivolumab in combination with gemcitabine/cisplatin, pemetrexed/cisplatin, or carboplatin/paclitaxel. The overall response rate (ORR) with the different combinations ranged from 42% to 50%. Nivolumab in combination with chemotherapy was studied in Part 2 of the Phase 3 trial CA209227. A summary of the efficacy results was presented at the European Society for Medical Oncology (ESMO) I-O in 2019. Across all randomized, squamous (SQ), and nonsquamous (NSQ)

populations, there were clinically meaningful improvements with nivolumab + chemotherapy in OS, ORR, and PFS, although in the primary endpoint population (NSQ), the results were not statistically significant. Specifically, OS results favored the nivolumab + chemotherapy arm in all randomized participants with median OS 18.3 month vs 14.7 month, HR 0.81 (95% CI, 0.67–0.97) and participants with SQ NSCLC with median OS 18.3 month vs 12.0 month, HR 0.69 (95% CI, 0.50–0.97). A trend towards improvement was seen in participants with NSQ NSCLC, with OS HR 0.86 (95.62% CI, 0.69–1.08; P = 0.1859); median OS 18.8 month vs 15.6 month; and 12-month OS rates 67.3% vs 59.2%. Progression-free survival and objective response rates also favored nivolumab + chemotherapy in NSQ, SQ, and all randomized participants. Grade 3 and 4 treatment-related adverse events occurred in 45% and 35% of all participants treated with nivolumab + chemotherapy and chemotherapy alone, respectively. The study design of CA0471009 aims to establish the contribution of BMS-986315 to the overall treatment of the triplet combination in NSCLC patients, so nivolumab in combination with chemotherapy is chosen as the control arm of the study.

5.4.2 Rationale for ORR as a Primary Endpoint in Part 2

ORR is an acceptable Phase 2 endpoint in oncology studies in NSCLC that allows results to be assessed earlier when compared with survival-based endpoints. Early access to ORR data is necessary due to the rapidly changing landscape in NSCLC and is considered sufficient to establish proof-of-concept to help guide further development of the investigational agent(s). An advantage of ORR over survival-based endpoints is the direct attribution of tumor response to therapy because in the absence of treatment, spontaneous tumor regression is highly unlikely. Furthermore, ORR has been demonstrated to be a potential surrogate endpoint for checkpoint inhibitor therapies in NSCLC [13]. A meta-analysis of 14 trials analyzed over 10,000 participants with advanced NSCLC submitted to the US Food and Drug Administration (FDA) between 2003 and 2013. In the patient-level responder analyses, this study demonstrated that patients who achieved a response had better PFS and OS compared with nonresponders (PFS: HR, 0.40; 95% CI, 0.38 to 0.42; OS: HR, 0.40; 95% CI, 0.38 to 0.43).[14] Consistently, another meta-analysis including 36 trials for first-line NSCLC also showed statistically significant association between OS and ORR across the trials (R^2 = 0.35; 95% CI, 0.13 to 0.57).[15]

In a meta-analysis conducted using pooled data from 63 trials and 78 immune checkpoint therapy treatment arms (n > 30,000), representing 15 different tumor types across different lines of therapies, including NSCLC, ORR, and 6-month DoR, was shown to be prognostic for 12-month OS.[16] The primary ORR assessment will be performed by BICR in Part 2 and will be further characterized by the durability and depth of responses to establish the contribution of components of BMS-986315 and nivolumab.

5.4.3 Rationale for 2-year Duration of Treatment

The optimal duration of immunotherapy is an important question and continues to be investigated. The immunotherapy interventions in Study CA0471009 include nivolumab alone or nivolumab plus BMS-986315. The 2-year duration of treatment is mainly based on nivolumab, the backbone of immunotherapies, and is considered to have an optimal benefit-risk profile in studying the

investigational immunotherapies in this study. Clinical trials across different tumor types in the nivolumab development program indicate that most of the responses occur early, with a median time to response of 2 to 4 months,[17,18,19,20,21] and emerging data suggest that benefit can be maintained in the absence of continued treatment. A recent analysis in a melanoma study suggests the majority of patients who discontinue nivolumab for toxicity maintain disease control in the absence of further treatment.[22,23]

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 participants 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 later 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.[24] 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) .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 an increased risk of progression in previously treated participants with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153, participants 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 participants still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in PFS compared with those who were randomized to stop treatment, with median PFS (post-randomization) not reached versus 10.3 months, respectively (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 participants on continued treatment to live longer (OS HR = 0.63, 95% CI, 0.33 to 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.[25]

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

5.5 Justification for Immunotherapy Dose(s)

Two BMS-986315 doses, 450 mg Q3W and 900 mg Q3W, were selected to be evaluated in co-administration with nivolumab 360 mg Q3W plus chemotherapy. [redacted].

In addition, both immunotherapy drugs will be co-administered as a single IV infusion. The PK and [redacted] PK samples will be collected for BMS-986315. Nivolumab pre-dose samples will be collected until the end of the 2-year treatment period and end of infusion (EOI) samples up to Cycle 5.

5.5.1 Nivolumab

Nivolumab PK has been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, classical Hodgkin's lymphoma, squamous cell cancer of the head and neck, colorectal cancer, and urothelial carcinoma, and has been safely administered at doses up to 10 mg/kg Q2W. Nivolumab monotherapy was originally approved as a body weight-based dose of 3 mg/kg Q2W and was updated to 240 mg Q2W, 360 mg Q3W, or 480 mg Q4W in various indications.[26] Less frequent 360 mg Q3W and 480 mg Q4W dosing regimens can reduce the burden to participants of frequent, lengthy IV treatments and allow the combination of nivolumab with other agents using alternative dosing regimens.

5.5.2 BMS-986315

Based on the totality of available data (eg, safety, PK, and pharmacodynamic [PD]) from preclinical murine studies and dose escalation of BMS-986315 as monotherapy and in combination with nivolumab in Study CA047004, 2 doses of BMS-986315 (450 mg Q3W and 900 mg Q3W) were selected to be evaluated with nivolumab 360 mg Q3W and chemotherapy in the proposed study, CA0471009. The 2 selected dosing regimens have adequate exposure separation to evaluate the differences between the dosing regimens. Both BMS-986315 and nivolumab will be co-administered as a single IV infusion.

In the ongoing study, CA047004, the highest dosing regimen currently evaluated is [redacted] mg [redacted] as monotherapy and in combination with nivolumab [redacted] mg [redacted]. This dosing regimen was considered tolerable with no observed DLTs. [redacted]
The geometric means of maximum observed serum concentration (Cmax) and AUC appear to increase dose proportionally. A linear extrapolation was used to estimate the equivalent Q3W doses using the PK data from CA047004.

In addition, preclinical data were utilized to aid in the selection of these two dosing regimens. An integrated analysis of all available PK/ receptor occupancy (RO)/antitumor efficacy data in mouse syngeneic models was conducted. [redacted]

[redacted]

5.6 Rationale for Exploratory Biomarker Research

[redacted] To evaluate the mechanism of action of BMS-986315 in combination with nivolumab and chemotherapy and explore potential pharmacodynamic and predictive markers for clinical response, comprehensive blood- and tumor-based patient selection and PD biomarker assessments are planned in this study.

[redacted]

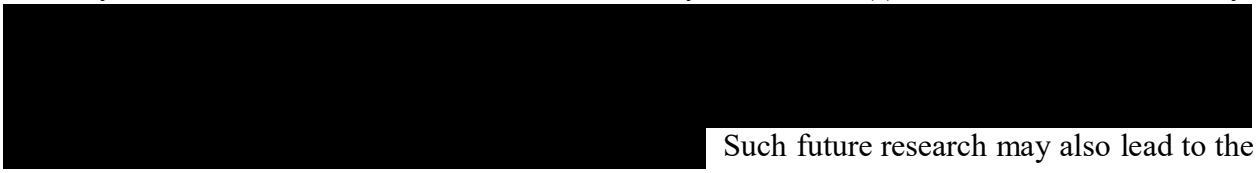
Baseline and pharmacodynamic measures may also be correlated to clinical outcomes. All relevant PD data collected, which display a change from baseline, and their associations with PK may be explored in PK/PD analysis to derive a quantitative relationship. The biomarker data may also be evaluated for associations with efficacy, safety, and/or select AEs.

Biomarker samples may also be used for research to develop methods, assays, prognostics, and/or diagnostics.

Digital imaging samples including CT/MRI scans will be used for research related to treatment efficacy using more advanced image analysis techniques.

5.7 Rationale for Optional Future Research

Future research may be performed using residual samples originally collected for another test required in this study from consented participants only. Future research is intended to allow for research aimed at emergent or future questions that are not addressed elsewhere in the protocol and may include research that is unrelated to the study intervention(s) and/or disease under study.



Such future research may also lead to the development of new diagnostic tests. The participant's decision to participate in this optional future research will not impact his/her ability to participate in the main study.

6 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1) Signed Written Informed Consent

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

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

2) Type of Participant and Target Disease Characteristics

a) Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1 at screening and confirmed prior to randomization.

b) Participants must have a life expectancy of at least 3 months at the time of first dose.

c) Participants must have histologically confirmed NSCLC per the 8th International Association for the Study of Lung Cancer classification of squamous or non-squamous histology with Stage IV or recurrent disease following multimodal therapy for locally advanced disease.

[redacted]

d) No prior systemic anti-cancer treatment (including tyrosine kinase inhibitors) given as primary therapy for advanced or metastatic disease.

e) Prior definitive chemoradiation for locally advanced disease is permitted as long as the last administration of chemotherapy or radiotherapy (whichever was given last) occurred at least 6-months prior to enrollment.

f) Prior adjuvant or neoadjuvant chemotherapy for early-stage lung cancer is permitted if completed at least 6-months prior to initiating study treatment.

g) Prior palliative radiotherapy to non-central nervous system (CNS) lesions must have been completed at least 2 weeks prior to treatment. Participants with symptomatic tumor lesions at baseline that may require palliative radiotherapy within 4 weeks of first treatment are strongly encouraged to receive palliative radiotherapy prior to treatment.

h) Participants must have measurable disease by CT or MRI per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix 7).

i) Target lesions may be located in a previously irradiated field if there is documented radiographic disease progression in that site after the completion of radiation therapy.

3) Age of Participant

a) Participant must be 18 years old or local age of majority inclusive at the time of signing the ICF.

4) Reproductive Status

Investigators shall counsel women of childbearing potential (WOCBP), and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention, the implications an unexpected pregnancy, and the potential of fetal toxicity occurring due to transmission of study drug, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

The investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

– Female Participants:

- Women of childbearing potential (WOCBP) must have a negative highly sensitive serum or urine pregnancy test (minimum sensitivity of 25 IU/L or equivalent units of human chorionic gonadotrophin) within 24 hours prior to the first dose of study drug.
- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive
- Additional requirements for pregnancy testing during and after study intervention are in Section 2 Schedule of Activities.
- 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
- Women who are not of childbearing potential (see Appendix 4) are exempt from contraceptive requirements.
- WOCBP must agree to follow instructions for method(s) of contraception as described below and included in the ICF.
- WOCBP are permitted to use hormonal contraception methods.
- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies: (1) Is not a WOCBP OR (2) Is a WOCBP and using a contraceptive method that is highly effective (failure rate of <1% per year), for the duration of treatment with BMS-986315 and nivolumab plus 5 months after last dose of these immunotherapies. A female participant who is a WOCBP must use a contraceptive method that is highly effective (failure rate of < 1% per year), for the duration of chemotherapy plus 7 months after last dose of chemotherapy (applicable to paclitaxel, pemetrexed, and carboplatin) or a total of 14 months after the last dose of cisplatin, or a duration specified by the local labels of the chemotherapy drugs received,

whichever is longer; and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period as contraception requirements listed above.

- Female participants who are not WOCBP must have documented proof that they are not of childbearing potential.

– Male Participants:

- Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception as described below and included in the ICF.
- Male participants are required to use a condom during the intervention period and for at least 6-months after the last chemotherapy (applicable to paclitaxel, pemetrexed, and carboplatin) dose of study intervention (or a total of 11 months for male participants receiving cisplatin), whichever is longer.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the intervention period and for at least 6-months after the last chemotherapy (applicable to paclitaxel, pemetrexed, and carboplatin) dose of study intervention (or a total of 11 months for male participants receiving cisplatin), whichever is longer.
- Male participants must refrain from donating sperm during the intervention period and for at least 6-months after the last chemotherapy (applicable to paclitaxel, pemetrexed, and carboplatin) dose (or a total of 11 months for male participants receiving cisplatin), whichever is longer.
- Azoospermic males are not exempt from contraceptive requirements and will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participant has undergone a successful vasectomy or if the partner is pregnant.
- Female partners of male participants should be advised to use a highly effective method of contraception during the study intervention period and for at least at least 6-months after the last chemotherapy (applicable to paclitaxel, pemetrexed, and carboplatin) dose of study intervention (or a total of 11 months for male participants receiving cisplatin), whichever is longer.
- Breastfeeding partners, should be advised to consult their health care providers about using appropriate highly effective contraception during the time the participant is required to use condoms.

5)

6.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

6) Medical Conditions

a) Mutation Status:

i. Epidermal growth factor receptor (EGFR) mutations which are sensitive to available targeted inhibitor therapy (including, but not limited to, deletions in exon 19 and exon 21 [L858R] substitution mutations) are excluded. [redacted]

[redacted]

ii. ALK receptor tyrosine kinase (ALK) and ROS proto-oncogene 1 (ROS1) translocations which are sensitive to available targeted inhibitor therapy are excluded. All participants with NSQ histology must have been tested for ALK and ROS1 mutation status; use of an FDA-approved or local Health Authority-approved test is strongly encouraged. [redacted]

iii. Participants with other known gene mutations, including NTRK fusion, MET exon 14 skipping mutation, B-Raf proto-oncogene (BRAF) V600E mutation, or RET rearrangement, which are sensitive to available targeted inhibitor therapy are excluded. If the test status is unknown or indeterminate for these four genes, the participants are eligible.

b) Participants with primary CNS disease, or tumors with CNS metastases as the only disease site, will be excluded.

c) Participants with untreated CNS metastases, except for either of the following two situations:

(1) The CNS metastases are asymptomatic and do not require immediate treatment.

(2) The CNS metastases 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 randomization. Brain imaging performed within 28 days prior to randomization must document radiographic stability of CNS lesions and should be performed after completion of any CNS-directed therapy.

d) Participants with leptomeningeal metastases (carcinomatous meningitis.)

e) Participants with concomitant second malignancies (except history of prior early-stage basal/squamous cell skin cancer, or noninvasive or in situ cancers who have undergone definitive treatment) 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.

f) Participants with an active, known, or suspected autoimmune disease. Participants with type 1 diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

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

h) Prior organ allograft.

i) Uncontrolled or significant cardiovascular disease.

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

k) Known human immunodeficiency virus (HIV) positive with an acquired immunodeficiency syndrome-defining opportunistic infection within the last year, or a current CD4 count <350 cells/µL. Participants with HIV are eligible if they have received antiretroviral therapy (ART) for at least 4 weeks prior to randomization as clinically indicated while enrolled on study and continue on ART as clinically indicated. CD4 counts and viral load of these participants should be monitored per standard of care by a local health care provider.

l) Participants with serious or uncontrolled medical disorders.

m) Participants must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before first treatment.

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

o) Participants with history of myocarditis, regardless of etiology.

p) Known medical condition that, in the investigator's opinion, would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results.

q) Previous SARS-CoV-2 infection within 10 days for mild or asymptomatic infections or 20 days for severe/critical illness and not recovered prior to first dose of study drug.

Note: Coronavirus disease 2019 (COVID-19) polymerase chain reaction (PCR) viral testing may be required prior to randomization based on specific country/regional guidelines, and the result of this testing may impact study participation. Testing results should be discussed with the Medical Monitor to confirm eligibility.

7) Tumor Tissue Requirements

[redacted]

8) Reproductive Status

a) Women who are breastfeeding.

b) Women who are pregnant.

9) Prior/Concomitant Therapy

a) Inability to comply with restrictions and prohibited treatments as listed in Section 7.7: Concomitant Therapy.

[redacted]

c) Treatment with anti-NKG2A agents.

d) Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive non-palliative radiation therapy, or standard or investigational agents for the treatment of NSCLC.)

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

f) 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.

g) Participants currently in other interventional trials, including those for COVID-19, may not participate in BMS clinical trials until the protocol-specific washout period is achieved. If a study participant has received an investigational COVID-19 vaccine or other investigational product designed to treat or prevent COVID-19 prior to screening, enrollment must be delayed until the biologic impact of the vaccine or investigational product is stabilized, as determined by discussion between the investigator and the Medical Monitor.

10) Physical and Laboratory Test Findings

a) Participants with ≥Grade 2 peripheral neuropathy.

b) Left ventricular ejection fraction (LVEF) assessment with documented LVEF < 50% by either transthoracic echocardiogram (TTE) or multiple gated acquisition (MUGA) scan (TTE preferred test) within 6-months prior to start of study treatment.

c) White blood cells < 2000/μL (SI units: < 2×10^9/L).

Note: If white blood cells > upper limit of normal (ULN), investigations and clinical work-up (eg, chest X-ray, C-reactive protein [CRP], procalcitonin, blood and urine culture) for presence of sub-clinical or clinical infection, and antibiotic treatment as needed, is recommended prior to randomization. All active infections diagnosed must resolve to baseline prior to first dose of study treatment.

d) Absolute neutrophil count (ANC) < 1500/μL (SI units: < 1.5×10^9/L).

Note: If ANC > ULN, investigations and clinical work-up (eg, chest X-ray CRP, procalcitonin, blood and urine culture) for presence of sub-clinical or clinical infection, and antibiotic treatment as needed, is recommended prior to randomization. All active infections diagnosed must resolve to baseline prior to first dose of study treatment.

e) Platelets < 100,000/μL (SI units: < 100×10^9/L).

f) Hemoglobin < 9.0 g/dL (SI units: < 90 g/L).

g) Creatinine clearance (CrCl) < 50 mL/min (measured or calculated using the Cockcroft-Gault formula).

h) Aspartate aminotransferase (AST)/alanine aminotransferase (ALT): > 3.0 x ULN (>5× ULN if liver metastases are present).

i) Total bilirubin (TB) > 1.5× ULN (except participants with Gilbert syndrome who must have a TB level of < 3.0× ULN).

11) Allergies and Adverse Drug Reactions

a) History of allergy or hypersensitivity to study drug components.

b) Any contraindication to any of the study drugs. Investigators should refer to local package insert or summary of product characteristics (SmPC).

12) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: Under certain specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply, and Sponsor approval is required.)
b) Participants who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.
c) Any other serious or uncontrolled medical disorder, active infection, physical exam finding, laboratory finding, altered mental status, or psychiatric condition that, in the opinion of the investigator, would limit a participant's ability to comply with the study requirements, substantially increase risk to the participant, or impact the interpretability of study results.

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

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently randomized in the study/included in the analysis population.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, as applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs) that occurred following consent.

