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Clinical Protocol CA2099NC / INCB 24360-309 / NCT03348904

A Phase 3, Randomized, Global Trial of Nivolumab and Epacadostat with Platinum Doublet Chemotherapy versus Platinum Doublet Chemotherapy in First-line Treatment of Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC)

ECHO 309, **E**pacadostat **C**linical Development in **H**ematology and **O**ncology

Check**M**ate **9NC**, **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation

Revised Protocol Number: 01

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(In collaboration with Bristol-Myers Squibb Research and Development)

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This study is co-funded by Incyte and Bristol-Myers Squibb Research and Development and will be executed by Bristol-Myers Squibb Research and Development on behalf of the sponsor, Incyte Corporation.

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

OVERALL RATIONALE FOR DRAFT REVISED PROTOCOL 01:

The CA2099NC revised protocol complies with the [redacted] to require ALK and ROS1 testing and to identify expected toxicities from study drugs.

SUMMARY OF KEY CHANGES FOR DRAFT REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2 Schedule of Assessments	ALK and ROS1 rearrangement tests are required as part of inclusion/exclusion criteria	ALK and ROS1 testing are required [redacted]
Section 6.2 Exclusion Criteria	Exclusion criteria 1b) was modified to exclude ALK and ROS1 rearrangements.	Exclusion criteria was updated [redacted]
[redacted]		
Appendix 12	Identify expected toxicities from study drugs	Appendix table added [redacted]
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized

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1 SYNOPSIS

Protocol Title: A Phase 3, Randomized, Global Trial of Nivolumab and Epacadostat with Platinum Doublet Chemotherapy versus Platinum Doublet Chemotherapy in First-line Treatment of Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC)

ECHO 309. **E**pacadostat **C**linical Development in **H**ematology and **O**ncology

CheckMate 9NC, **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation

Study Phase: 3

Rationale: Stage IV non-small cell lung cancer (NSCLC) patients have limited treatment options. Despite treatment with platinum chemotherapy, the standard of care for first-line therapy for patients with metastatic NSCLC, median survival is approximately 10 months and 5-year survival rate is less than 5%. Blockade of immune-checkpoint pathways is now an important therapeutic modality for treatment of NSCLC cancer as demonstrated by the clinical utility of PD-1/PD-L1 antibodies. However, multiple immune inhibitory mechanisms occur concurrently within the tumor microenvironment suggesting that combination therapies may be required for optimal therapeutic benefit. Ongoing studies are exploring combinations of checkpoint inhibitors as well as combinations of checkpoint inhibitors with chemotherapy. The indoleamine-2,3-dioxygenase (IDO) pathway is a distinct key immune regulatory pathway responsible for induction and maintenance of tumor tolerance. Small molecule inhibitors of IDO1 may provide an innovative method to treat advanced malignancies in combination with other anticancer strategies. IDO1 inhibitors are currently being broadly investigated in combination with immune-based therapies and chemotherapy in multiple tumor types.

This study is being conducted to evaluate the combination of nivolumab, a PD-1 antibody, plus epacadostat, an inhibitor of IDO1, in combination with platinum chemotherapy compared with platinum chemotherapy alone, in participants with treatment naïve, Stage 4, or recurrent NSCLC. A third arm of nivolumab plus placebo for epacadostat in combination with platinum chemotherapy will allow estimation of the contribution of components.

Study Population: Participants with treatment naïve, Stage 4 or recurrent NSCLC; unresectable after standard-of-care therapy may enroll.