6.4.1 Re-testing During Screening or Lead-in Period

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

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

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

Testing for asymptomatic SARS-CoV-2 infection, for example 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 COVID-19-related sequelae that may place the participant at a higher risk of receiving investigational treatment
- Negative follow-up SARS-CoV-2 RT-PCR or viral antigen test based on institutional, local or regional guidelines

7 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

Study intervention includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational/Auxiliary [Medicinal] Product (Non-IP/Non-IMP/AxMP) as indicated in Table 7.1-1.

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

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

7.1 Study Interventions Administered

During Part 1 and Part 2, participants will receive one of the treatment regimens by arm described in Table 7.1-1 and Table 7.1-2. BMS-986315 will be administered in a blinded manner, while nivolumab and chemotherapy will be unblinded. Dose reductions are not permitted for immunotherapy study treatments.

The chemotherapy products used in this clinical trial are authorized and will be used in accordance with the terms of their marketing authorizations.

Table 7.1-1: Study Intervention(s) Administered

Type/ Intervention Name/ Dose Formulation	Unit Dose Strength(s)	IMP/Non-IMP/ AxMP Blinded or Open-label Use	Sourcing	Packaging and Labeling	Current/ Former Name(s) or Alias(es)
BMS-986315 Concentrate for Solution for Infusion	[redacted] mg/mL	IMP, Open-label Part 1) IMP, Blinded (Part 2)	Centrally Provided by Sponsor	Vial (one or more vials per carton)	Anti-NKG2A
Nivolumab Solution for Injection	10 mg/mL	IMP, Open-label	Centrally Provided by Sponsor	Vial (one or more vials per carton)	Opdivo (BMS-936558)
Pemetrexed Powder for Concentrate for Solution for Infusion[a]	500 mg per vial	IMP, Open-label	Centrally Provided by Sponsor/Locally Sourced by Study Site	Vial (one or more vials per carton)	Pemetrexed
Cisplatin Concentrate for Solution for Infusion[a]	1 mg/mL	IMP, Open-label	Centrally Provided by Sponsor/Locally Sourced by Study Site	Vial (one or more vials per carton)	Cisplatin
Carboplatin Concentrate for Solution for Infusion[a]	10 mg/mL	IMP, Open-label	Centrally Provided by Sponsor/Locally Sourced by Study Site	Vial (one or more vials per carton)	Carboplatin
Paclitaxel Concentrate for Solution for Infusion[a]	6 mg/mL	IMP, Open-label	Centrally Provided by Sponsor/Locally Sourced by Study Site	Vial (one or more vials per carton)	Paclitaxel

Abbreviations: IMP, Investigational Medicinal Product; Non-IMP/AxMP, Non-investigational/Auxiliary Medicinal Product; NKG2A, natural killer group 2 member A.

[a] These products may be obtained by the investigational sites as local commercial product in certain countries if allowed by local regulations. In these cases, products may be a different pack size/potency than listed in the table. These products should be prepared/stored/administered in accordance with the package insert or summary of product characteristics (SmPC).

Table 7.1-2: Study Arm(s)

Arm Title/Arm Type	Intervention Description/ Dosage Levels	Route of Administration
Part 1 Safety Lead-in: [redacted]	BMS-986315 450 mg Q3W Nivolumab 360 mg Q3W 4 Cycles of Histology-based Chemotherapy Q3W[a]	IV Infusion
Part 1 Safety Lead-in: [redacted]	BMS-986315 900 mg Q3W Nivolumab 360 mg Q3W 4 cycles of Histology-based Chemotherapy Q3W[a]	IV Infusion
Part 2: Arm A [a]	Nivolumab 360 mg Q3W 4 cycles of Histology-based Chemotherapy Q3W	IV Infusion
Part 2: Arm B [a]	BMS-986315 900 mg Q3W Nivolumab 360 mg Q3W 4 cycles of Histology-based Chemotherapy Q3W	IV Infusion
Part 2: Arm C [a]	BMS-986315 450 mg Q3W Nivolumab 360 mg Q3W 4 cycles of Histology-based Chemotherapy Q3W	IV Infusion

Abbreviations: AUC, area under the concentration-time curve; [redacted]; IV, intravenous; Q3W: every 3 weeks; SQ, squamous.

[a] Histology-based chemotherapy: NSQ (non-squamous): Carboplatin AUC 5 or 6 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 (optional maintenance therapy with 500 mg/m^2 Q3W pemetrexed alone). SQ: paclitaxel 200 mg/m^2 + carboplatin AUC 6.

7.1.1 Immunotherapy Dosing

Participants will receive nivolumab and BMS-986315, followed by chemotherapy on Day 1 of every 3-week cycle. In Part 1 and Part 2 Arms B and C, nivolumab will be co-administered with BMS-986315 in a single bag IV over approximately 60 minutes. Arm A participants will receive nivolumab IV over 60 minutes. [redacted] Participants should be carefully monitored for infusion reactions during co-administration. If an acute infusion reaction is noted, participant should be managed according to Section 7.4.7. The 4 cycles of chemotherapy will be administered in all arms per Section 7.1.2. At the time of completion of the 4 cycles of chemotherapy, participants who have not experienced disease progression will continue to receive immunotherapy Q3W starting on Day 1 of the following cycle:

- There will be no dose escalations or reductions of immunotherapy allowed.

- Premedications are not recommended for the first dose of immunotherapy.
- Participants should receive immunotherapy until progression, unacceptable toxicity, withdrawal of consent, completion of 2 calendar years (24 months) of treatment, or the study ends, whichever occurs first.
- Doses of immunotherapy may be interrupted, delayed, or discontinued, depending on how well the participant tolerates the treatment according to Section 7.4.1.
- Dosing visits must not be skipped, only delayed. See Section 7.4 and Section 8.1.
- The assessment for discontinuation of immunotherapy should be made separately from the assessment to discontinue chemotherapy.
- If criteria for discontinuation of immunotherapy are met, PDCT may continue until 4 cycles have been completed.
- If criteria for discontinuation of PDCT are met, immunotherapy may continue until progression or unacceptable toxicity, whichever occurs first.
- If a participant meets criteria for discontinuation and investigator is unable to determine whether the event is related to all or any 1 study drug, the participant should discontinue all study drugs and be taken off the treatment phase of the study.

The immunotherapy injections can be infused undiluted or diluted. If needed, infusions can be flushed with diluent to complete the dose and clear the line before starting the chemotherapy infusion(s).

The second infusion will always be the chemotherapy study drug(s) and will start after the infusion line has been flushed, filters changed, and the participant has been observed to ensure no infusion reaction has occurred. The time between immunotherapy and chemotherapy infusions is expected to be approximately 30 minutes but may be more or less depending on the situation. Instructions for dilution and infusion of immunotherapy injections will be provided in the Pharmacy Manual. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. For details on prepared drug storage, preparation, and administration, please refer to the IBs and/or Pharmacy Manual. The selection and timing of dose for each participant is provided in Table 7.1-2 Table 7.1-1 and Table 7.1-2.

7.1.2 Chemotherapy Dosing

In all 3 study arms, 4 cycles of the histology-based PDCT option selected by the investigator will be administered on Day 1 Q3W. Participants with NSQ histology may also receive optional maintenance therapy with 500 mg/m^2 pemetrexed alone on Day 1 of each 3-week cycle until disease progression or unacceptable toxicity, or other reasons specified in the protocol (Section 8.1.2).

Histology-based PDCT:

- Squamous histology: Carboplatin AUC 6 + paclitaxel 200 mg/m^2
- Non-squamous histology: Carboplatin AUC 5 or 6 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 (optional maintenance therapy with 500mg/m^2 Q3W pemetrexed)

•

All chemotherapy agents' preparation, premedication, administration, monitoring, and management of complications are to follow local prescription guidelines and regulations. The dose of chemotherapy may be capped per local standards.

Note: The investigator must decide prior to randomization whether or not a participant with NSQ histology will receive cisplatin, if eligible.

7.1.2.1 Paclitaxel and Carboplatin

Participants will receive paclitaxel 200 mg/m^2 as a 180-minute IV infusion with carboplatin at a dose of AUC 6 as a 30-minute IV infusion on Day 1 of a 3-week cycle, or at doses per the local prescribing information. The infusion time can follow local institutional standards.

Paclitaxel dosing calculations should be based on the body surface area calculation. The dose may remain the same if the participant's weight is within 10% of the baseline weight or prior dose weight.

Carboplatin should be given following paclitaxel on Day 1 of each cycle, and the carboplatin dose will be calculated using the Calvert formula as follows:

Carboplatin dose (mg) = target AUC × (CrCl [mL/min] + 25)

CrCl calculation is based on the Cockcroft-Gault formula and should include the most recent serum creatinine and most recent weight. NOTE: If calculation of the CrCl by the Cockcroft-Gault formula yields a result of > 125 mL/min, then a CrCl should be calculated by an alternative formula per institutional standards or capped at 125 mL/min.

The dose of carboplatin may be capped per local standards.

Premedications for use with paclitaxel include the following:

- Oral or IV corticosteroid should be given according to local standard at a dose equivalent to dexamethasone 20 mg 12 hours and 6 hours prior to paclitaxel administration (oral or IV).
- IV diphenhydramine (or its equivalent) 50 mg and H2-blocker (per local standard of care) should be administered 30 to 60 minutes prior to paclitaxel infusion.
- Doses of paclitaxel and/or carboplatin may be interrupted, delayed, reduced, or discontinued, depending on how well the participant tolerates the treatment.

•

7.1.2.2 Pemetrexed and Cisplatin

Pemetrexed dosing calculations should be based on the body surface area calculation. The dose may remain the same if the participant's weight is within 10% of the weight used to calculate the previous dose.

Premedications for use with pemetrexed include the following:

- Oral or IV corticosteroid should be given according to local standards at a dose equivalent to dexamethasone 4 mg twice daily (BID) on the day prior to, the day of, and the day after the administration of pemetrexed.

- Oral folic acid 350 to 1000 mcg daily should be given starting 1 week prior to the first dose of pemetrexed, with at least 5 doses of folic acid administered in the 7 days prior to the first dose. Oral folic acid should be continued daily throughout the treatment with pemetrexed and for 21 days after the last dose of pemetrexed. Intramuscular (IM) injection of vitamin B12 1000 mcg should be given approximately 1 week prior to the first dose of pemetrexed and repeated every 3 cycles thereafter during pemetrexed treatment. Subsequent injections of vitamin B12 may be given on the same day as pemetrexed (participant with NSQ histology may begin folic acid and vitamin B12 prior to randomization in anticipation of pemetrexed).
- Antiemetic premedication will be administered according to local standards. Recommended antiemetic treatments are dexamethasone (dosing according to local standards; an equivalent dose of another corticosteroid may be substituted) and a 5-HT3 receptor antagonist (type per investigator discretion and local standards of care). Additional use of antiemetic premedications may be employed at the discretion of the investigator.
-

Participants will receive pemetrexed at a dose of 500 mg/m^2 as a 10-minute IV infusion on Day 1 with cisplatin at a dose of 75 mg/m^2 infusion as per local standard practice on Day 1 of a 3-week treatment cycle for up to 4 cycles.

Dosing calculations should be based on the body surface area calculation and may be capped per local standards. The dose may remain the same if the participant's weight is within 10% of the baseline weight or prior dose weight.

Cisplatin will be administered to participants at least 30 minutes following the end of the pemetrexed infusion. Pretreatment hydration for cisplatin can follow local standard of care or use 1 to 2 liters of fluid (per local standards) infused IV for 8 to 12 hours prior to cisplatin infusion (recommended). Adequate hydration and urinary output must be maintained for at least 24 hours following cisplatin administration. Administration and monitoring should be performed according to local standards. Use of mannitol following the cisplatin infusion should also follow local standards of care.

Doses of pemetrexed and/or cisplatin may be interrupted, delayed, reduced, or discontinued, depending on how well the participant tolerates the treatment. See Section 7.4.2, Section 7.4.3, and Section 8.1 for more details.

All participants who will receive cisplatin should have audiometric testing performed prior to initiation of therapy and prior to subsequent doses of cisplatin, or as per local standards of care.

Participants who discontinue cisplatin alone may, at the investigator's discretion, be switched to pemetrexed/carboplatin for the remainder of the PDCT (up to 4 cycles in total). Dosing for pemetrexed/carboplatin for such participants should follow the instructions in Section 7.1.2.3.

7.1.2.3 Pemetrexed and Carboplatin

Pemetrexed dosing calculations should be based on the body surface area calculation. The dose may remain the same if the participant's weight is within 10% of the weight used to calculate the previous dose.

Premedications for use with pemetrexed:

- Oral or IV corticosteroid premedication for pemetrexed should be given according to local standards at a dose equivalent to dexamethasone 4 mg BID on the day prior to, the day of, and the day after the administration of pemetrexed.
- Oral folic acid 350 to 1000 mcg daily should be given starting 1 week prior to the first dose of pemetrexed, with at least 5 doses of folic acid administered in the 7 days prior to the first dose. Oral folic acid should be continued daily throughout the treatment with pemetrexed and for 21 days after the last dose of pemetrexed. IM injection of vitamin B12 1000 mcg should be given approximately 1 week prior to the first dose of pemetrexed and repeated every 3 cycles thereafter during pemetrexed treatment. Subsequent injections of vitamin B12 may be given on the same day as pemetrexed (participant with NSQ histology may begin folic acid and vitamin B12 prior to randomization in anticipation of pemetrexed).
-

Participants will receive pemetrexed at a dose of 500 mg/m^2 as a 10-minute IV infusion on Day 1, followed by carboplatin at a dose of AUC 5 or 6 as a 30-minute IV infusion on Day 1 of a 3-week treatment cycle, for up to 4 cycles.

Pemetrexed dosing calculations should be based on the body surface area calculation. The dose may remain the same if the participant's weight is within 10% weight used to calculate the previous dose.

The carboplatin dose will be calculated using the Calvert formula as follows:

$$\text{Carboplatin dose (mg)} = \text{Target AUC} \times (\text{CrCl [mL/min]} + 25)$$

CrCl calculation is based on the Cockcroft-Gault formula (see inclusion criterion in Section 6.1) and should include the most recent serum creatinine and most recent weight. NOTE: If calculation of the CrCl by the Cockcroft-Gault formula yields a result of > 125 mL/min, then a CrCl should be calculated by an alternative formula per institutional standards or capped at 125 mL/min.

Doses of pemetrexed and/or carboplatin may be interrupted, delayed, reduced, or discontinued, depending on how well the participant tolerates the treatment. All chemotherapy agents' preparation, premedication, administration, monitoring, and management of complications are to follow local prescription guidelines and regulations. The dose of chemotherapy may be capped per local standards.

7.1.2.4 Optional Continuation Maintenance

After Cycle 4 of chemotherapy, participants with NSQ histology who have SD or response are permitted to receive pemetrexed 500 mg/m^2 Q3W alone as maintenance therapy until disease progression, unacceptable toxicity, or the maximum duration of treatment (2 years) has been reached.

7.2 Assignment to Study Intervention

After the participant's initial eligibility is established and informed consent has been obtained, the participant must be enrolled into the study via the Interactive Response Technology (IRT). Specific instructions for using IRT will be provided to the investigational site in a separate document. The

investigator or designee will register the participant for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- Date that informed consent was obtained
- Date of birth (specifically the year of birth)
-

All eligible participants will be initially assigned to Part 1 (Safety Lead-in) until the decision is made to start Part 2.

[redacted]

Once enrolled in IRT, enrolled participants who have met all eligibility criteria will be randomized through IRT. The following information is required for participant randomization:

- Participant number
- Date of birth (specifically the year of birth)
- Gender
- Histology (SQ or NSQ)
  - Participants with mixed histology should be classified according to the predominant histology
  - Participants with adenosquamous histology should be classified as NSQ histology

[redacted]

[redacted]

7.3 Blinding

Part 1 of the study is an open-label safety lead-in with no randomization.

Part 2 is a randomized, double-blind study. [redacted] Access to treatment codes will be restricted from all participants and site and

BMS personnel or their designee prior to primary database lock or the decision to unblind the study.

If program-wide decision(s), including but not limited to, regulatory interactions, requires further discussion for the IA results, restricted study team members will be unblinded to the study data to support the discussion. Site-facing Sponsor personnel will not be unblinded to maintain study integrity. Personnel who will have the access to the IA results to support these activities will be documented in the trial master file prior to access of the results.

Blinding of study intervention assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual participant in which knowledge of the IP is critical to the participant's management, the blind for that participant may be broken by the investigator. The participant's safety takes priority over any other considerations in determining whether a treatment assignment should be unblinded.

Before breaking the blind of an individual participant's treatment, the investigator should determine that the unblinded information is necessary (ie, that it will alter the participant's immediate management). In many cases, particularly when the emergency is clearly not related to the IP, the problem may be properly managed by assuming that the participant is receiving the IP. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The actual task of unblinding can be delegated by the investigator to a designee assigned the task on the Delegation of Authority. The Principal Investigator or appointed designee should only perform the emergency unblinding after the decision to unblind the participant has been documented.

For this study, the method of unblinding for emergency purposes is by IRT transaction by which the site users can unblind a participant in the event of an emergency. Please consult the IRT manual for further information on how to unblind in an emergency.

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to preserve the blind.

Any request to unblind a participant for non-emergency purposes should be discussed with the Medical Monitor.

The designated staff of BMS may be unblinded (obtain the randomization codes) prior to database lock to facilitate the bioanalytical analysis of PK samples and immunogenicity. A bioanalytical scientist in the Bioanalytical Sciences department of BMS (or a designee in the external central bioanalytical laboratory) will be unblinded to (may obtain) the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples.

7.4 Dosage Modification

No dose reductions or escalations for immunotherapy are permitted.

7.4.1 Dose Modification Criteria for Immunotherapy

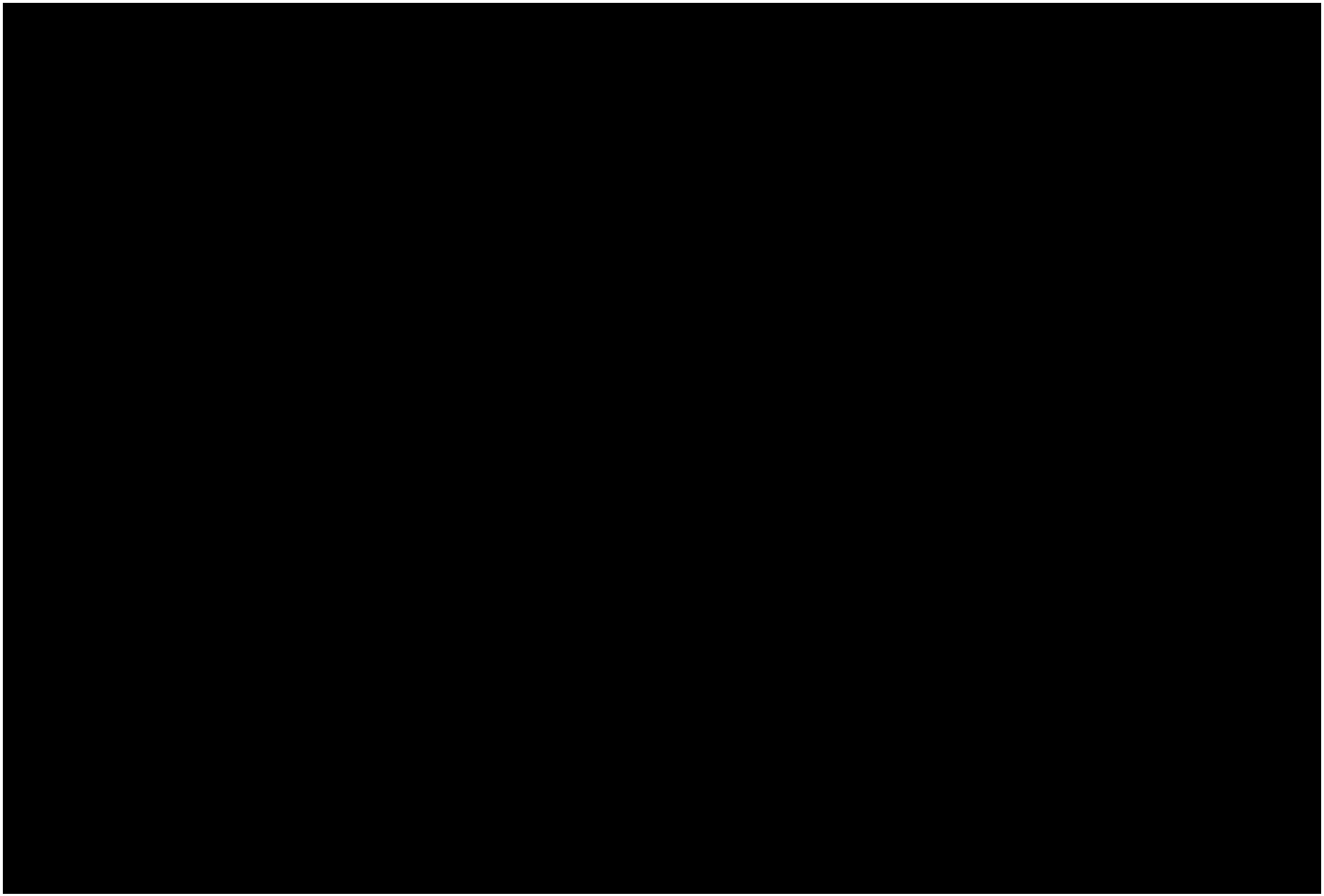
All AEs/SAEs must be graded using Common Terminology Criteria for Adverse Events (CTCAE) v5.

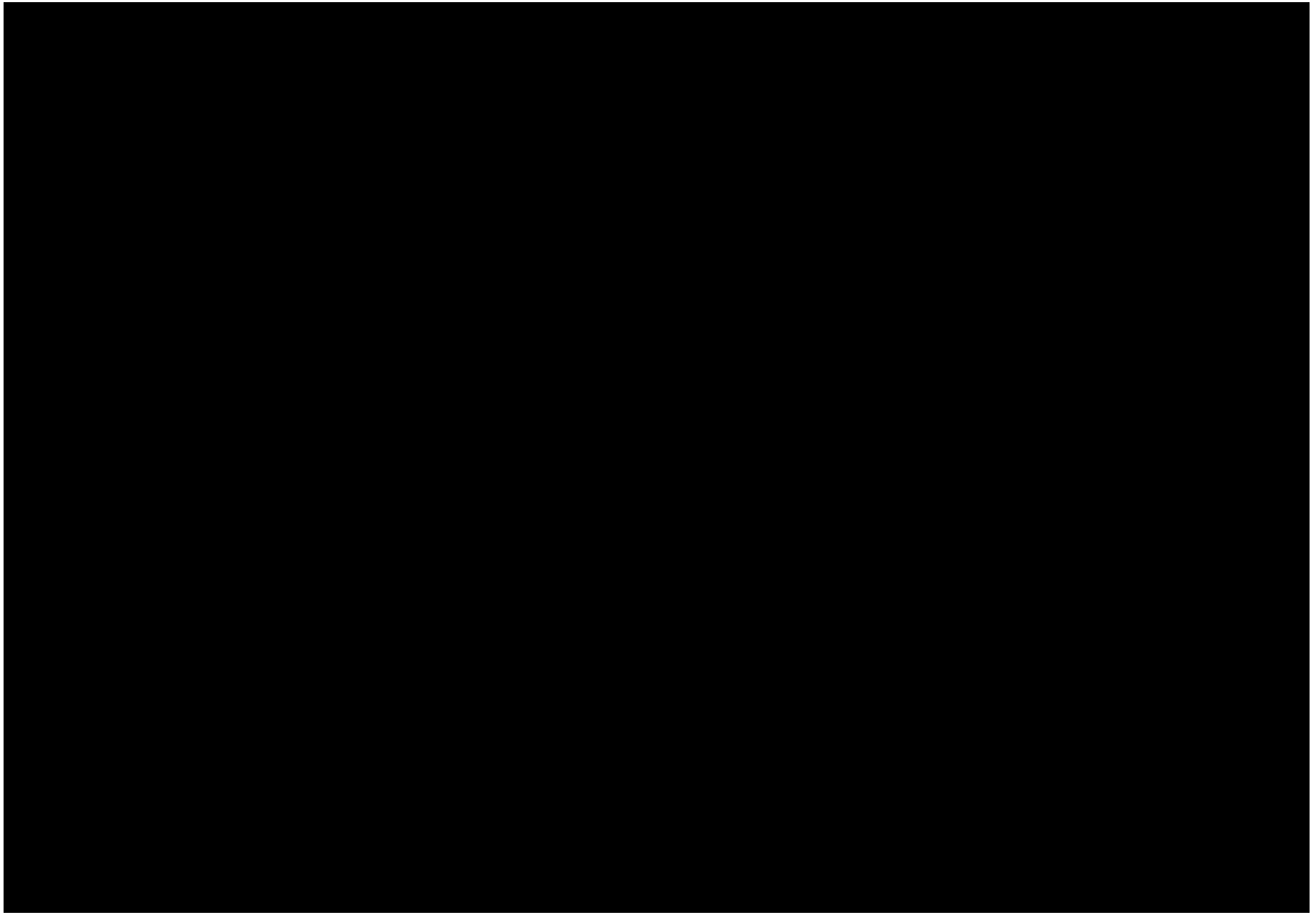
The criteria for dose delay, resumption, and discontinuation for immunotherapy have been integrated to apply to immunotherapy treatment with either nivolumab or nivolumab plus BMS-986315, henceforth referred to as immunotherapy. Delay immunotherapy dosing for any AE, laboratory test result abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication. Specific management guidelines (dose delay, resumption, and discontinuation) for expected AEs and SAEs for nivolumab and nivolumab + BMS-986315 combination therapy can be found in [redacted]. Additional information on management of AEs and SAEs nivolumab and nivolumab + BMS-986315 combination therapy is found in Appendix 6:

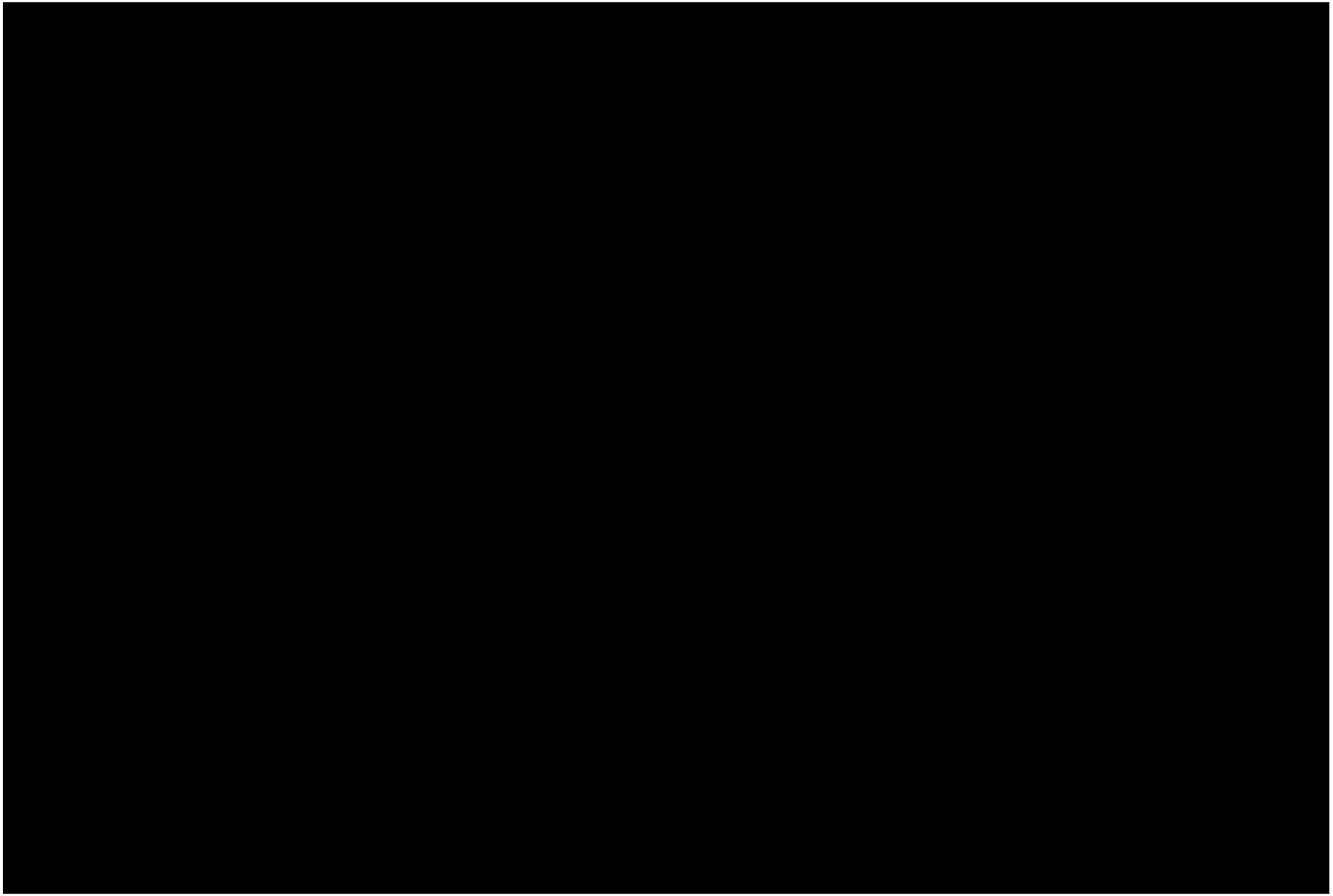
For participants who require delay of immunotherapy, re-evaluate weekly, or more frequently, if clinically indicated, and resume dosing when criteria to resume treatment are met (see Section 7.4.4). Continue tumor assessments per protocol even if dosing is delayed. The decision for immunotherapy dose delay, resumption, and discontinuation should apply to both nivolumab and BMS-986315 in participants receiving nivolumab + BMS-986315 combination therapy.

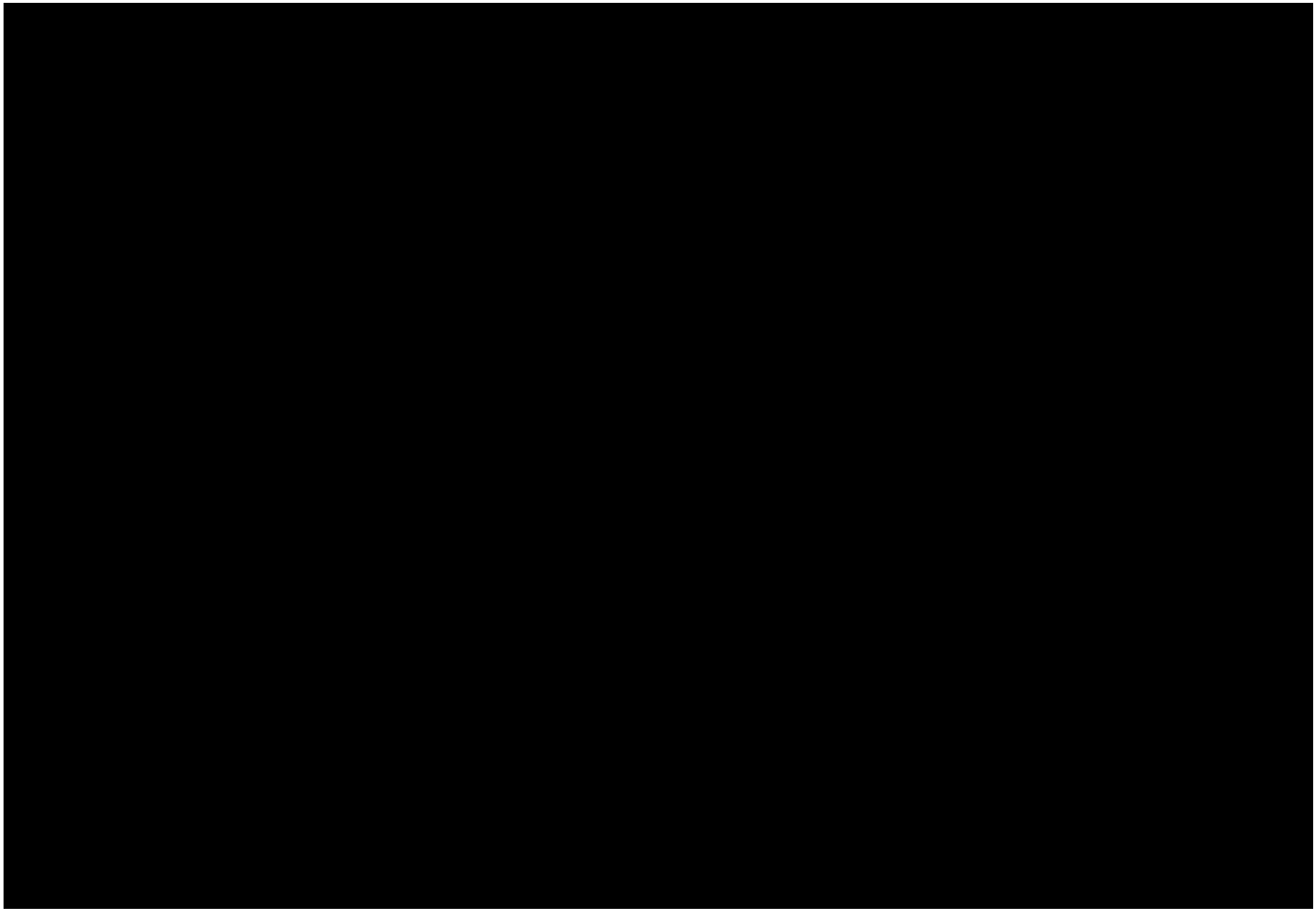
The assessment for dose delays of immunotherapy should be made separately from the assessment to delay chemotherapy.

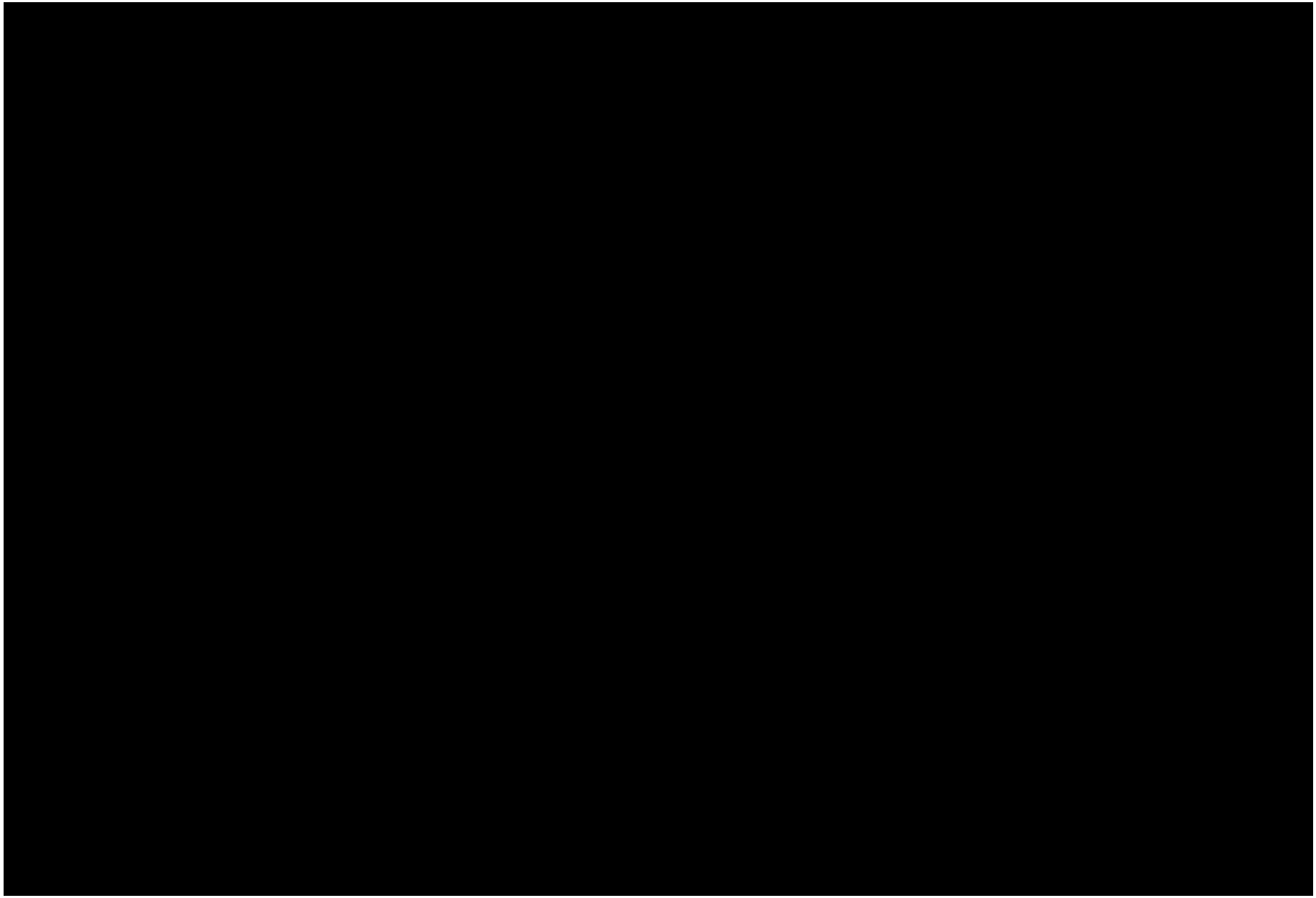
Study treatment must also be delayed for SARS-CoV-2 infection, either confirmed or suspected.