Key Inclusion Criteria

- Histologically confirmed stage IV or recurrent NSCLC per the 8th International Association for the Study of Lung Cancer (IASLC) of squamous or non-squamous histology
- No prior systemic therapy (including targeted therapy for EGFR and ALK/ROS1) given as primary therapy for advanced disease
- Participants with tumors not expressing PD-L1 or expressing PD-L1 at levels between 1 and 49% assessed using validated test at central laboratory in fresh or recent archival tissue obtained no greater than 3 months prior to study enrollment

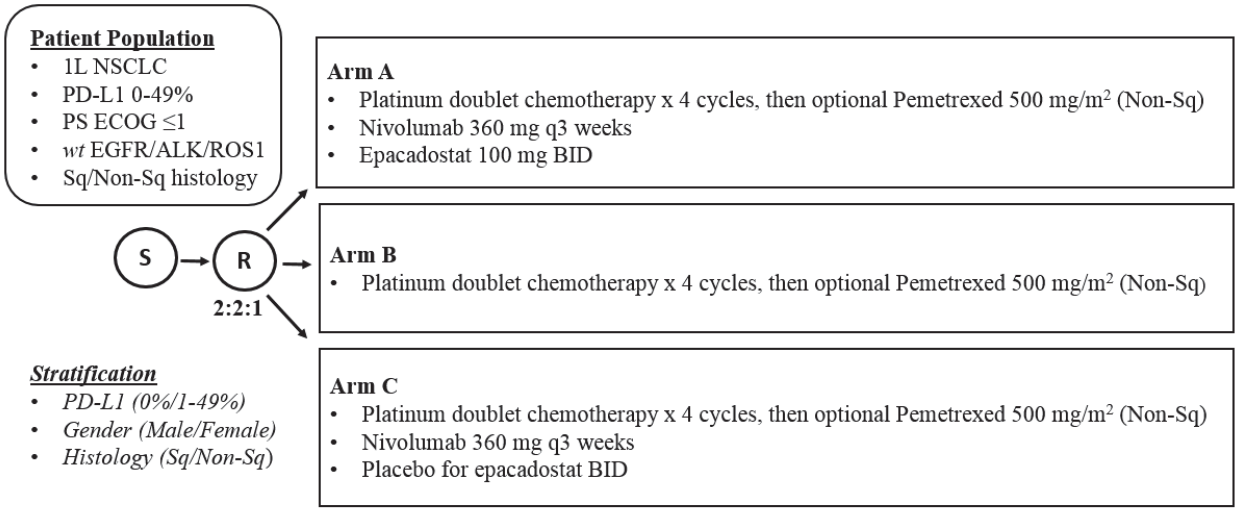
- ECOG Performance Status of ≤ 1
- Measurable disease by CT or MRI per RECIST 1.1 criteria
- **Key Exclusion Criteria**
- Participants with known EGFR mutations, ALK translocations, or ROS1 rearrangements, which are sensitive to available targeted inhibitor therapy
- Participants with interstitial lung disease or active, non-infectious pneumonitis including symptomatic and/or requiring treatment
- Unevaluable PD-L1status or PD-L1 status of ≥ 50% by a central laboratory
- Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, or hypothyroidism only requiring hormone replacement, skin disorders not requiring systemic treatment are permitted to enroll.
- Participants with untreated CNS metastases. Participants are eligible if CNS metastases have been adequately treated and have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to randomization.

Objectives and Endpoints:

Objective	Endpoint
Primary	
To compare overall survival (OS) and progression-free survival (PFS) per blinded independent central review (BICR) of nivolumab plus epacadostat in combination with chemotherapy (Arm A) to chemotherapy (Arm B) in treatment naïve, Stage 4 or recurrent NSCLC participants whose tumors express PD-L1 at 0 to 49%.	OS PFS assessed by BICR
Secondary	
To compare objective response rate (ORR) and to estimate of duration of response (DOR) as assessed by BICR of nivolumab plus epacadostat in combination with chemotherapy (Arm A) to chemotherapy (Arm B) in treatment naïve, Stage 4 or recurrent NSCLC participants whose tumors express PD-L1 at 0 to 49%.	ORR and DOR assessed by BICR
To estimate OS, and PFS, ORR, and DOR per BICR assessment, of nivolumab and placebo for epacadostat in combination with chemotherapy (Arm C) in treatment naïve, Stage 4 or recurrent NSCLC participants whose tumors express PD-L1 at 0 to 49%.	OS PFS, ORR, and DOR per BICR assessment

Objective	Endpoint
[redacted]	

Overall Design:



Co-Primary Endpoints: OS and PFS (Arm A vs Arm B)

Protocol CA2099NC/INCB 24360-309 is a phase 3, randomized, 3 arm trial in participants ≥ 18 years old with treatment naïve, Stage 4 or recurrent NSCLC. Participants must have tumors not expressing PD-L1 (0%) or expressing PD-L1 at levels between 1 and 49% for whom platinum doublet chemotherapy is standard therapy. Patients with PD-L1 levels of ≥ 50% are eligible to receive pembrolizumab monotherapy as first line treatment for their disease and are therefore excluded from the study.

The primary objective of the study is to compare PFS and OS in participants treated with nivolumab plus epacadostat in combination with platinum doublet chemotherapy versus platinum doublet chemotherapy alone. A third arm will assess the efficacy of nivolumab plus placebo for epacadostat in combination with platinum doublet chemotherapy in order to estimate the contribution of components. Participants will be stratified by PD-L1 status (0% and 1-49%), gender (male and female), and histology (squamous and non-squamous).

The study will be open labelled, except that administration of epacadostat will be double blinded between Arm A and Arm C. Epacadostat will be administered to all participants in Arm A; placebo for epacadostat will be administered to all participants in Arm C. All participants in Arms A and C will receive unblinded nivolumab. All participants in the study (Arms A, B, and C) will receive platinum doublet chemotherapy.

Platinum doublet chemotherapy will be based on tumor histology, for up to 4 cycles:

- Squamous histology: gemcitabine with cisplatin, or gemcitabine with carboplatin, or paclitaxel with carboplatin

- Non-squamous histology: Pemetrexed with either cisplatin or carboplatin; optional continuation maintenance therapy with pemetrexed

Treatment Arms and Duration: Approximately 630 participants will be randomized into 1 of the 3 treatment arms in a 2:2:1 ratio in the study. These arms include:

- Arm A: nivolumab plus epacadostat in combination with platinum doublet chemotherapy (n = 252)
- Arm B: platinum doublet chemotherapy (n = 252)
- Arm C: nivolumab plus placebo for epacadostat in combination with platinum doublet chemotherapy (n = 126)

Participants will undergo tumor assessments by CT or MRI every 6 weeks (±7 days) from the date of randomization until Week 48 and then every 12 weeks (±7 days) until progression or treatment is discontinued, whichever occurs later. Tumor scans will be evaluated by blinded independent central review (BICR). [redacted]

The post-treatment follow-up begins when the decision to discontinue a participant from all treatment is made. Participants without BICR-confirmed disease progression will continue to have tumor assessments (if clinically feasible) according to the schedule in Table 2-3.

Participants will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after the last dose of study medication.

After completion of the first 2 follow-up visits, participants will be followed every 3 months for survival. Survival follow-up visits may be performed by phone contact or office visit. BMS may request that survival data be collected on all randomized participants outside of the protocol-defined window. At that time of this request, each participant will be contacted to determine their survival status unless the participant had withdrawn consent for all contact.

The total duration of the study from start of randomization to final analysis of PFS is expected to be approximately 25 months, assuming 18 months accrual duration. Final analysis of OS is expected to be 38 months after the start of randomization. The study will end once survival follow-up has concluded.

Number of Participants: Approximately 900 participants will be screened and approximately 630 participants will be randomized.

Study treatment:

Study Drug for CA2099NC / INCB 24360-309		
Medication	**Potency**	**IP/Non-IP**
Nivolumab	10 mg/ml	IP
Carboplatin	10 mg/ml	IP
Cisplatin	1 mg/ml	IP
Epacadostat	100 mg and 25 mg tablets	IP
Epacadostat matching placebo (100 mg and 25 mg tablets)	Not applicable	IP
Gemcitabine	1000 mg/vial	IP
Pemetrexed	500 mg/vial	IP
Paclitaxel	100 mg/vial (6mg/mL)	IP

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA2099NC / INCB 24360-309)