7.4.2 Dose Delay Criteria for Chemotherapy

Chemotherapy drugs should be delayed for any of the events listed below. The delay should occur on treatment Day 1

- Absolute neutrophil count (ANC) < 1500/µL (SI units: < 1.5×10^9/L)
- Platelets < 100,000/µL (SI units: < 100×10^9/L)
- Any Grade ≥ 2 non-skin, non-hematologic, drug-related AE (excluding Grade 2 alopecia, Grade 2 fatigue, and Grade 2 laboratory test result abnormalities (abnormality))
- Any Grade ≥ 3 skin, drug-related AE
- Any Grade ≥ 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, AST, ALT, or TB:
  - Grade 3 lymphopenia does not require dose delay.
  - Delay dosing if AST or ALT increases to > 3x and ≤ 5x upper limit of normal (ULN) or Tbili increases to > 1.5x and ≤ 3x ULN, regardless of baseline value.
  - In participants with liver metastasis, delay dosing if (1) Baseline AST/ALT is >1x and ≤3x ULN and increases to >5x and ≤10x ULN; (2) Baseline AST/ALT is >3x and ≤5x ULN and increases to >8x and ≤10x ULN
-

Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication. Investigators should consult local labeling for the chemotherapy drugs being administered to any given participant for additional guidance on dose delays.

Dose modifications listed are specific to US Prescribing Information (USPI). Variations may apply per local label. Participants receiving cisplatin with pemetrexed must discontinue cisplatin if the calculated CrCl decreases to < 50 mL/min (based on the Cockcroft-Gault formula). The other drug (pemetrexed) may be continued, and the platinum agent may, at the investigator's discretion, be switched to carboplatin for the rest of the cycles when the participant meets re-treatment criteria. Note that pemetrexed can only be administered if CrCl is ≥45 mL/min (calculated per Cockcroft Gault formula).

If a participant receiving carboplatin with paclitaxel must discontinue carboplatin, paclitaxel may be continued at the investigator's discretion.

If any non-hematologic AE meeting the dose delay criteria above is felt to be related to only 1 particular agent in the PDCT regimen, then that agent alone may be omitted for that cycle while the other agent is given. In order to maintain synchronized dosing of the regimen, the omitted agent should be resumed with the next scheduled cycle once the AE has improved and re-treatment criteria are met. Please refer to Section 7.4.3.2 to determine if dose reduction of the resumed agent is required.

If both drugs in the PDCT regimen are delayed, then the participant should be re-evaluated weekly or more frequently if clinically indicated until re-treatment criteria are met (as per Section 7.4.4.2).

Study treatment must also be delayed for SARS-CoV-2 infection, either confirmed or suspected.

Dosing of immunotherapy *and* both chemotherapy agents should be delayed if any criteria for immunotherapy *or both* PDCT agents are met.

7.4.3 Dose Reductions

7.4.3.1 Dose Reduction for Immunotherapy

No dose reductions for immunotherapy are permitted.

7.4.3.2 Dose Reduction for Chemotherapy

Dose reductions for chemotherapy may be required and will be performed according to Section 7.4.2 or per institutional guidelines. Chemotherapy dose reductions are permanent; once the dose of any chemotherapy agent is reduced, it may not be re-escalated in subsequent cycles, except as noted when starting pemetrexed maintenance therapy. The dose reductions for each agent in the PDCT regimen are not linked and may be adjusted independently as summarized in Table 7.4.3.2-1.

Table 7.4.3.2-1: Dose Reduction for Chemotherapy

Dose Level	Carboplatin	Pemetrexed	Paclitaxel	Cisplatin
Starting dose	AUC 6 or AUC 5	500 mg/m^2	200 mg/m^2	75 mg/m^2
First dose reduction	AUC 5 (if starting dose is AUC 6) or AUC 4 (if starting dose is AUC of 5)	375 mg/m^2	150 mg/m^2	56 mg/m^2
Second dose reduction	AUC 4 (if starting dose is AUC 6) or AUC 3 (if starting dose is AUC 5)	250 mg/m^2	100 mg/m^2	38 mg/m^2
Third dose reduction	Discontinue	Discontinue	Discontinue	Discontinue

Abbreviation: AUC, area under the concentration-time curve.

Dose modifications listed are specific to US prescribing information (USPI). Variations may apply per local label.

Any participant with 2 prior dose reductions for 1 agent who experiences a toxicity that would cause a third dose reduction must be discontinued from that agent.

7.4.3.3 Chemotherapy: Dose Reductions for Hematologic Toxicity

Dose modifications for hematologic toxicities (according to CTCAE v5) are summarized in Table 7.4.3.3-1. Dose adjustments are based on nadir blood counts (assessed as per local standards) since the preceding drug administration. Dose level adjustments for PDCT are relative to that of the preceding administration. Generally, both chemotherapy agents in the PDCT regimen should be dose reduced together for hematologic toxicity. After the first cycle, growth factors may be used to assist hematologic recovery. For incidences of chemotherapy-induced anemia or cancer-associated anemia, red blood cell transfusions are recommended. In participants who refuse RBC transfusions, erythropoiesis-stimulating agents may be administered as per local standards.

Use local standards of care for other previously described supportive measures. Additionally, prophylactic antibiotics may be used according to local standards of care. Investigators are strongly recommended to have a high index of suspicion for infection and consider starting broad spectrum antibiotics early for any fever or signs of infection in participants with neutropenia. Please report any antibiotic or growth factor use on the electronic Case Report Form (eCRF).

Dose modifications listed are specific to USPI. Variations may apply per local label.

Table 7.4.3.3-1: Dose Modifications for Hematologic Toxicity (Based on Nadir Counts)

Toxicity	Carboplatin	Paclitaxel	Pemetrexed	Cisplatin
Neutrophil Count Decreased				
Grade 4 ($< 500/mm^3$ or $< 0.5 \times 10^9/L$)	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level
Platelet Count Decreased				
Grade 3 ($< 50,000 - 25,000/mm^3$; $< 50.0 - 25.0 \times 10^9/L$)	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level
Grade 4 ($< 25,000/mm^3$; $< 25.0 \times 10^9/L$)	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level

7.4.3.4 Chemotherapy: Dose Reductions for Non-hematologic Toxicities

Dose adjustments for chemotherapy for non-hematologic toxicities during treatment are described in Section 7.4.3.2. All dose reductions should be made based on the worst-grade toxicity. Participants experiencing any of the toxicities during the previous cycle should have chemotherapy delayed until retreatment criteria are met, and then reduced for all subsequent cycles by 1 dose level or discontinued as appropriate. Dose levels for the 2 drugs in the PDCT regimen are not linked and may be reduced independently, as summarized.

Table 7.4.3.4-1: Dose Adjustments for Chemotherapy for Non-hematologic Toxicities

Toxicity	Carboplatin	Paclitaxel	Pemetrexed	Cisplatin
Febrile neutropenia Grade ≥ 3	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level
Diarrhea Grade ≥ 3	No change	Reduce 1 dose level	Reduce 1 dose level	No change
Allergic reaction[a] Grade ≥ 3	Discontinue	Discontinue	Discontinue	Discontinue
Neuropathy Grade 2	Reduce 1 dose level	Reduce 1 dose level	No change	Reduce 1 dose level
Neuropathy Grade 3-4	Discontinue	Discontinue	Discontinue	Discontinue
CrCl < 50 mL/min	No change	Discontinue if CrCl < 20 mL/ min	No change	Discontinue
Other Grade ≥ 3 toxicity (except for fatigue and transient arthralgia and myalgia)	Adjust as medically indicated	Adjust as medically indicated	Adjust as medically indicated	Adjust as medically indicated

Abbreviations: CrCl, creatinine clearance; USPI, US Prescribing Information.

[a] Only the drug(s) causing the hypersensitivity reaction or acute infusion reaction (≥ Grade 3) require(s) discontinuation. All other drugs may be continued.

Note: Dose modifications listed are specific to USPI. Variations may apply per local label.

7.4.4 Criteria to Resume Dosing

7.4.4.1 Criteria to Resume Treatment with Immunotherapy

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

Participants with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment after **all of the following**: 1) at least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (eg, RT-PCR or viral antigen); 2) resolution of acute symptoms (including at least 24 hours have 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 treatment in a participant with a dosing delay lasting > 8 weeks, the Medical Monitor (or designee) must be consulted. Continue tumor assessments per protocol even if dosing is delayed. Continue periodic study visits to assess safety and laboratory studies every 8 weeks or more frequently if clinically indicated during such dosing delays.

7.4.4.2 Criteria to Resume Treatment with Chemotherapy

Participants may resume treatment with chemotherapy when the ANC returns to ≥ 1500/μL (SI units: ≥ 1.5×10^9/L), the platelet count returns to ≥ 100,000/μL (SI units: ≥ 100×10^9/L), and all other drug-related toxicities have returned to baseline or Grade 1 (or Grade 2 for alopecia and fatigue).

If a participant fails to meet criteria for re-treatment, then re-treatment should be delayed, and the participant should be re-evaluated weekly or more frequently as clinically indicated. Any participant who fails to recover from toxicity attributable to chemotherapy to baseline or Grade 1 (except Grade 2 alopecia and fatigue) within 6 weeks from the last dose given should discontinue the drug(s) that caused the delay.

When resuming chemotherapy treatment, please follow the dose-reduction recommendations in Section 7.4.3.2.

Participants with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment after **all of the following**: 1) at least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (eg, RT-PCR or viral antigen); 2) resolution of acute symptoms (including at least 24 hours 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.

7.4.5 Management Algorithms for Immuno-Oncology Agents

I-O agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab and BMS-986315 are considered IO agents in this protocol. Because of the potential for clinically meaningful TRAEs requiring early recognition and prompt intervention, management algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary (note for participants with dyspnea, complete blood count should be measured)
- Hepatic
- Endocrinopathy
- Skin
- Neurological
- Myocarditis
-
- The above algorithms are included in Appendix 6 of this protocol.

7.4.6 Dose-limiting Toxicities

[redacted]

For the purpose of guiding decisions regarding dose escalation in Part 1 (Safety Lead-in), DLTs will be defined based on the incidence, intensity, and duration of the AEs for which no clear alternative cause is identified and will exclude events clearly related to disease progression or intercurrent illness.

Participants experiencing a DLT that is attributed to immunotherapy alone will be allowed to stop immunotherapy (both nivolumab and BMS-986315) and continue chemotherapy. Participants who withdraw from the study during the DLT evaluation period for reasons other than a DLT may be replaced with a new participant at the same dose level.

[redacted]

[redacted]

•

Safety lead-in participants should discontinue treatment if they experience any adverse event, laboratory abnormality, or intercurrent illness (regardless of causality) which, in the opinion of the investigator, presents a substantial clinical risk to the participant with continued immunotherapy with or without chemotherapy. Such discontinuation, however, will not be considered a DLT unless it meets at least one of the DLT criteria defined above. Treatment delay, dose modifications, and discontinuation criteria (Section 7.4) are to be followed for the management of safety lead-in participants.

7.4.7 Treatment of Immunotherapy Infusion Reactions

Since nivolumab and BMS-986315 contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to National Cancer Institute (NCI) CTCAE v5 guidelines.

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

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

Remain at bedside and monitor participant until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or

equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional immunotherapy administrations.

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

Stop the infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 mg to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further immunotherapy will be administered at that visit. Administer diphenhydramine 50 mg IV and remain at bedside and monitor the participant until resolution of symptoms. The amount of study drug infused must be recorded on the eCRF.

For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before immunotherapy infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

For Grade 3 or 4 symptoms (severe reaction, Grade 3: prolonged [ie, 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 immunotherapy. 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 subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the investigator is comfortable that the symptoms will not recur. Immunotherapy will be permanently discontinued. 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 intervention is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the Sponsor. If concerns regarding the quality or appearance of the study intervention arise, the study intervention should not be dispensed, and the Sponsor should be contacted immediately.

Study intervention not supplied by the Sponsor will be stored in accordance with the package insert.

IP/IMP/Non-IMP/AxMP documentation (whether supplied by the Sponsor or not) must be maintained and must include all processes required to ensure the 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).

All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition of records).

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention.

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

7.5.1 Retained Samples for Bioavailability/Bioequivalence/Biocomparability

At the time of receipt of the IP by the investigator or designee, the Sponsor will specify the appropriate number of containers or units to select for retention, the conditions of sample storage, required duration of sample retention, and provisions for returning or disposing of the IP. When samples are selected, containers or units should be placed in packaging with a tamper-evident seal provided by the Sponsor or sourced by the site. Package labeling should clearly identify the contents as retention samples and state that the IP should be stored in the restricted area with limited access.

Additional details regarding the retention process will be provided in the Pharmacy Manual (or in other written documentation) provided to the site.

7.6 Study Intervention Compliance

Treatment compliance will be monitored by drug accountability as well as the participant's medical record and eCRF. This will be source data verified by the BMS Unblinded Site Monitor through regularly scheduled monitoring visits.

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):

- [redacted]
- Treatment with anti-NKG2A agents other than the study drug.
- Any concurrent anti-neoplastic therapy. (ie, chemotherapy, hormonal therapy, immunotherapy, extensive non-palliative radiation therapy, or standard or investigational agents for the treatment of NSCLC)
- Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio, and measles, mumps, rubella) during treatment and until 100 days post last dose.
- Immunosuppressive doses of systemic corticosteroids. (except as stated in Section 7.7.3)
- 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 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.

The investigator must also adhere to the contraindications, precautions, and drug interactions found in the USPI or local label for each of the chemotherapy agents.

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 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 participant recovers from the procedure, whichever is longer. Prior to resuming study drug treatment, surgically-related AEs should resolve to ≤ Grade 1 or baseline and participant 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 participant with a dosing interruption lasting > 8 weeks after the last dose.

7.7.2.1 Imaging Restrictions and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen per imaging study. Imaging contraindications and contrast risks are to be considered in this assessment. Participants with renal insufficiency are to be assessed as to whether they should receive contrast and if so, which contrast agent and dose are appropriate. Specific to magnetic resonance imaging (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; therefore, MRI contrast is contraindicated. In addition, participants may be excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. These restrictions will be outlined in the Imaging Manual.

Gentle hydration before and after IV contrast should follow local standard of care. The ultimate decision to perform MRI in an individual participant enrolled in this study rests with the site radiologist, the investigator, and standards set by the local Ethics Committee.

7.7.3 Permitted Therapy

Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).

Adrenal replacement steroid doses > 10 mg daily prednisone are permitted.

A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

Regular concomitant use of bisphosphonates and RANK-L inhibitors for prevention or reduction of skeletal-related events in participants with bone metastases is allowed if initiated prior to first dose of study treatment.

Prior palliative radiotherapy must have been completed at least 2 weeks prior to treatment.

7.7.3.1 Palliative Local Therapy

Palliative local therapy, including palliative radiation therapy and palliative surgical resection, to symptomatic non-target bone lesions, skin lesions, or CNS lesions is permitted prior to discontinuation of study treatment for participants who do not have evidence of overall clinical or radiographic progression per RECIST v1.1. Palliative local therapy to lesions causing hemoptysis may also be permitted prior to discontinuation of study treatment in participants who do not have evidence of overall clinical or radiographic progression per RECIST v1.1, provided that the lesions undergoing palliative local therapy are not the only sites of measurable disease and the case is discussed with and approved by the BMS Medical Monitor.

Participants requiring palliative local therapy should be evaluated for objective evidence of disease progression prior to the initiation of such therapy, particularly if the most recent tumor assessment

was more than 4 weeks prior to the start of local therapy. If progression per RECIST v1.1 is identified on any tumor assessments prior to the initiation of palliative local therapy, then participants must either discontinue study drug treatment or they must meet criteria to continue treatment beyond progression (Section 8.1.1) in order to resume immunotherapy after palliative local therapy. If radiographic progression per RECIST v1.1 is identified prior to the initiation of palliative local therapy, sites must request a BICR from the third-party radiologist. However, the initiation of palliative local therapy need not be delayed awaiting the assessment by the BICR.

The potential for overlapping toxicities with radiotherapy and immunotherapy currently is not known; however, anecdotal data suggest that it is tolerable. As concurrent radiotherapy and the immunotherapy regimens evaluated in this study have not been formally evaluated, whenever palliative radiotherapy is required for a tumor lesion, then immunotherapy should be withheld for at least 1 week before, during, and 1 week after radiation. Participants should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs should resolve to Grade ≤ 1 prior to resuming immunotherapy.

7.8 Continued Access to Study Intervention After the End of the Study

At the conclusion of the study, if the study intervention is not available as an approved treatment in the local country, participants who continue to demonstrate clinical benefit will be eligible to receive BMS-supplied study intervention for maximum treatment duration as specified in Section 7.1.

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 nivolumab or BMS-986315 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

The discontinuation of specific sites or of the study as a whole is detailed in Appendix 2.

8.1 Discontinuation of Study Intervention

Participants MUST discontinue IP (and Non-IMP/AxMP at the discretion of the investigator) for any of the following reasons as listed below. Also refer to Section 7.4 for more information on study intervention discontinuation.

- Participant's request to stop study intervention. Participants who request to discontinue study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information.
- Any clinical AE, laboratory test result abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Termination of the study by the Sponsor.

- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical illness (eg, infectious disease). (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 Sponsor approval is required.)
- Pregnancy (refer to Section 9.2.5).
- Significant noncompliance with protocol (eg, procedures, assessments, medications, etc). The investigator should discuss such issues with the Medical Monitor.

All participants who discontinue study intervention should comply with protocol-specified follow-up procedures as outlined in Section 2: Schedule of Activities. 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 intervention 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 per local regulatory requirements in each region/country and entered on the appropriate CRF page.

8.1.1 Immunotherapy Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of disease progression.

Participants treated with immunotherapy (nivolumab [± BMS-986315]) will be permitted to continue treatment beyond initial RECIST v1.1-defined progression disease, assessed by the investigator as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Tolerance of study treatment
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Participant provides written informed consent prior to receiving additional immunotherapy treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts or other alternative treatment options will still apply.

Radiographic assessment/scan(s) should continue in accordance with the Schedule of Activities for the duration of the treatment beyond progression and should be submitted to the central imaging vendor. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with immunotherapy.

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

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

8.1.2 Post-study Intervention Study Follow-up

In this study, ORR and PFS 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 intervention 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: Study Design until death or the conclusion of the study.

If progression as per BICR has not occurred before treatment discontinuation, tumor assessments should continue according to the Schedule of Activities, [redacted].

Participants should undergo 100 days of safety follow-up post last dose of study drug.

BMS may request that survival data be collected on all randomized participants outside of the protocol-defined window (see Section 5.1.1). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contacts or is lost to follow-up.

8.2 Discontinuation From the Study

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

- 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 intervention 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.
-

8.2.1 Individual Discontinuation Criteria

- A participant may withdraw completely from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. Stopping study intervention is not considered withdrawal from the study.
- At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the Schedule of Activities (Section 2). See the Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from both the study intervention and the study at that time.
- 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

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- 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 **3** documented phone calls, faxes, or emails, as well as lack of response by participant to **1** registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the participant's contact information or other public vital status data, such as public health registries and databases, necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, to obtain updated contact information.

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

9 STUDY ASSESSMENTS AND PROCEDURES

Images will be submitted to a central imaging vendor for BICR at any time during the study. Prior to scanning first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA0471009 Imaging Manual provided by the central imaging vendor.

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 drug-related toxicities resolve, return to baseline, or are deemed irreversible.

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary AEs, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the BMS-986315 and nivolumab IBs.

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

9.1 Efficacy Assessments

9.1.1 Imaging Assessment for the Study

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

[redacted]

[redacted]

9.1.1.1 Methods of Measurement

Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should be performed for tumor assessments. Images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging time points. Tumor measurements should be made by the same investigator or radiologist for each assessment, whenever possible. Changes in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the investigator using the RECIST 1.1 criteria. In case of a contraindication for either contrast agent or MRI (eg, incompatible pacemaker), it), it is strongly recommended to use the following guidance:

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

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

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

Use of CT component of a Positron emission tomography–computed tomography (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 1.1 measurements. However, if a site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST 1.1 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 scans or PET scans are not adequate for assessment of RECIST 1.1 response in target lesions. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those non-target organs may be evaluated less frequently. For example, bone scans

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

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

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

9.1.1.2 Imaging and Clinical Assessment

Tumor assessments should continue 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 1.1 criteria. Investigators will report the number and size of new lesions that appear while on study. The timepoint of tumor assessments will be reported on the eCRF based on the investigator's assessment using RECIST1.1 criteria (See Appendix 8 for specifics of RECIST 1.1 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 best overall response (BOR) of SD requires a minimum of 35 days on study from randomization to the date of the first imaging assessment.

9.1.1.3 BICR Confirmation of Progression or Recurrence

Sites should submit all scans to the central imaging vendor on a rolling basis throughout the duration of the study. BICR of scans will occur on a rolling basis, blinded to treatment arm, clinical data, and investigator assessment of submitted scans. When progression per RECIST v1.1 criteria is assessed by the investigator, the site will inform the central imaging vendor in order for BICR assessment of progression to be performed. The BICR will be completed, and the results provided to the site as specified in the imaging vendor documents, provided there are no pending imaging queries to the site. All details on the timelines and associated process requirements will be outlined in the Imaging Manual.

Participants whose progression is not confirmed by the BICR will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule or sooner if clinically indicated. Also, if participants discontinue treatment without radiographic progression, tumor assessments will continue according to the protocol-specified schedule, as noted in Section 2 (Schedule of Activities) until progression has been confirmed by BICR.

All study treatment decisions will be based on the investigator's assessment of tumor images and not on the BICR assessment.

9.2 Adverse Events

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

AEs will be reported by the participant.

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

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

Use CTCAE v5 definitions and grading for safety reporting of all AEs and SAEs on the Case Report Form.

Refer to Appendix 3 for SAE reporting.

9.2.1 Period and Frequency for Collecting AE and SAE Information

The IB represents the reference safety information to determine expectedness of SAEs for expedited reporting.

All AEs and 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. All SAEs and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection must be collected from the date of the participant's written consent until 100 days following discontinuation of dosing. For participants randomized and never treated with study drug, SAEs should be collected for 30 days from the date of randomization.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure (eg, a follow-up skin biopsy).

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

All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.

The investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of updated information being available.

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

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

9.2.2 Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AEs 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.

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

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

9.2.3 Follow-up of AEs and SAEs

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.2), will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3) 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 toward the safety of participants and the safety of a product under clinical investigation are met.

An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

The Sponsor or designee must report AEs to regulatory authorities and ethics committees according to local applicable laws and regulations. A suspected, unexpected serious adverse reaction (SUSAR) is a subset of SAEs and must 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 intervention, it is discovered that a female participant is pregnant or may have been pregnant at the time of study intervention exposure including at least 5 months after the last dose of immunotherapy, 7 months after the last dose of chemotherapy (applicable to paclitaxel, pemetrexed, and carboplatin) or 14 months after the last dose of cisplatin,

the investigator must immediately notify the Sponsor Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the Sponsor designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

In all cases, the study intervention will be discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety).

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

Any pregnancy that occurs in a female partner of a male participant at the time of study intervention exposure (see Section 6) including 6-months after last dose of chemotherapy (applicable to paclitaxel, pemetrexed, and carboplatin) or a total of 11 months after the last dose for male participants receiving cisplatin should be reported to the Sponsor or designee. For the Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an ICF for disclosure of this information. Information on this pregnancy will be collected and recorded on the Pregnancy Surveillance Form.

If any sexual activity involving penile intercourse (eg, vaginal, anal, oral) has occurred between a male participant and a pregnant partner(s) without the use of a condom for the duration of treatment with BMS-986315 and nivolumab and chemotherapy, and for a total of 6-months after last dose of chemotherapy (applicable to paclitaxel, pemetrexed, and carboplatin) or a total of 11 months after the last dose for male participants receiving cisplatin should be reported to the Sponsor or designee even if the male participant has undergone a successful vasectomy (refer to Section 6 for details). In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner(s) must sign an ICF for disclosure of this information. Information on the pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the Adverse Events – Non-serious and Serious Events CRF page. 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 requires the participant to have study intervention discontinued or interrupted
- Any laboratory test result abnormality that requires the participant to receive specific corrective therapy
-

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

9.2.7 Potential Drug-induced Liver Injury

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

A potential DILI is defined as follows:

- Aminotransferase (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) elevation > 3× upper limit of normal (ULN)
- AND
- Total bilirubin > 2× ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
- AND
- No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.
-

9.2.8 Other Safety Considerations

Any significant worsening of conditions noted during interim or final physical examinations, ECG, radiographic imaging, or any other potential safety assessment required or not required by the protocol should also be recorded as a non-serious AE or SAE, as appropriate, and reported accordingly.

9.2.9 AEs of Special Interest

Not applicable.

9.3 Overdose

For this study, any dose of immunotherapy greater than the planned dose within a 24-hour period will be considered an overdose. Overdoses that meet the regulatory definition of an SAE will be reported as SAEs (see Appendix 3).

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 an SAE will be reported as SAEs (see Appendix 3.)

9.4 Safety

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

9.4.1 Physical Examinations

Refer to Section 2: Schedule of Activities.

9.4.2 Vital Signs and Oxygen Saturation

Refer to Section 2: Schedule of Activities. Vital signs include oxygen saturation, body temperature, respiratory rate, seated blood pressure, and seated heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.

9.4.3 Electrocardiograms

Refer to Section 2: Schedule of Activities.

9.4.4 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- Local laboratory tests may be used to guide clinical decisions and determine eligibility for dosing.
- A local laboratory will perform the analyses and will provide reference ranges for these tests.
- During screening and treatment, unless otherwise indicated [redacted], results of clinical laboratory tests must be reviewed prior to dosing.

Clinical safety laboratory assessments are provided in [redacted]

[redacted]

9.4.5 *Imaging Safety Assessment*

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the study investigator per standard medical/clinical judgment. See Section 7.7.2.1 for additional details.

9.5 Pharmacokinetics and Immunogenicity

Pharmacokinetic and immunogenicity (IMG) assessment data for BMS-986315 in combination with nivolumab and chemotherapy in Parts 1 and 2 will be collected from study participants assigned to the study . All time points are relative to the start of BMS-986315 administration. All on-treatment time points are intended to align with days on which study drug is administered; if dosing occurs on a different day, the PK and IMG sampling should be adjusted accordingly. If it is known that a dose is going to be delayed, then the pre-dose sample should be collected just prior to the delayed dose. However, if a pre-dose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected. . Pharmacokinetic parameters of BMS-986315 will be derived, if feasible, from serum concentration versus time data following Cycle 1 Day 1 and Cycle 5 Day 1. Trough concentrations of nivolumab will be summarized. PK parameters that will be assessed are shown in Table 9.5-1.

Table 9.5-1: Pharmacokinetic Parameters to be Assessed

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
AUC(TAU)	Area under the serum concentration-time curve in 1 dosing interval
Ctau	Serum concentration at the end of a dosing interval
Ctrough	Trough observed serum concentrations (this includes pre-dose concentrations [C0] and Ctau)
PK Parameters of BMS-986315 that May be Assessed Following the Dose Administration in Cycle 5 Day 1	
Css-avg	Average serum concentration over a dosing interval (AUC[TAU]/tau) at steady state
AI_AUC	AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose.
DF	Degree of fluctuation or fluctuation index (to be calculated at steady state)
T-HALFeff	Effective elimination half-life that explains the degree of AUC accumulation observed
Nivolumab	
Ctrough	Trough observed serum concentrations (this includes pre-dose concentrations [C0] and Ctau)

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

Sparse nivolumab concentration-time data will be collected and may be used in an integrated population PK or exposure-response (ER) analysis along with data from other nivolumab studies, which will be the subject of a separate report. BMS-986315 PK and biomarker data may be utilized in a population PK, PKPD, or ER analysis.

Treatment assignments will be released to the bioanalytical laboratory in order to minimize unnecessary analysis and/or reanalysis of PK/IMG samples. Separate samples will be collected for PK and IMG assessments.

Concentration and anti-drug antibodies (ADA) (anti-BMS-986315 and anti-nivolumab) analyses for BMS-986315 and nivolumab will be performed by using validated immunoassays. Samples with a positive ADA response may also be analyzed for neutralizing ADA response to BMS-986315 and/or nivolumab. Neutralizing ADA testing is conditional upon assay availability. ADA effects on safety, efficacy, and PK may be evaluated, if applicable.

Bioanalytical samples designated for assessments (eg, immunogenicity, PK, or biomarker) from the same collection time point may be used interchangeably for analyses, if required (including, but not limited to insufficient volume for complement assessment, to follow-up on suspected immunogenicity related AE, etc). Additionally, residual bioanalytical samples will be archived for up to 20 years after the end of the study or the maximum period allowed by applicable law and may be used for potential exploratory bioanalysis (including, but not limited to analysis of drug-ADA immune complexes, metabolite analyses, etc) and/or for additional method purposes

(including but not limited to cross validation, ADA/PK selectivity, cut point, etc.). Further details of sample collection, processing, and shipment will be provided in the laboratory/procedure manual. Blood samples should be drawn from a site other than the infusion site (ie, contralateral arm) on days of infusion. If the infusion was interrupted, the interruption details will also be documented on the CRF. Further details of sample collection, processing, and shipment will be provided in the laboratory/procedure manual.

9.5.1 Pharmacokinetic Sample Collection Windows

It is expected that every effort be made to collect PK samples at the times indicated in the protocol.

The following time window serve as a guideline for PK sample collections:

[redacted]

-

9.6 Immunogenicity Assessments

Antibodies to BMS-986315 and nivolumab will be evaluated in serum samples collected from all participants who receive a dose of the respective drugs. Additionally, serum samples should be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study.

Pre-dose samples will be collected on all participants prior to the administration of the first dose to determine baseline status; any sampling time points that coincide with dosing should have samples drawn for immunogenicity before the administration of the drug; samples must be drawn from a site other than the infusion site (ie. contralateral arm) on the day of infusion Samples that are confirmed positive will be titered. All samples collected for detection of anti-drug antibodies will also be evaluated for serum concentrations of the drug to enable interpretation of the anti-drug antibody data.

Samples may be stored for up to 20 years after the end of the study or the maximum period allowed by applicable law (or according to local regulations) at a facility selected by the Sponsor to enable further analysis of immune responses to BMS-986315.

9.7 Biomarkers

Biomarkers are increasingly playing a key role in the development of cancer therapeutics. By evaluating treatment-induced changes in molecular markers measured in tissue and body fluids, the activity of experimental agents may be assessed and the details of their mechanisms of action may be elucidated. To explore potential pharmacodynamic and predictive markers for clinical response to BMS-986315 in combination with nivolumab and chemotherapy, the following samples for biomarker research are required and will be collected from all participants in this study as specified: (i) tumor tissue, (ii) serum, (iii) plasma, and (iv) whole blood. [redacted] Blood and tumor tissue samples will be collected in this study at baseline and on treatment to identify markers associated with clinical activity and mechanism of action of BMS-986315 in combination with nivolumab and chemotherapy. Biomarker samples will be stored in the Sponsor-designated storage facility. The manager of these samples will ensure that they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than 20 years after the end of the study or the maximum period allowed by applicable law. Complete instructions on the collection, processing, handling, and shipment of all samples described herein will be provided to sites in a separate Laboratory Manual.

9.7.1 Biomarker Assessments in Tumor

[redacted]

Tumor tissues may be analyzed by IHC assays to determine the abundance of TILs and expression of immunoregulatory proteins [redacted]. Baseline and pharmacodynamic measures may also be correlated to clinical outcomes.

[redacted]

9.7.2 Biomarker Assessments in Peripheral Blood

Blood samples will be collected prior to and during treatment from all participants. These blood samples may be assessed for changes in quantity or phenotype of immune cell subsets, changes in soluble factors [redacted], cytokines and chemokines, changes in immune cell functionality, changes in gene expression, and/or circulating tumor DNA (ctDNA). These biomarkers may be used to assess pharmacodynamic changes by dose, and potential associations with efficacy measures. Several sample analyses will be completed and are described briefly below.

9.7.2.1 Whole Blood for Immunophenotyping

Flow cytometry may be used to assess baseline and serial on-treatment alterations in composition/activation status of immune-cell subsets present in the whole blood samples obtained from all participants in each treatment arm. Lymphocyte subsets to be assayed may include, but not be limited to, CD8+ and CD4+ T-cell subsets, NK cells and sub-populations of those cells as defined by the expression of activation, exhaustion, or signaling markers, [redacted].

9.7.2.2 Exploratory Serum Biomarkers

Serum factors including cytokines, chemokines, and other relevant immunomodulatory soluble factors may be determined by different immunoassay methods. Examples of specific analytes to be assessed may include, but are not limited to, factors induced by IFN-γ signaling [redacted], cytolytic markers [redacted]. The impact of baseline level of soluble circulating proteins and the serial on-treatment alterations may be correlated to clinical outcomes.

9.7.2.3 Plasma for Circulating Tumor DNA

Plasma samples will be collected at specific time points indicated [redacted]. Baseline plasma ctDNA levels may be assessed for association with tumor mutational burden (TMB) and/or potential association with efficacy. Dynamic changes in ctDNA levels may also be evaluated for the patient response to treatment.

9.7.2.4 Whole Blood DNA/RNA Analysis

Whole blood collected from participants prior to study treatment initiation may be used to generate genomic DNA for the understanding of genetic variation analyses. [redacted]

[redacted]. Whole exome or whole-genome sequencing methods may be used for this analysis.

Genomic expression analysis of RNA derived from whole blood collected pre treatment and on study may provide information on the broad effects of BMS-986315 combined with nivolumab and chemotherapy versus nivolumab with chemotherapy alone on gene expression that regulates immune modulation. [redacted]

9.7.2.5 Peripheral Blood Mononuclear Cells (PBMCs)

Whole blood samples may be collected for isolation and cryopreservation of PBMCs. [redacted] These cryopreserved samples may be used for functional activation tests or for additional assays if new biology suggests analysis beyond the immunophenotyping described above.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

It is expected that the objective response rate (ORR) with first-line Stage IV or recurrent NSCLC randomized to the BMS-986315 with nivolumab in combination with chemotherapy will be improved as compared to participants receiving nivolumab in combination with chemotherapy.

10.2 Sample Size Determination

The sample size of the study is calculated to have a sufficient probability of making the correct decision and have a low probability of making an incorrect decision.

- Part 1 safety lead-in: [redacted] participants will be enrolled in the safety lead-in Phase. [redacted] A Bayesian optimal interval design (BOIN) with overdose control will be used to safeguard participants' safety.
- Part 2, [redacted] participants will be randomized [redacted] The experimental arm may be dropped if no additional benefit compared to control arm is seen. In such a case, the study will be terminated.

  [redacted]

[redacted]

10.3 Analysis Sets

For the purposes of analysis, the following populations are shown in Table 10.3-1:

Table 10.3-1: Population Description

Population	Description
Enrolled	All participants who sign informed consent and obtained a participant number.
Randomized	All participants who were randomized using IRT.
Treated	All participants who have received any amount of study intervention.
Response-evaluable	All participants who receive at least one dose of study intervention, have a baseline tumor assessment with measurable disease, and 1 of the following: 1) at least 1 evaluable on-treatment tumor assessment, 2) clinical progression, or 3) death prior to the first on-treatment tumor evaluation.
PK	All participants who received at least one dose of BMS-986315/nivolumab and have at least one evaluable serum concentration-time data.
Biomarker	All participants who take at least one dose of study treatment and have at least one non-missing biomarker assessment, excluding the disqualified assessments.
DLT-evaluable	A participant who received 2 doses of BMS-986315, nivolumab and PDCT and completed the DLT observation period, or a participant who experienced a DLT after receiving a minimum of a partial dose of BMS-986315.
Immunogenicity	All treated participants who have baseline and at least 1 post-baseline preinfusion immunogenicity assessment.

Abbreviations: DLT, dose limiting roxicity; IRT, Interactive Response Technology; PK, pharmacokinetics.

10.4 Statistical Analyses

This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. More detailed description of the statistical analyses will be described in the statistical analysis plan (SAP). The SAP will describe the selection of participants to be included in the analyses and procedures, accounting for missing, unused, and spurious data.

A description of the participant population will be included in the clinical study report, including subgroups of age, gender, race, and other study-specific populations and demographic characteristics.

Participant characteristics and/or demographic data may be pooled across studies for future analysis.

10.4.1 Efficacy Endpoint(s)

The Efficacy Endpoints are shown in Table 10.4.1-1.

Table 10.4.1-1: Efficacy Endpoint(s)

Endpoint	Statistical Analysis Methods	Timeframe
Primary Analysis		
ORR by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 per BICR assessment	Objective response rate (ORR) is defined as the number of participants who achieve a best overall response (BOR) of confirmed complete response (CR) or confirmed partial response (PR), based on BICR assessments (using RECIST 1.1), divided by the number of all randomized participants. BOR is defined as the best response, recorded between the date of randomization and the date of first objectively documented progression per RECIST 1.1. For participants without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination. The number and percentage of participants in each category of BOR per BICR (complete response [CR], partial response [PR], stable disease [SD], progressive disease, or unable to determine [UTD]) will be presented, by treatment group. [redacted] Formal statistical testing for the difference of ORR will only be performed between Arm B and Arm A. The difference of ORR between Arm B and Arm A will be estimated along with its exact two-sided 90% confidence interval for all randomized subjects using Cochran-Mantel-Haenszel (CMH) method of weighting, adjusting for the stratification factors. The descriptive summary of differences of ORR between Arm A and Arm C or between Arm B and Arm C will be provided along with their 2-sided 95 % confidence intervals.	Up to 5 years
Secondary/Exploratory Analysis		
PFS by RECIST 1.1 per BICR assessment	PFS is defined as the time between the date of randomization and the first date of documented progression, per BICR assessments (using RECIST 1.1), or death due to any cause, whichever occurs first. Participants who did not progress or die will be censored on the date of their last evaluable tumor assessment. Participants who did not have any on-study tumor assessments and did not die will be censored on their date of randomization. The PFS function for each treatment group will be estimated using the KM product limit method and will be displayed graphically. A two-sided 95% CI for median PFS in each treatment group will be computed via the log-log transformation method. PFS rates at fixed time points (eg, 3, 6 months, depending on the minimum follow-up) will be presented along with their associated 95% CIs. These estimates will be derived from the Kaplan Meier estimate and corresponding CIs will be derived based on Greenwood's formula for variance derivation and the log-log transformation applied on the survivor function. Hazard Ratio and its 95% confidence interval for PFS between the experimental arm and the control arm will be estimated using the stratified Cox proportional model.	Up to 5 years

Table 10.4.1-1: Efficacy Endpoint(s)

Endpoint	Statistical Analysis Methods	Timeframe
DCR by RECIST 1.1 per BICR assessment	Disease control rate (DCR) is defined as the number of participants who achieve a BOR of confirmed CR, confirmed PR, or stable disease (SD), based on BICR assessments (using RECIST 1.1) divided by the number of all randomized participants. Estimates of DCR, along with its exact two-sided 95% CI by Clopper and Pearson, will be presented by treatment group.	Up to 5 years
DoR by RECIST 1.1 per BICR assessment among responders	Duration of response (DoR) is defined as the time between the date of first documented response (CR or PR) that is subsequently confirmed, to the date of the first objectively documented tumor progression as determined by BICR (per RECIST 1.1), or death due to any cause, whichever occurs first. Participants who die without a reported prior progression will be considered to have an event on the date of their death. Participants who neither progress nor die will be censored on the date of their last evaluable tumor assessment. DoR will be evaluated for responders (confirmed CR or PR) only. DoR will be analyzed using similar method as PFS.	Up to 5 years
TTR by RECIST 1.1 per BICR assessment	• TTR assessed by BICR is defined as the time between the date of randomization and the first confirmed documented response (CR or PR) per RECIST 1.1 criteria. TTR will be summarized by treatment group in all responders using descriptive statistics and frequency statistics by time point.	Up to 5 years

Abbreviations: BICR, blinded independent central review; BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; KM, Kaplan Meier; ORR, objective response rate; PD, progressive disease; PFS, progression free survival; PR, partial response, RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; UTD, unable to determine; TTR, time to response.