Procedure	Screening Visit[a]	Notes All windows are based on calendar days
Eligibility Assessments		
Informed Consent	X	Register in Interactive Response system to obtain participant number.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to randomization.
Medical History	X	All medical history relevant to the disease under study.
Tumor Sample Submission	X	See Section 9.8.3 Recent sample or archival (archival tissue is to be obtained within 3 month prior to enrollment). Formalin-fixed paraffin-embedded (FFPE) tumor tissue block (adequate tissue block for 25 FFPE slides) or a minimum of 25 unstained tumor tissue sections are acceptable. Specimens must be tested by central laboratory to determine PD-L1 status. Samples should be sent to the central lab at least 7-10 prior to randomization. Results must be available prior to randomization in Interactive Response Technology (IRT).
EGFR Mutation Status ALK and ROS1 Translocation Status	X	To be performed prior to randomization for all **non-squamous** participants. • EGFR mutation, ALK, and ROS1 tests should be done locally. • EGFR mutation test is mandatory for participants with non-squamous histology, and to be performed using PCR-based assay or next generation sequencing from tumor tissue. Tests other than PCR or next generation sequencing will be requested to repeat using PCR or next generation sequencing-based methods. • ALK and ROS1 rearrangement tests are mandatory for participants with non-squamous histology. Participants with known ALK/ROS1 translocations which are sensitive to available targeted inhibitor therapy are excluded. • If EGFR, ALK, and/or ROS1 tests cannot be performed locally, additional slides may be required for central lab testing.
Body Imaging	X	See Section 9.1.1 Must be performed within 28 days prior to randomization

Table 2-1: Screening Procedural Outline (CA2099NC / INCB 24360-309)

Procedure	Screening Visit[a]	Notes All windows are based on calendar days
Brain Imaging	X	See Section 9.1.1 MRI of the brain without and with contrast is required for all participants within 28 days prior to randomization. CT of the brain (with and without contrast) can be performed if MRI is contraindicated.
Safety Assessments		
Targeted Physical Examination, Measurements, Vital Signs, and Performance Status	X	Includes height, weight, BMI, Performance Status (Appendix 5), BP, temperature, and HR. Within 14 days prior to randomization.
Assessment of Signs and Symptoms	X	Within 14 days prior randomization
Serious Adverse Events Assessment	X	Serious Adverse Events from time of consent. See Section 9.2
Concomitant Medication Use	X	Within 14 days prior to randomization. Document vaccine and antibiotic use within 30 days prior to randomization.
Laboratory/Other Tests		
Hematology, Chemistry, Serology, Coagulation		Must be performed within 14 days prior to randomization. Please see Section 9.4.2.1 for clinical safety laboratory assessments.
Pregnancy test	X	WOCBP only: Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done at screening visit and within 24 hours of first dose of study therapy.
ECG (12-lead)	X	12-lead ECG required at Screening. Clinically significant abnormal ECG findings (by investigator judgment) will require triplicate ECGs. See Section 9.4.2.2
Study Treatment		
Randomize	X	PD-L1 status must be confirmed as 0 to 49% prior to randomization. Participants must begin study treatment within 3 days of randomization.

Abbreviations: BMI, body mass index; BP, blood pressure; C1D1, Cycle 1, Day 1; C2D1, Cycle 2, Day 1; CBC, complete blood count; ECG, electrocardiogram; ; HR, heart rate; [redacted]; SAE, serious adverse event; WOCBP, women of childbearing potential.

[a] 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.