10.4.2 Safety Endpoint(s)

The Safety Endpoints are shown in Table 10.4.2-1

Table 10.4.2-1: Safety Endpoint(s)

Endpoint	Statistical Analysis Methods	TimeFrame
Primary Secondary and Exploratory Analyses		
Safety	Incidence and severity of AEs/SAEs, treatment-related AEs/SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, adverse events of special interest (AESI), deaths and laboratory abnormalities. Safety analysis will be performed in all treated participants. Descriptive statistics of safety will be presented using NCI CTCAE v5.0 by treatment group. All on-study AEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v5.0 criteria by system organ class and preferred term. On-study laboratory parameters including hematology, chemistry, liver function and renal function will be summarized using worst grade per NCI CTCAE v5.0 criteria.	100 days after discontinuation of study treatment

Abbreviations: AE adverse event; AESI, adverse events of special interest; CTCAE, Common Terminology Criteria for Adverse Event; DLT, dose-limiting toxicity; NCI, National Cancer Institute; SAE, serious adverse event; TRAE, treatment-related adverse event.

10.4.3 Other Analyses

PK and biomarker exploratory analyses will be described in the SAP. The population PK analysis and pharmacodynamic analyses may also be presented separately from the main CSR.

10.5 Interim Analyses for Part 2

Interim Analysis for Efficacy

[redacted]. The ORR comparison is conducted between Arm B and Arm A. [redacted]

[redacted]

Bayesian optimal interval (BOIN) design

Part 1 will employ the Bayesian optimal interval (BOIN) to find the maximum tolerated dose (MTD). The BOIN design is implemented in a simple way similar to the traditional 3+3 design but is more flexible and possesses superior operating characteristics that are comparable to those of the more complex model-based designs.

The target toxicity rate for the MTD is $\phi = 0.3$ and the maximum sample size is 12. As shown in Figure 10.5-1, the BOIN design uses the following rule, optimized to minimize the probability of incorrect dose assignment, and to guide dose escalation/de-escalation:

- If the observed DLT rate at the current dose is ≤ 0.236, escalate the dose to the next higher dose level
- If the observed DLT rate at the current dose is > 0.359, de-escalate the dose to the next lower dose level
- Otherwise, stay at the current dose.

For the purpose of overdose control, doses j and higher levels will be eliminated from further examination [redacted], where p_j is the true DLT rate of dose level $j, j = 1,\cdots, 2$. This posterior probability is evaluated based on the beta-binomial model $y_j \mid p_j \sim \text{binomial}(p_j)$ with $p_j \sim \text{uniform}(0,1)$, where y_j is the number of participants experienced DLT at dose level j. When the lowest dose is eliminated, stop the trial for safety. The above dose escalation/de-escalation and elimination rule can be equivalently presented in Table 10.5-2, which will be used to conduct the trial.

Table 10.5-2: Dose Escalation/Deescalation Rule for the BOIN Design

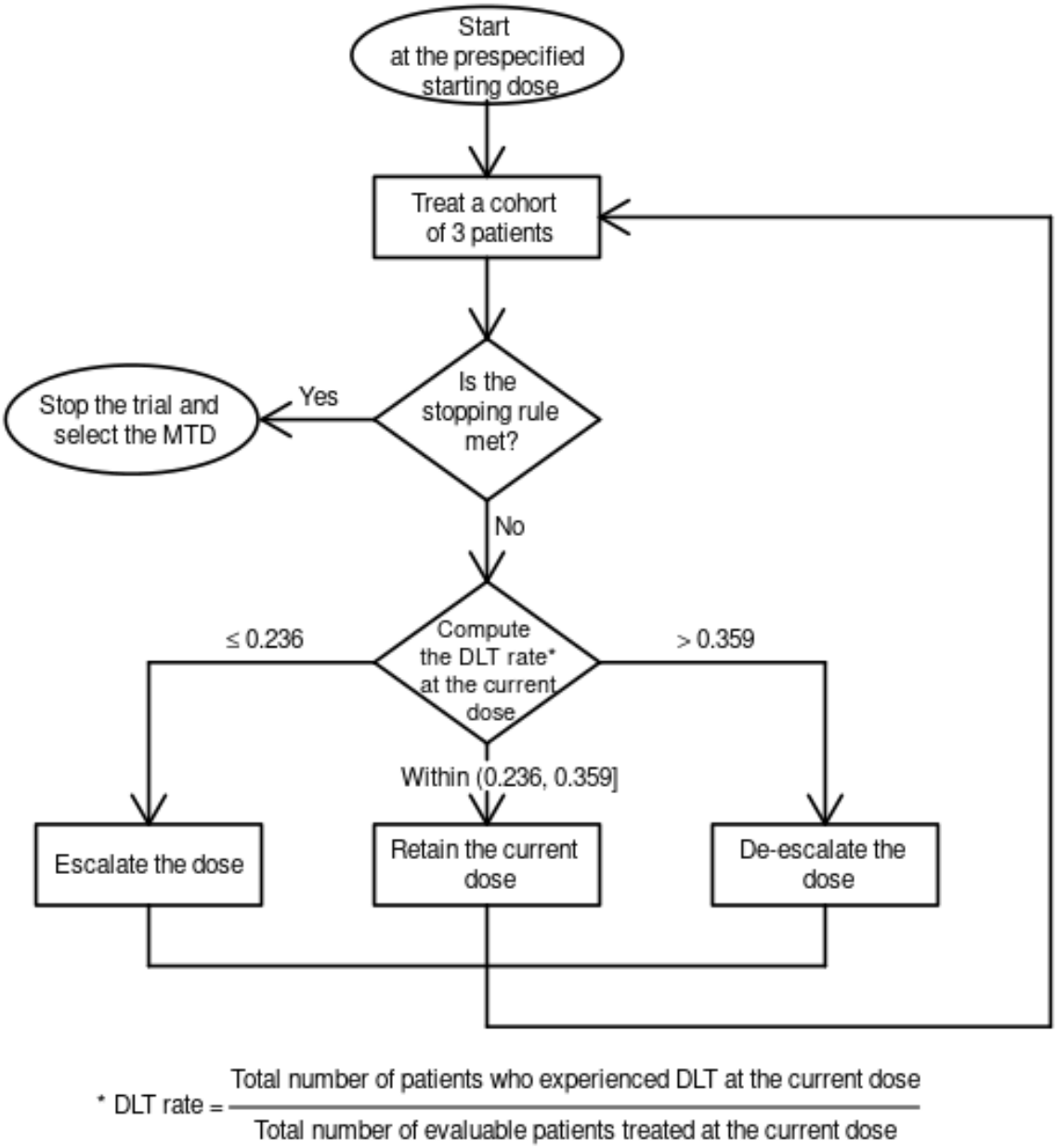
Number of evaluable participants treated at current dose	3*	4*	5*	6	7	8	9	10	11	12
Escalate if # of DLT ≤	0	0	1	1	1	1	2	2	2	2
Deescalate if # of DLT ≥	2	2	2	3	3	3	4	4	4	5
Eliminate if # of DLT ≥	2	3	3	3	4	4	5	5	5	6

Abbreviations: BOIN, Bayesian Optimal Interval; DLT, dose limiting toxicity.

Note. "# of DLT" is the number of patients with at least 1 DLT. When none of the actions (ie, escalate, de-escalate or eliminate) is triggered, stay at the current dose for treating the next cohort of patients.

* Dose esclation recommendation will occur when [redacted] participants within a cohort have completed a [redacted] DLT period or have been sufficiently followed. Dose de-esclation decision may be made as early as [redacted] subjects have completed the DLT period based on totality of data.

Figure 10.5-1: BOIN Design Flow Chart



Abbreviations: DLT, dose limiting toxicity; MTD, maximum tolerated dose.

11 REFERENCES

[1] Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet. 2019;393(10183):1819-1830. doi:10.1016/S0140-6736(18)32409-7.

[2] Hellmann M, Paz-Ares I, Caro R et al. Nivolumab plus ipilimumab in advanced non-small cell lung cancer. N Engl J Med 2019: 81:2020-2031.

[3] Wang Y, Zhao S, Chen J et al. The KEYNOTE-189 trial as a new paradigm making cure a reality for metastatic non-squamous non-small cell lung cancer. Transl Lung Cancer Res. 2020; 9:2184-2187.

[4] Paz-Ares L, Vicente D, Tafreshi A et al. A randomized, placebo-controlled trial of pembrolizumab plus chemotherapy in patients with metastatic squamous NSCLC: protocol-specified final analysis of KEYNOTE 407. J Thorac Oncol 2020; 15:1657-1669.

[5] Paz-Ares L, Ciuleau TE, Cobo M et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, Phase 3 trial. Lancet Oncol 2021; 22:198-211.

[6] Herbst RS, Majem M, Barlesi F et al. COAST: an open-label, Phase II, multidrug platform study of durvalumab alone or in combination with oleclumab or monalizumab in patients with unresectable, stage III non-small-cell lung cancer. J Clin Oncol 2022; 0:3383-3393.

[7] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics [published correction appears in CA Cancer J Clin. 2011 Mar-Apr;61(2):134]. CA Cancer J Clin. 2011;61(2):69-90. doi:10.3322/caac.20107.

[8] BMS-986315: Investigator's Brochure Version 3. Bristol-Myers Squibb Company; 2023 Document Control No. 930146552.

[9] BMS-986315: Study of BMS-986315 Alone and in Combination With Nivolumab or Cetuximab in Participants With Advanced Solid Tumors (Study CA047-004). Bristol-Myers Squibb Company; study ongoing.

[10] BMS-936558: An Open-Label, Randomized Phase 3 Trial of Nivolumab, or Nivolumab plus Ipilimumab, or Nivolumab plus platinum doublet chemotherapy versus platinum doublet chemotherapy in Subjects with Chemotherapy-Naïve Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC) (Study CA209227). Bristol-Myers Squibb Company; study ongoing.

[11] BMS-986016: A Phase 2 Randomized Study of Relatlimab plus Nivolumab in Combination with Chemotherapy vs. Nivolumab in Combination with Chemotherapy as First Line Treatment for Participants with Stage IV or Recurrent Non-small Cell Lung Cancer (NSCLC) (Study CA224104). Bristol-Myers Squibb Company; study ongoing.

[12] Rizvi NA, Hellmann MD, Brahmer JR, et al. Nivolumab in Combination With Platinum-Based Doublet Chemotherapy for First-Line Treatment of Advanced Non-Small-Cell Lung Cancer. J Clin Oncol. 2016;34 :2969-2979. doi:10.1200/JCO.2016.66.9861.

[13] United States Food and Drug Administration. Surrogate Endpoint Table 2022 Available from: URL:https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure.

[14] Blumenthal GM, Karuri SW, Zhang H, et al. Overall response rate, progression-free survival, and overall survival with targeted and standard therapies in advanced non-small-cell lung cancer: US Food and Drug Administration trial-level and participant-level analyses. J Clin Oncol. 2015;33(9):1008-1014. doi:10.1200/JCO.2014.59.0489.

[15] Goring S, Varol N, Waser N, et al. Correlations between objective response rate and survival-based endpoints in first-line advanced non-small cell lung Cancer: A systematic review and meta-analysis. Lung Cancer. 2022;170:122-132. doi:10.1016/j.lungcan.2022.06.009.

[16] Peey-Sei Kok, Won-Hee Yoon, et al. Tumor Response End Points as Surrogates for Overall Survival in Immune Checkpoint Inhibitor Trials: A Systematic Review and Meta-Analysis. JCO Precision Oncology 2021;5;1151-1159.

[17] Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. N Engl J Med. 2015;373:123-35.

[18] Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. N Engl J Med. 2015;373:1627-39.

[19] Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med. 2015;373:23–34.

[20] Hellmann MD, Rizvi NA, Goldman JW, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, Phase 1, multicohort study. Lancet Oncol. 2017;18:31-41.

[21] Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015;373:1803-13.

[22] Schadendorf D, Hodi FS, Robert C, et al. Pooled analysis of long-term survival data from Phase II and Phase III trials of ipilimumab in unresectable or metastatic melanoma. J Clin Oncol. 2015;33:1889-94.

[23] Schadendorf D, Wolchok JD, Hodi FS, et al. Efficacy and quality of life outcomes in patients with advanced melanoma (MEL) who discontinued treatment with nivolumab (NIVO) plus ipilimumab (IPI) due to toxicity in a Phase III trial (CheckMate 067). Presented at 2016 Annual Meeting of the European Association of Dermato-Oncology; 2016 Aug 31-Sep 3, Vienna, Austria.

[24] Felp A, Font E, Gettinger SN, Burgio MA, et al. Three-year follow-up from Checkmate 017/057: nivolumab versus docetaxel in patients with previously treated advanced non-small lung cancer (NSCLC). Poster discussion presentation at: European Society of Medical Oncology Annual Meeting; 2017 Sep 8-12; Madrid, Spain.

[25] Spigel DR, McLeod M, Hussein MA, et al. Oral presentation at: European Society of Medical Oncology Annual Meeting; 2017 Sep 8- 12; Madrid, Spain.

[26] Investigator Brochure Nivolumab Bristol Myers Squibb Company 2022, Document Control No. 930038243.

12 APPENDICES

APPENDIX 1 LIST OF ABBREVIATIONS

Term	Definition
[redacted]	[redacted]
ADA	anti-drug antibodies
AE	adverse event
AI_AUC	AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose.
ALK	ALK receptor tyrosine kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(0-T)	Area under the serum concentration-time curve from time zero to time of last quantifiable concentration
AUC(TAU)	Area under the serum concentration-time curve in 1 dosing interval
AxMP	Auxiliary Medicinal Product
BICR	blinded independent central review
BMI	Body mass index
BMS	Bristol-Myers Squibb Company
BOIN	Bayesian optimal interval
BOR	best overall response
BP	blood pressure
BRAF	B-Raf proto-oncogene
C	Cycle
[redacted]	[redacted]
CD8	cluster of differentiation 8
CI	confidence interval
Cmax	Maximum observed serum concentration
CONSORT	Consolidated Standards of Reporting Trials
CPK	creatine phosphokinase
CR	complete response
CrCl	creatinine clearance
CRP	C-reactive protein
Css-avg	Average serum concentration over a dosing interval (AUC[TAU]/tau) at steady state

Term	Definition
CT	computed tomography
Ctau	Serum concentration at the end of a dosing interval
Ctrough	Trough observed serum concentrations (this includes pre-dose concentrations [C0] and Ctau)
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CTLA-4	cytotoxic T lymphocyte–associated antigen 4
D	Day
DCR	disease control rate
DF	Degree of fluctuation or fluctuation index (to be calculated at steady state)
[redacted]	[redacted]
DLT	dose-limiting toxicity
DAC	Data Assessment Committee
DNA	deoxyribonucleic acid
DoR	duration of response
[redacted]	[redacted]
ECG	electrocardiogram
[redacted]	[redacted]
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EOI	end of infusion
[redacted]	[redacted]
ESMO	European Society for Medical Oncology
ER	exposure-response
FDA	US Food and Drug Administration
[redacted]	[redacted]
FSH	follicle-stimulating hormone
[redacted]	
HCV	hepatitis C virus

Term	Definition
Hgb	Hemoglobin
[redacted]	[redacted]
HIV	human immunodeficiency virus
HLA-E	MHC class I antigen E
HR	hazard ratio
IA	interim analysis
IASLC	International Association for the Study of Lung Cancer classification
IB	Investigator Brochure
ICF	informed consent form
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IMAE	immune-mediated adverse event.
IMG	Immunogenicity
IMP	Investigational Medicinal Product
IA	interim analysis
I-O	Immuno-Oncology
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITIM	immunoreceptor tyrosine-based inhibitory motif
IV	intravenous(ly)
LAG-3	lymphocyte activation gene 3
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MET	MET proto-oncogene
[redacted]	[redacted]
MHC	major histocompatibility complex
[redacted]	[redacted]
MRI	magnetic resonance imaging
MUGA	multiple gated acquisition scan
MTD	maximum tolerated dose
NK	natural killer
NKG2A	natural killer group 2 member A
NTRK	neurotrophic tyrosine receptor kinase

Term	Definition
Non-IMP	Non-investigational Medicinal Product
NQ	non-quantifiable
NSCLC	Non-Small Cell Lung Cancer
NSCLC-SAQ	Non-Small Cell Lung Cancer Symptom Assessment Questionnaire
NSQ	non-squamous
ORR	objective response rate
OS	overall survival
[redacted]	[redacted]
PCR	polymerase chain reaction
PD	Pharmacodynamic(s)
PDCT	platinum doublet chemotherapy
PD-1	programmed cell death 1
PD-L1	programmed death-ligand 1
[redacted]	[redacted]
PET-CT	Positron emission tomography–computed tomography
PFS	progression free survival
PK	pharmacokinetic(s)
PR	partial response
[redacted]	[redacted]
Q3W	every 3 weeks
Q4W	every 4 weeks
[redacted]	
QD	daily
RECIST	Response Evaluation Criteria in Solid Tumors
RET	RET proto-oncogene
RNA	ribonucleic acid
ROS1	ROS proto-oncogene 1
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
[redacted]	[redacted]
SD	stable disease
[redacted]	[redacted]

Term	Definition
SmPC	summary of product characteristics
SMT	Safety Management Team
SQ	Squamous
[redacted]	
T-HALFeff	Effective elimination half-life
TIL	tumor-infiltrating lymphocytes
Tmax	Time of maximum observed serum concentration
TMB	tumor mutational burden
TRAE	treatment-related adverse event
[redacted]	[redacted]
TTE	transthoracic echocardiogram
TTR	time to response
ULN	upper limit of normal
US	United States
USPI	US prescribing information
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines
- Applicable laws, regulations, and requirements

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, Investigator's Brochure, product labeling information, ICF, participant recruitment materials (eg, advertisements), and any other written information to be provided to participants.