Table 2-2: Short-term Procedural Outline (CA2099NC / INCB 24360-309)

Procedure	Cycle 1 Day 1 (Cycle = 21 days)	During Each Subsequent Treatment Visit[a] (Cycle = 21 days)	Notes[b]
Study Drug			
Dispense Study Drug	X	X	First dose to be administered within 3 calendar days of randomization. For participants with squamous cell histology on gemcitabine, gemcitabine is dispensed and administered on Day 1 and Day 8 of each 21 day cycle, through cycle 4.
Safety Assessments			
Targeted Physical Examination, Vital Signs, Performance Status	X	X	Weight, BP, HR, Temperature, and Performance Status (see Appendix 5). Targeted physical examination as clinically indicated.
Adverse Event Assessments	Continuously		Record at each visit. SAEs should be approved in RAVE within 5 days from entry.
Concomitant Medication Review	Continuously		Record at each visit.
Laboratory Tests			
Hematology, Chemistry, Coagulation	X	X	Refer to Section 9.4.2 for clinical safety laboratory assessments
Pregnancy Test	X	X	WOCBP only: Serum or urine pregnancy test (minimum sensitivity of 25 IU/L or equivalent units of HCG).
ECG (12-lead)	X	See notes	Pre-dose 12-lead ECG on C1D1, C2D1, and end of treatment. Clinically significant abnormal ECG findings (by investigator judgment) will require triplicate ECGs. See Section 9.4.2.2
Efficacy Assessments			
Body Imaging	See notes		See Section 9.1.1 Tumor assessments should occur every 6 weeks (± 7 days) until Week 48, then every 12 weeks (± 7 days) from randomization until BICR confirmed disease progression, lost to follow-up, or withdrawal of consent.

Table 2-2: Short-term Procedural Outline (CA2099NC / INCB 24360-309)

Procedure	Cycle 1 Day 1 (Cycle = 21 days)	During Each Subsequent Treatment Visit[a] (Cycle = 21 days)	Notes[b]
Brain Imaging	See notes		See Section 9.1.1. Participants with a history of brain metastasis should have surveillance MRI approximately every 12 weeks (± 7 days) from randomization or sooner if clinically indicated.
[redacted]			

Abbreviations: BMI, body mass index; BP, blood pressure; C1D1, Cycle 1, Day 1; C2D1, Cycle 2, Day 1; CBC, complete blood count; ECG, electrocardiogram; HR, heart rate; [redacted]; SAE, serious adverse event; WOCBP, women of childbearing potential.

[a] If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs (except for Efficacy Assessments [Body Imaging and Brain Imaging])

[b] 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.

Table 2-3: Long-term Procedural Outline (CA2099NC / INCB 24360-309)

Procedure	Follow-Up Visit 1 and 2[a]	Survival Follow-up[b]	Notes[c]
Safety Assessments			
Targeted Physical Examination	X		As clinically indicated
Adverse Events Assessment	Continuously		Record at each visit. See Section 9.2 Nonserious AEs are collected for 100 days post-treatment. SAEs should be approved in RAVE within 5 days from entry.
Review of Concomitant Medications	Continuously		Record at each visit. Document subsequent cancer therapy
Laboratory Tests			
Hematology, Chemistry, Coagulation	X		At Follow-up visit 1. Repeat at Follow-up Visit 2 if toxicities are present. Refer to Section 9.4.2 for clinical safety laboratory assessments
Pregnancy Test	See notes		WOCBP only: Once every 4 weeks for 5 months after the last dose of nivolumab.
Efficacy Assessment			
Body Imaging	See notes		See Section 9.1.1 • Only for participants without BICR confirmed progression. • Radiographic assessments for participants who have not experienced BICR-confirmed PD should be obtained every 6 weeks (± 7 days) from randomization until Week 48 and not delayed until follow-up visits 1 and 2. • After week 48 and if follow-up visits 1 & 2 have been completed, scans should be obtained every 12 weeks (±7days) until BICR confirmed PD, lost to follow-up, or withdrawal of consent.
Brain Imaging	See notes		See Section 9.1.1. Participants with a history of brain metastasis should have surveillance MRI approximately every 12 weeks (± 7 days) from randomization or sooner if clinically indicated.
[redacted]			

Table 2-3: Long-term Procedural Outline (CA2099NC / INCB 24360-309)

Procedure	Follow-Up Visit 1 and 2[a]	Survival Follow-up[b]	Notes[c]
[redacted]			
Participant Survival Status			
Survival Status	X	X	During safety follow-up and every 3 months during survival phase; may be accomplished by visit, phone contact or email, to include assessment of subsequent anti-cancer therapy

Abbreviations: BMI, body mass index; BP, blood pressure; C1D1, Cycle 1, Day 1; C2D1, Cycle 2, Day 1; CBC, complete blood count; ECG, electrocardiogram: HR, heart rate; [redacted]; SAE, serious adverse event; WOCBP, women of childbearing potential.