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

The investigator is responsible for providing oversight of the conduct of the study at the site and adherence to requirements of the following where applicable:

- ICH guidelines
- United States (US) Code of Federal Regulations, Title 21, Part 50 (21CFR50)

- European Regulation 536/2014 for clinical studies
- European Medical Device Regulation 2017/745 for clinical device research
- the IRB/IEC
- all other applicable local regulations

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, by the local Health Authority), except where necessary to eliminate an immediate hazard(s) to study participants.

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

- IRB/IEC
- Regulatory authority(ies), if applicable according to 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, by the local Health Authority must be sent to Bristol-Myers Squibb Company (BMS).

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the ICF 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 participants currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new participants prior to enrollment.

FINANCIAL DISCLOSURE

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information, in accordance with 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 study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

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

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

The investigator or his/her representative must:

- Obtain IRB/IEC written approval/favorable opinion of the written ICF and any other information to be provided to the participant prior to the beginning of the study and after any revisions are completed for new information.
- Provide a copy of the ICF and written information about the study in the language in which the participant is proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Explain the nature of the study to the participant and answer all questions regarding the study.
- Inform the participant that his/her participation is voluntary. The participant will be required to sign a statement of informed consent that meets the requirements of 21 CFR Part 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Allow time necessary for the participant to inquire about the details of the study.
- Obtain an ICF signed and personally dated by the participant and by the person who conducted the informed consent discussion.
- Include a statement in the participant's medical record that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Re-consent the participant to the most current version of the ICF(s) during his/her participation.
- Revise the ICF 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 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 participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the participant's signed ICF, and, in the US, the participant's signed HIPAA authorization.

The ICF must also include a statement that BMS and local and foreign regulatory authorities have direct access to participant records.

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

BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS

The mission of BMS is to transform patients' lives through science by discovering, developing, and delivering innovative medicines that help them prevail over serious diseases.

BMS is committed to doing its part to ensure that patients have a fair and just opportunity to achieve optimal health outcomes.

BMS is working to improve the recruitment of a diverse participant population with the goal that the clinical trial becomes more reflective of the real-world population and the people impacted by the diseases studied.

RECRUITMENT AND INFORMED CONSENT PROCEDURES

Potential participants may be identified by the recruiting investigational team (called "site") within the affiliated clinic/hospital, and/or group practice, through their own chart/database review, using the inclusion/exclusion criteria defined by the protocol. Potential participants may also be referred to the site by medical doctors from surrounding hospitals/practices or directly contact one of the investigative "sites" following study and site identification through a public registry, such as clinicaltrials.gov or euclinicaltrials.eu. The investigator has access to the participant's medical file, so, the medical data will remain confidential without the sponsor having access to them. Recruitment material will also be utilized as an additional tool to recruit participants per local regulations and requirements.

The principal investigator or sub-investigator, or a qualified designee of the investigator's research team will approach potential participants to discuss the option of participating in the clinical trial and the consent process. Informed consent will be obtained by the principal investigator or a qualified delegate on the principal investigator's research team from each participant prior to enrollment into the study. The participant will be provided the opportunity to read the information sheet and consent form and have all their questions and concerns addressed before giving consent in writing.

DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY

BMS collects and processes personal data of study participants, patients, health care providers, and researchers for biopharmaceutical research and development to advance innovative, high-quality medicines that address the medical needs of patients. BMS ensures the privacy, protection, and confidentiality of such personal data to comply with applicable laws. To achieve these goals, BMS has internal policies that indicate measures and controls for processing personal data. BMS adheres to these standards to ensure that collection and processing of personal data are limited and proportionate to the purpose for which BMS collects such personal data. This purpose is clearly and unambiguously notified to the individual at the time of collection of personal data. In the true spirit of science, BMS is dedicated to sharing clinical trial information and data with participants, medical/research communities, the media, policy makers, and the general public. This is done in a manner that safeguards participant privacy and informed consent while respecting the integrity of national regulatory systems. Clinical trial data, health-related research, and pharmacovigilance activities on key-coded health data transferred by BMS across national borders is done in compliance with the relevant data protection laws in the country and GCP requirements.

BMS protects Personal Information with adequate and appropriate security controls as indicated under the data protection laws. To align with the recommended security standards, BMS has

adopted internal security standards and policies to protect personal data at every stage of its processing.

To supplement these standards, BMS enters into Clinical Trial Agreements (CTAgs) with confidentiality obligations to ensure proper handling and protection of personal data by third parties accessing and handling personal data.

BMS takes unauthorized access and disclosure of Personal Information very seriously. BMS has adopted the security standards that include National Institute of Standards and Technology Cybersecurity Framework for studies in the US. BMS aligns with these standards to continuously assess and improve its ability to protect, detect, and respond to cyber attacks and other unauthorized attempts to access personal data. These standards also aid in mitigating possible adverse effects. Furthermore, BMS Information Technology has defined 6 principles to protect our digital resources and information:

1) Responsibilities of IT Personnel
2) Securing the BMS Digital Infrastructure
3) Identity and Access Management
4) External Partner Connections
5) Cyber Threat Detection and Response
6) Internal Cyber Incident Investigation

SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the electronic Case Report Form (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

- The investigator may need to request previous medical records or transfer records depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the source data location list/map or equivalent document.

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

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

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

STUDY INTERVENTION RECORDS

Records for study intervention (whether supplied by BMS, its vendors, or the site) must substantiate study intervention 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 the following: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • non-study disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence/biocomparability, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability per the Delegation of Authority Form
Sourced by site and not supplied by BMS or its vendors (examples include Investigational Product sourced from the site's stock or commercial supply or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study intervention integrity in accordance with requirements applicable under law and the standard operating procedures/standards of the sourcing pharmacy

BMS or its 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

The terms "participant" and "subject" refer to a person who has consented to participate in the clinical research study. Typically, the term "participant" is used in the protocol and the term "subject" is used in the Case Report Form (CRF).

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 test result abnormalities that are reported or identified during the study.

For sites using the Sponsor or designee electronic data capture (EDC) tool, eCRFs will be prepared for all data collection fields except for fields specific to serious adverse events (SAEs) and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance Form, respectively. If the electronic SAE form is not available, a paper SAE form can be used.

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

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

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

Each individual electronically signing eCRFs must meet Sponsor or designee training requirements and must only access the BMS EDC tool using the unique user account provided by the 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 non-compliance 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 source documents.

In addition, the study may be evaluated by the 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 the 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 its 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 its 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 its designee.

Records collected throughout the study will be stored in the BMS clinical data management system for a duration of the life of the product plus 25 years.

RETURN OF STUDY INTERVENTION

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

If	Then
Study interventions supplied by BMS (including its vendors)	Any unused study interventions supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor, unless study intervention containers must be immediately destroyed as required for safety or to meet local regulations (eg, cytotoxic or biologic agents). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. However, unused Investigational Medicinal

If	Then
	Product must be reconciled by the site monitor/clinical research associate prior to destruction. If study interventions will be returned, the return will be arranged by the responsible study monitor.
Study interventions sourced by site, not supplied by BMS (or its vendors; eg, study interventions sourced from the site's 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 of study interventions, 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 standard operating procedures 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 (eg, incinerator, licensed sanitary landfill, or licensed waste-disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Study Monitor to review throughout the clinical trial period.

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

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

STUDY AND SITE CLOSURE

The Sponsor/designee reserves the right to close the study site or to terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to, the following:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should ensure appropriate participant therapy and/or follow-up.

DISSEMINATION OF CLINICAL STUDY DATA

To benefit potential study participants, patients, health care 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 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

A Signatory Investigator must be selected to sign the Clinical Study Report (CSR).

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

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

In the European Union (EU), the summary of results and summary for laypersons will be submitted within 1 year of the end of trial in EU/European Economic Area and third countries.

SCIENTIFIC PUBLICATIONS

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

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

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

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

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

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

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

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

ADVERSE EVENTS

Adverse Event Definition:
An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition occurring in a clinical investigation participant after signing of informed consent, whether or not considered related to the study intervention.
An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory test result), symptom, or disease temporally associated with the study intervention.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, electrocardiograms, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal laboratory test results or other safety assessment findings 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 the condition 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/serious adverse event (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 the definition above, then it cannot be an SAE, even if serious conditions are met.

SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death.
Is life threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event that 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 department or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event). • Elective surgery that was planned prior to signing consent. • Admissions per protocol for a planned medical/surgical procedure. • Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy). • Medical/surgical admission other than to remedy ill health and planned prior to enrollment in the study. Appropriate documentation is required in these cases. • Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, 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 results in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [eg, 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 department or at home for allergic bronchospasm and 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: Potential Drug-induced Liver Injury of the protocol for the definition of a potential DILI.)

Pregnancy and DILI must follow the same transmission timing and processes to BMS as those used for SAEs. (See Section 9.2.5: Pregnancy of the protocol for reporting pregnancies.)

EVALUATING AES AND SAES

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated. • The investigator will also consult the Investigator's Brochure 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 the 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 the Sponsor. • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study using National Cancer Institute Common Terminology Criteria for Adverse Events NCI-CTCAE v.5.0.
An event is defined as "serious" when it meets at least 1 of the pre-defined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

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 intervention or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or the designee) using the same procedure used for transmitting the initial SAE report.

All AEs/SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study intervention, and pregnancies must be reported to BMS (or the designee) promptly and not to exceed 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 electronic Case Report Form (eCRF).
  - The paper SAE Report Form is intended only as a back-up option when the electronic data capture system is unavailable/not functioning for transmission of the eCRF to BMS (or the designee).
    - In this case, the paper form is transmitted via email or confirmed fax transmission.
    - When paper forms are used, the original paper forms are to remain on site.
- Pregnancies must be recorded on paper Pregnancy Surveillance Forms and transmitted via email or confirmed fax transmission.

SAE Email Address: [redacted]

SAE Fax Number: *Will be provided by local site monitor.*

SAE Telephone Contact (required for SAE and pregnancy reporting): *Will be provided by local site monitor.*

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

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

DEFINITIONS

Women of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

- Premenarchal
- Pre-menopausal 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.

- Post-menopausal female
  - A post-menopausal state is defined as 12 months of amenorrhea in a woman over the age of 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 to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. Suggested guidelines for the duration of the washout periods for HRT types are presented below. Investigators should use their 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 at which the study intervention (Investigational Medicinal Product [IP/IMP] and other study interventions ie, Non-IMP/AxMP required for study) or any active major metabolites have decreased to a concentration that is no longer considered relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed-adverse-effect level or the time required for 5 half-lives of the study intervention to pass.

METHODS OF CONTRACEPTION

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

Highly Effective Contraceptive Methods That Are <u>User Dependent</u> *Failure rate of < 1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol.)[b] – Oral (birth control pills) – Intravaginal (rings) – Transdermal • Combined (estrogen- and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy.
• Progestogen-only hormonal contraception associated with inhibition of ovulation. (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol.)[b] – Oral – Injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy.
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol.)[b] • Intrauterine device.

• Intrauterine system (IUS). (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol.)[b,c] • Bilateral tubal occlusion.
• Vasectomized partner. Having a vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A vasectomy is a highly effective contraception method provided that the participant is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participants have undergone a successful vasectomy or if their partner is pregnant or breastfeeding.
• Sexual abstinence. *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • Continuous abstinence must begin at least 30 days prior to initiation of study therapy. • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2 of the protocol. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participant chooses to forego complete abstinence. • Periodic abstinence (including, but not limited to, calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactation amenorrhea method (LAM) are not acceptable methods of contraception for this study.
NOTES: [a] Typical use failure rates may differ from failure rates when contraceptive methods are used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the Investigational Medicinal Product and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. For information specific to this study

regarding permissibility of hormonal contraception, refer to Section 6.1: Inclusion Criteria and Section 7.7.1: Prohibited and/or Restricted Treatments of the protocol.

[c] IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. For information specific to this study regarding permissibility of hormonal contraception, refer to Section 6.1: Inclusion Criteria and Section 7.7.1: Prohibited and/or Restricted Treatments of the protocol.

Less Than Highly Effective Contraceptive Methods That Are User Dependent

Failure rate of > 1% per year when used consistently and correctly.

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously.
- Diaphragm with spermicide.
- Cervical cap with spermicide.
- Vaginal sponge with spermicide.
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action. (This method of contraception cannot be used by WOCBP participants in studies in which hormonal contraception is prohibited.)

Unacceptable Methods of Contraception

- Periodic abstinence (calendar, symptothermal, post-ovulation methods).
- Withdrawal (coitus interruptus).
- Spermicide only.
- LAM.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of pregnancy information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5: Pregnancy of the protocol and Appendix 3.

APPENDIX 5 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS	
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

Reference: Oken MM, Creech RH, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655.

APPENDIX 6 IMAE 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.

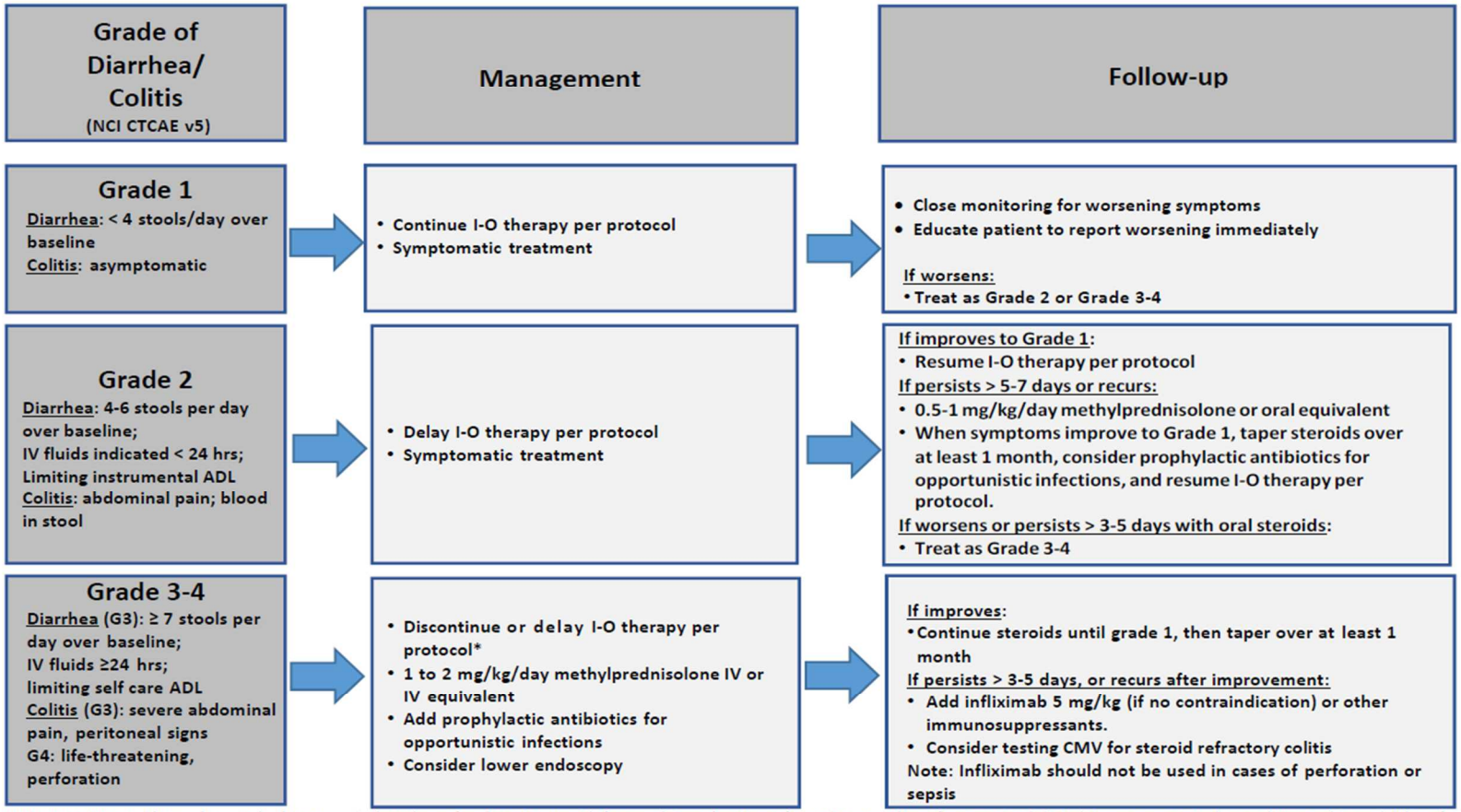
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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