[a] Participants must be followed for at least 100 days after last dose of study treatment. Follow-up visit 1 (FU1) should occur 30 days from the last dose (± 7) days or can be performed on the date of discontinuation if that date is greater than 42 days from last dose. Follow-up visit 2 (FU2) occurs approximately 100 days (± 7 days) from last dose of study drug. Both Follow Up visits should be conducted in person.

[b] Survival Follow-up visits to occur every 3 months (± 14 days) from Follow-up Visit 2. Survival visit may be conducted in person or by telephone. BMS/Incyte may request that survival data be collected on all randomized participants outside of the 3 month specified window. At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact.

[c] 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.

3 INTRODUCTION

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality worldwide, accounting for approximately 18% of all cancer deaths.[1] Platinum-based doublet chemotherapy with paclitaxel and pemetrexed is a standard of care first-line therapy for NSCLC patients (without sensitizing epidermal growth factor receptor [EGFR] mutations or anaplastic lymphoma kinase [ALK] translocation) with squamous and nonsquamous histologies, respectively.[2],[3] Bevacizumab and maintenance therapy with pemetrexed have improved clinical outcomes,[4,5,6], but most participants will eventually progress.[7] NSCLC has a median survival of approximately 10 months, and a 5-year survival rate of less than 5%.[3]

Targeting the immune system is a proven and effective approach for the treatment of cancer, and immunotherapy is now an accepted therapy in several tumor types. The blocking of immune cell co-inhibitory receptors such as cytotoxic T-lymphocyte–associated protein-4 (CTLA-4) by ipilimumab; programmed cell death protein 1 (PD-1) by nivolumab, pembrolizumab, and avelumab; and programmed cell death ligand 1 (PD-L1) by atezolizumab provide a critical mechanism for activating the host immune response against the tumor.[7]

Nivolumab is a fully human immunoglobulin (Ig) G4 antibody that blocks the programmed death receptor-1 (PD-1). Nivolumab is approved in the U.S. and Europe to treat metastatic NSCLC in patients with progression on or after platinum chemotherapy.

The approval of nivolumab in squamous NSCLC was based on the results of the CheckMate 017 (CA209017) study, a randomized trial of nivolumab versus docetaxel in patients who had disease progression during or after first-line chemotherapy. The median OS for participants in the nivolumab arm was 9.2 months, compared to 6 months for those in the docetaxel arm (HR = 0.59). Improvement in OS and PFS was observed for nivolumab regardless of PD-L1 expression, though there was a trend for better efficacy for those with PD-L1 expressing tumors.[8] Treatment-related AEs of Grade 3 or 4 were reported in 7% of patients in the nivolumab group, compared with 55% of those in the docetaxel group.

The approval of nivolumab in non-squamous NSCLC was based on a second phase 3 study, CheckMate 057 (CA209057), of nivolumab versus docetaxel in participants with previously-treated disease.[9] The median OS for participants in the nivolumab arm was 12.2 months versus 9.4 months for those in the docetaxel arm (hazard ratio [HR] = 0.59). Interaction p-values, reported for PD-L1 expression subgroups by each of the predefined expression levels, suggested a clinically important signal of a predictive association. Treatment-related AEs of Grade 3 or 4 were reported in 10% of patients in the nivolumab group, compared with 54% of those in the docetaxel group.

Superior activity of PD-1-directed monotherapy over platinum chemotherapy regimen in participants with previously untreated advanced NSCLC was demonstrated in an open-label phase 3 study with the PD-1 antibody, pembrolizumab (KEYNOTE-024).[10] Eligibility in this study was restricted to participants with PD-L1 expression ≥ 50% on tumor cells. The pembrolizumab monotherapy group showed a significantly longer median PFS of 10.3 months compared with

6.0 months with chemotherapy group (HR= 0.50). Estimated OS at 6 months was 80% in the pembrolizumab group versus 72% in the chemotherapy group (HR for death = 0.60). The ORR was greater in participants treated with PD-1 inhibitor versus chemotherapy (45% vs 28%). Treatment-related AEs of any grade were less frequent (occurring in 73% vs 90% of participants), as were ≥ Grade 3 treatment-related AEs (27% vs 53%).

Nivolumab as monotherapy versus chemotherapy in patients with advanced NSCLC was evaluated in CheckMate 026 (CA209026), a phase 3, open-label, randomized study. Patients enrolled in the trial had received no prior systemic treatment for advanced disease and tested positive for PD-L1 expression (≥1%).[11] The trial randomized patients to receive either nivolumab or investigator's choice of platinum doublet chemotherapy in squamous patients and non-squamous patients. The primary endpoint of PFS was assessed in patients with ≥ 5% PD-L1 tumor expression. The study did not meet its primary objective of demonstrating a statistically significant improvement in PFS for nivolumab versus chemotherapy. PFS was 4.2 months in the nivolumab arm versus 5.9 months in the chemotherapy arm (HR = 1.15). The OS was similar in both arms (nivolumab 14.4 months versus chemotherapy 13.2 months, HR = 1.02), despite 60% of participants in the chemotherapy arm subsequently receiving nivolumab. A full evaluation of the CheckMate 026 data remains in progress to understand the difference between the KEYNOTE-024 and CheckMate 026 studies.

The IDO1 pathway is another key regulatory component responsible for the induction and maintenance of tumor immune tolerance. IDO1-driven oxidation of tryptophan results in a strong inhibitory effect on the development of T-cell–mediated responses by blocking T-cell activation and inducing T-cell apoptosis.[12] Both the reduction in local tryptophan levels and the production of tryptophan catabolites that are inhibitory to cell proliferation contribute to the immunosuppressive effects.[13] IDO1 activity also promotes the differentiation of naive T cells to cells with a regulatory phenotype (Treg).[14] Since increased Treg activity has been shown to promote tumor growth, and Treg depletion has been shown to allow an otherwise ineffectual antitumor immune response to occur,[15] IDO1 expansion of Tregs may provide an additional mechanism whereby IDO1 could promote an immunosuppressive environment. Preclinical studies demonstrate that IDO1 inhibition dramatically increases the efficacy of various chemotherapeutic agents (eg, platinum compounds, taxane derivatives, and cyclophosphamide) without increased toxicity.[16] Clinically, IDO1 appears to be chronically activated in participants with cancer, and IDO1 activation correlates with more extensive disease.[17,18] IDO1 has subsequently been found to be overexpressed by a wide variety of human tumor cell types, as well as by the dendritic cells (DCs) that localize to the tumor-draining lymph nodes.[19,20] Increased expression of IDO1 in tumor cells has been shown to be an independent prognostic variable for reduced OS in participants with melanoma and ovarian, colorectal, and pancreatic cancer. [21,22,23,24,25]

Epacadostat (INCB 24360) is an experimental potent and selective inhibitor of IDO1. Epacadostat is being developed for the treatment of malignant diseases. The pharmacology, PK, and toxicology have been extensively characterized in nonclinical studies. The safety and efficacy of epacadostat

is being explored in clinical studies as monotherapy and in combination with immunotherapies and chemotherapy (see Epacadostat Investigator Brochure).