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

GI Adverse Event Management Algorithm

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

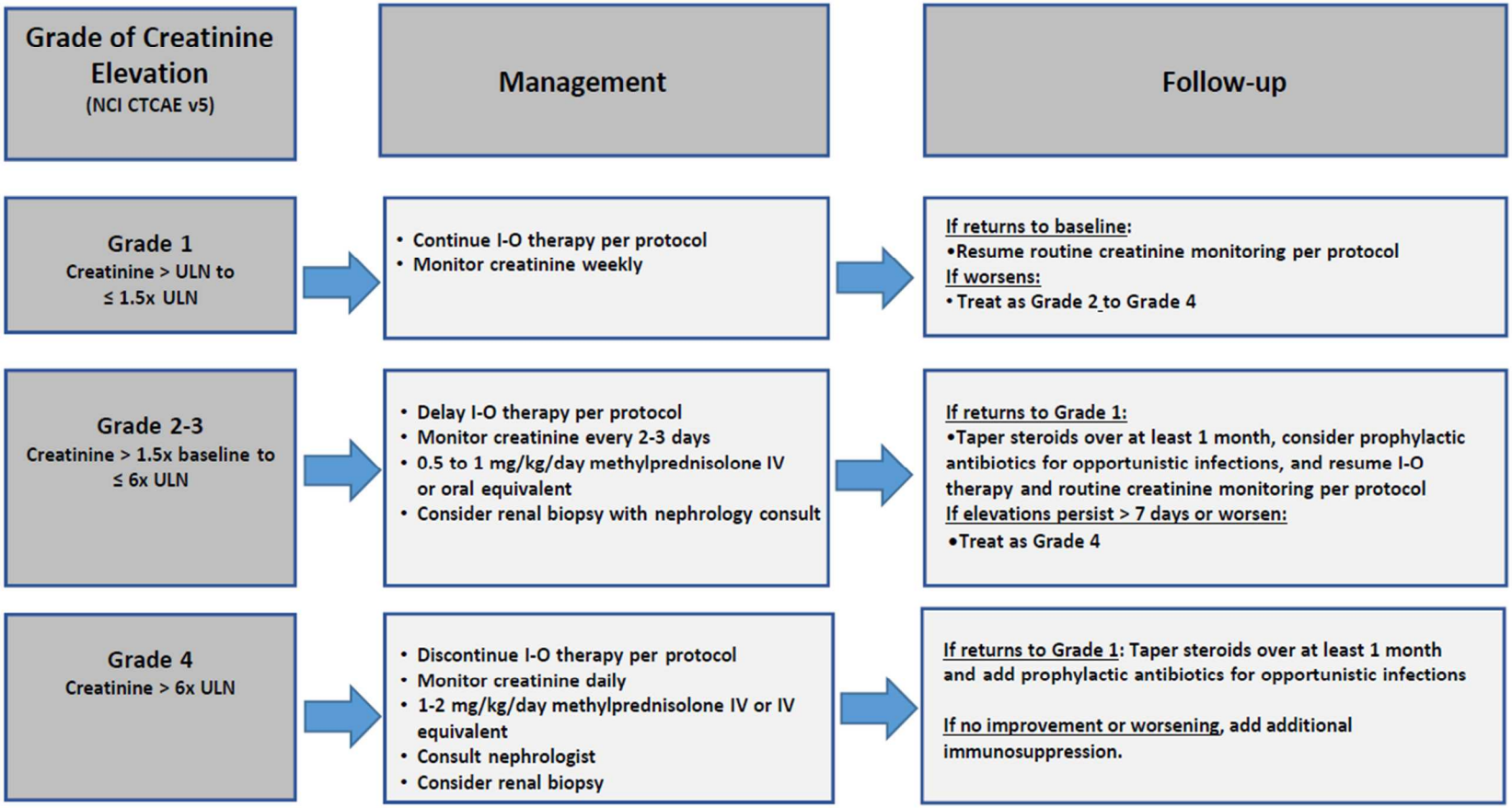


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

Renal Adverse Event Management Algorithm

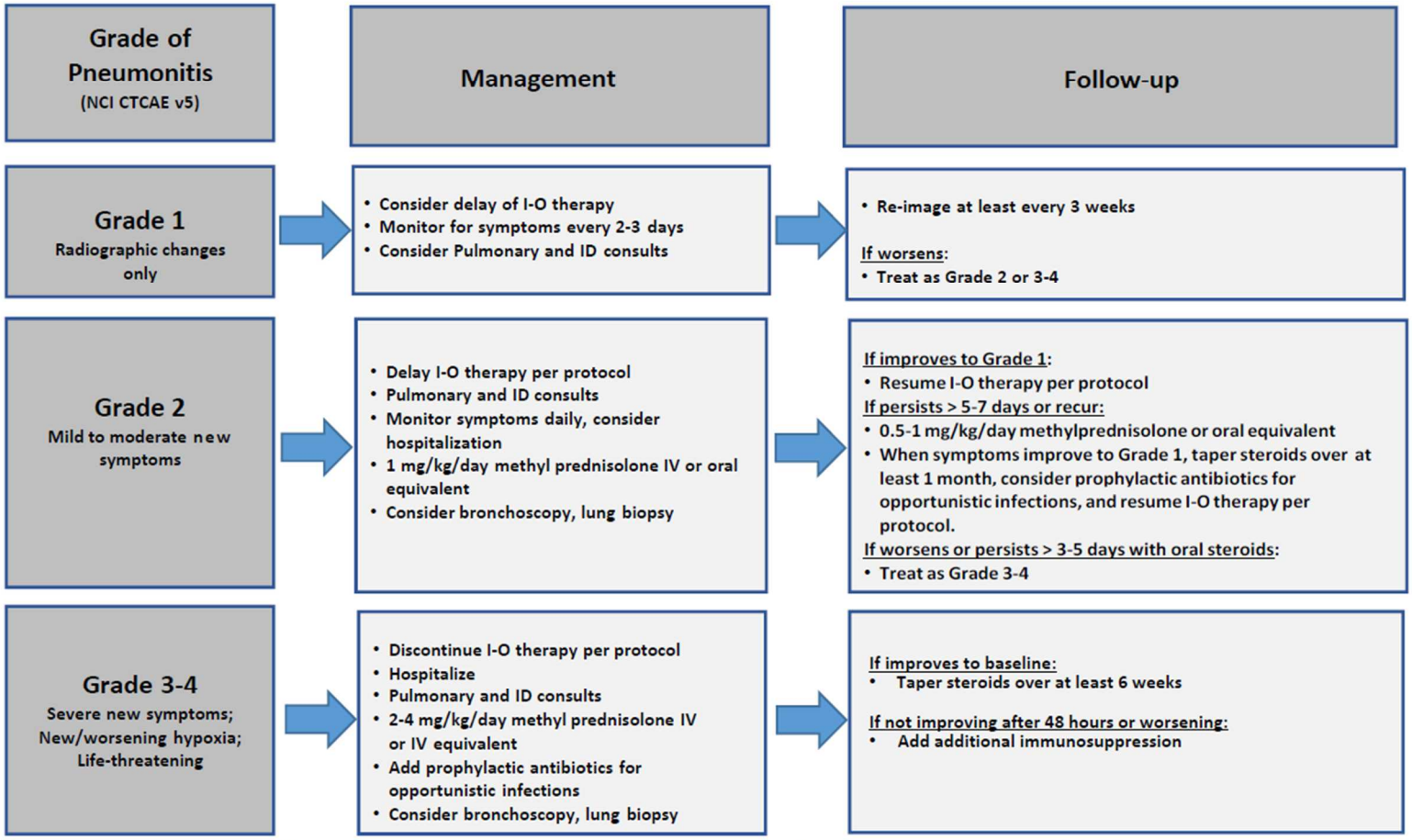
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

Pulmonary Adverse Event Management Algorithm

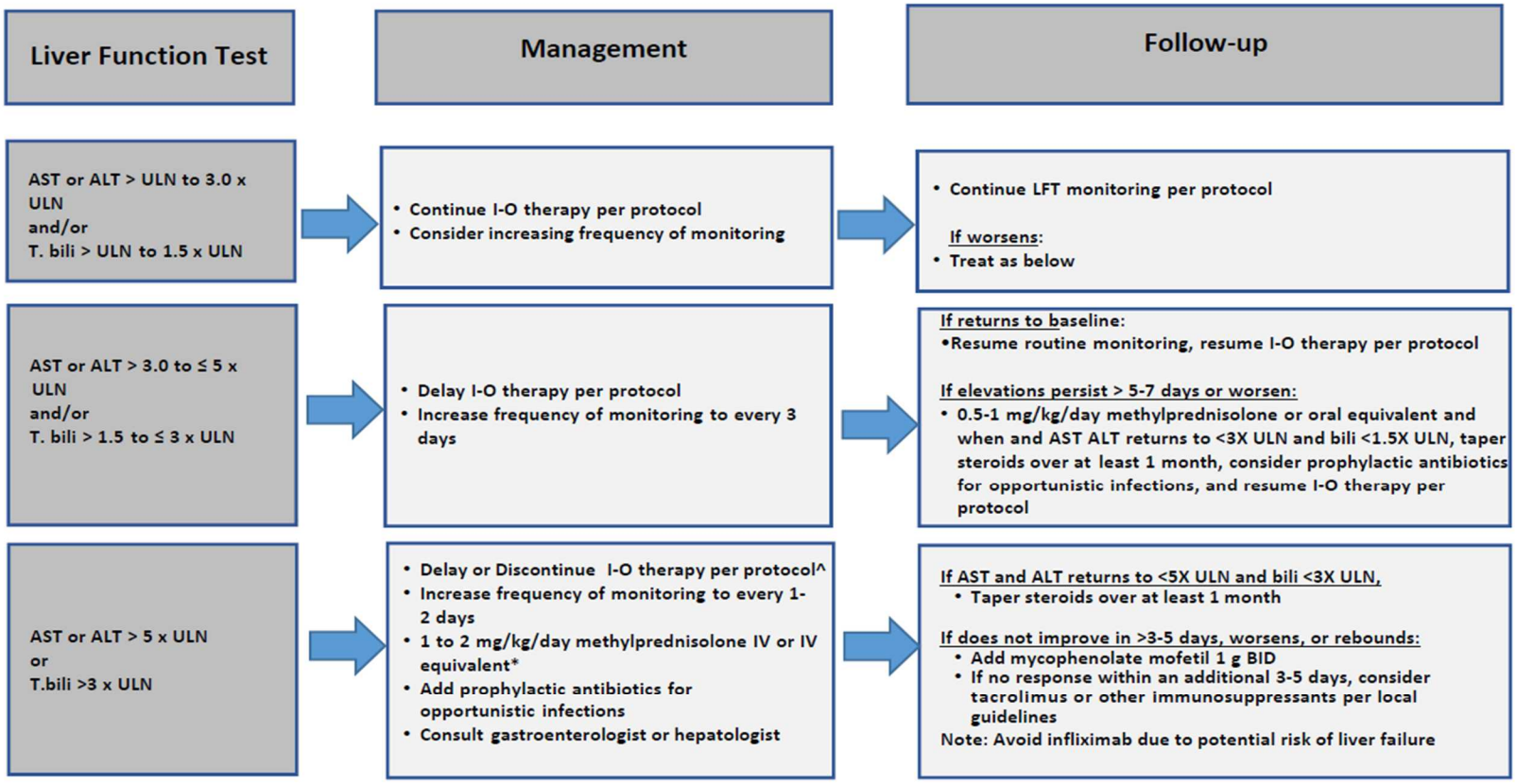
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Evaluate with imaging and pulmonary consultation.



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

Hepatic Adverse Event Management Algorithm

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



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
^ Please refer to protocol dose delay and discontinue criteria for specific details.
*The recommended starting dose for AST or ALT > 20 x ULN or bilirubin >10 x ULN is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Adverse Event Management Algorithm

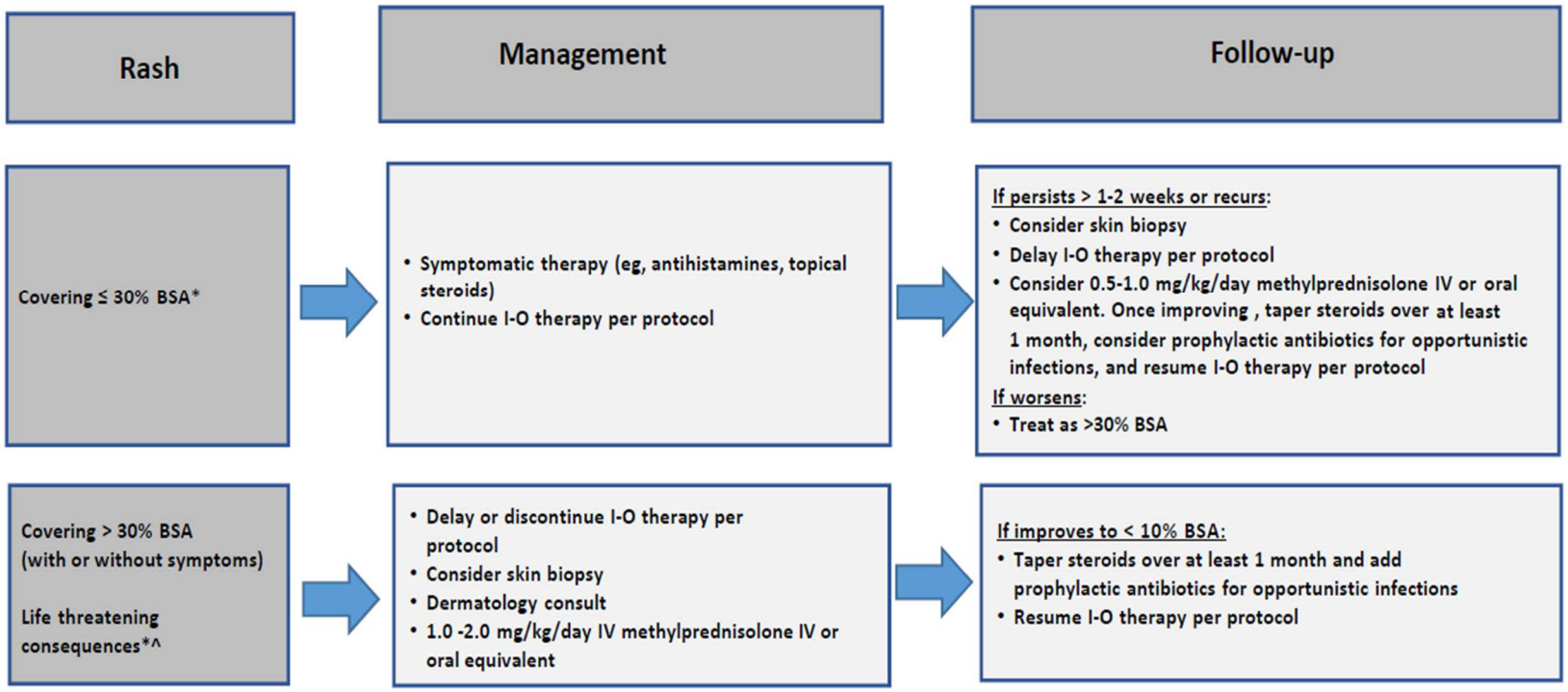
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider visual field testing, endocrinology consultation, and imaging.

Endocrinopathy	Management	Follow-up
Asymptomatic TSH abnormality or Hyperglycemia requiring no medical intervention	• Continue I-O therapy per protocol • If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: o include fT4 at subsequent cycles as clinically indicated; o consider endocrinology consult	• Monitor TSH as per protocol • Monitor blood sugar • If symptomatic or blood sugar requiring initiation of treatment or change in management, manage as below
Symptomatic endocrinopathy or hyperglycemia requiring initiation of treatment or change in daily management or work up	• Evaluate endocrine function; consider endocrinology consult • Consider pituitary scan Symptomatic with abnormal lab/pituitary scan: • Delay I-O therapy per protocol • 1-2 mg/kg/day methylprednisolone IV or PO equivalent for hypophysitis • Initiate appropriate hormone/medical therapy No abnormal lab/pituitary MRI scan but symptoms persist: • Continue IO therapy. Repeat labs in 1-3 weeks /MRI in 1 month Hyperglycemia: Screen for Diabetic Ketoacidosis (DKA). If negative, continue IO and treat diabetes. If DKA hold IO, admit, manage DKA. Steroids not recommended for DKA/hyperglycemia	If improves (with or without hormone replacement): • Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections • Resume I-O therapy per protocol • Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	• Delay or discontinue I-O therapy per protocol • Rule out sepsis • Stress dose of IV steroids with mineralocorticoid activity • IV fluids • Consult endocrinologist	• Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component • If adrenal crisis resolves and patient is adequately controlled with physiologic hormone replacement, patient can resume IO therapy per protocol.

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

Skin Adverse Event Management Algorithm

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



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

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

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

Neurological Adverse Event Management Algorithm

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

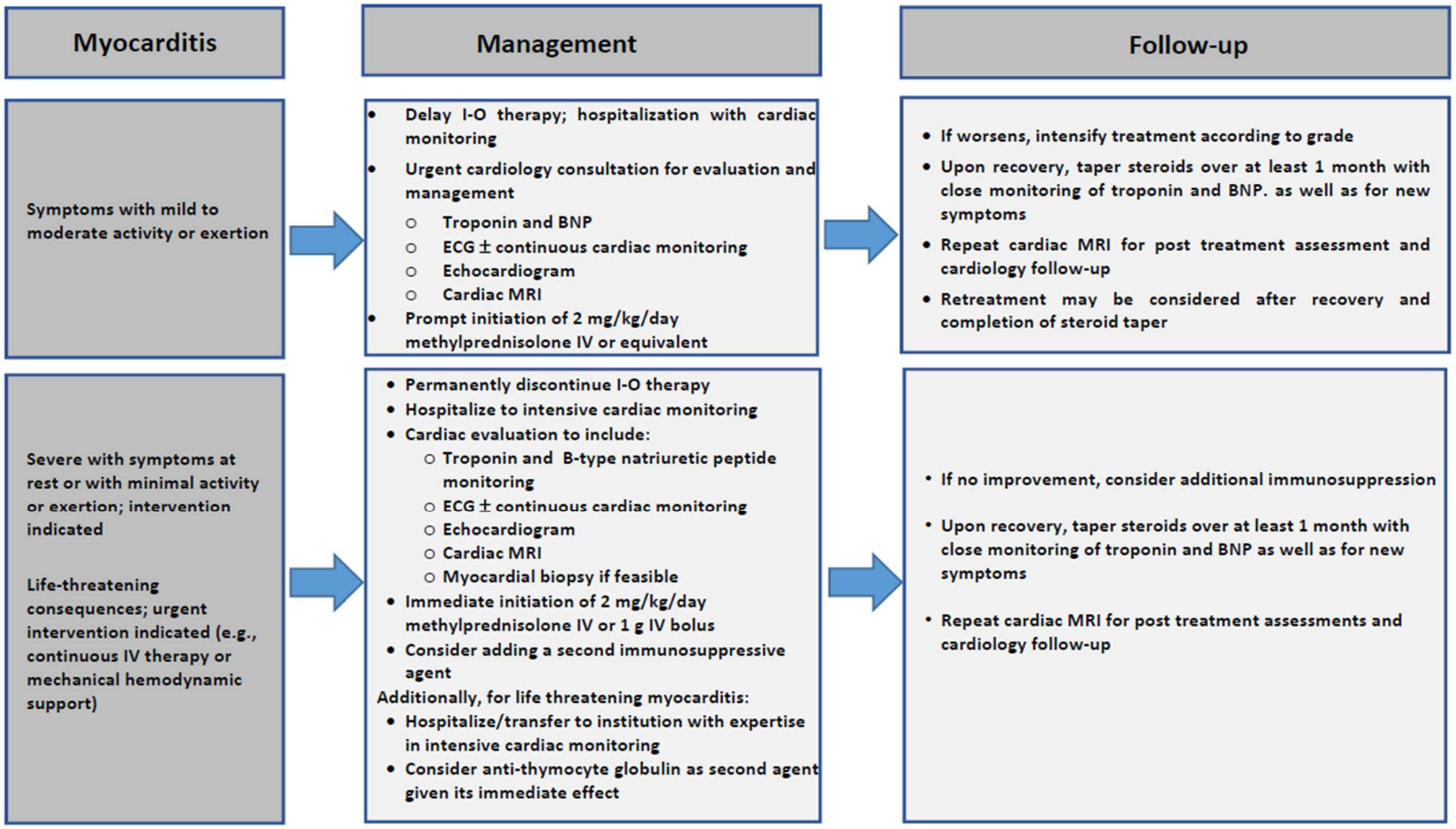
Grade of Neurological Toxicity (NCI CTCAE v5)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol • Discontinue I-O for select AEs^	• Continue to monitor per protocol. If worsens: • Treat as Grade 2 or Grade 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Discontinue I-O for select AEs^ • Consider neurology consult • Treat symptoms per local guidelines • Consider 0.5 to 1 mg/kg/day methylprednisolone IV or PO equivalent	If returns to baseline: • Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1-2 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

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

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

Myocarditis Adverse Event Management Algorithm

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



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

APPENDIX 7 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 < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, inflammatory breast disease, lymphangitic involvement of 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 (< 10 mm 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

[1] 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.

REFERENCES

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