IDO and the PD-1 ligand, PD-L1, have been shown to be co-expressed in multiple cancer types and correlate with poor prognosis. Since multiple immune mechanisms are present concurrently within the tumor microenvironment, combination therapies may be required for optimal therapeutic effect.[26] Data supporting epacadostat combined with nivolumab in participants with advanced cancers, including NSCLC and other solid tumors, is reported in a phase 1/2 dose escalation and cohort expansion trial (ECHO-204; INCB 24360 204). In the phase 1 dose escalation period (n=36), participants received epacadostat 25, 50, 100, or 300 mg twice daily (BID) in combination with nivolumab 3 mg/kg every 2 weeks; in the phase 2 cohort expansion (205 patients), participants with advanced cancers, including NSCLC and other solid tumors, received epacadostat 100 mg or 300 mg BID in combination with nivolumab 240 mg every 2 weeks. Safety and tolerability was assessed in participants receiving ≥ 1 epacadostat and nivolumab dose.[27] The combination was generally well tolerated up to the maximum 300 mg epacadostat dose. No DLT was observed in phase 1. Most common treatment-related AEs in patients treated with epacadostat were rash, fatigue, and nausea. Rash was the most common grade ≥ 3 treatment-related AE. Treatment-related AEs led to discontinuation in 7% (100 mg BID epacadostat) and 13% (300 mg BID epacadostat) of patients. There were no treatment-related deaths.

Chemotherapy has largely been thought to be immunosuppressive and exert its effect via direct cytotoxicity. However, there is an emerging body of evidence to suggest that some chemotherapies may influence an immune response to tumors via induction of immunogenic cell death (ICD), elimination of immunosuppressive cells, or sensitization of tumor cells to immune effector cells.[28] Platinum agents have demonstrated immunogenic effects via ICD and enhancement of effector immune response through PD-L1 receptor expression.[29] Paclitaxel and 5-FU have been shown to restore antitumor activity of CD8+ T cells.[30,31]

Collectively, these data show that the immunogenic effects of conventional chemotherapy and rapid emergence of chemotherapy resistance may present as a good rationale to combine chemotherapy doublets with immunotherapy, particularly checkpoint inhibitors.[32,33] Combining immune checkpoint inhibitors with platinum doublets may also provide a rapid and large initial response through the action of the cytotoxic chemotherapy, thus releasing tumor antigens in the tumor microenvironment to be recognized by the immune system.

In the phase 1 CheckMate 012 study, 56 patients received first-line nivolumab (5 or 10 mg/kg) plus platinum doublet chemotherapy concurrently every 3 weeks for 4 cycles followed by nivolumab alone until progression or unacceptable toxicity. Platinum doublet regimens included gemcitabine-cisplatin (squamous histology), pemetrexed-cisplatin (non-squamous histology) or paclitaxel-carboplatin (all histologies).[33] No dose-limiting toxicities occurred during the first 6 weeks of treatment. The most commonly reported (≥ 30% of patients) treatment-related AEs of any grade were fatigue, nausea, decreased appetite, and alopecia. The most common (≥ 5% of

patients) treatment-related Grade 3 or 4 AEs were pneumonitis, fatigue, and acute renal failure. A greater proportion of patients reported onset of treatment-related select AEs during the combination period (2 to 29%) than during nivolumab monotherapy (2 to 12%). Treatment-related AEs led to discontinuation of all study therapy in 21% of patients. Grade 3 or 4 treatment-related AEs led to discontinuation in 14% of patients. The observed frequencies of immune-related AEs with combination therapy affecting the skin, gastrointestinal (GI), renal, and pulmonary organs was greater than expected with single-agent nivolumab. However, all select AEs were effectively managed with corticosteroids, and none resulted in death.

Confirmed ORRs ranged from 33% to 47%. An additional 27 to 58% of patients across all arms had BOR of stable disease, with 7 to 33% of patients had stable disease lasting ≥ 21 weeks. Median PFS ranged from 4.8 to 7.1 months; median OS ranged from 11.6 to 19.2 months. Duration of response was similar in patients regardless of PD-L1 levels; no clear association was observed between PD-L1 levels and PFS or OS.

Results from the open label cohort (123 participants), phase 2 KEYNOTE-021study investigating the efficacy of the combination of first-line PD-1 inhibition (pembrolizumab) and platinum doublet chemotherapy (carboplatin-pemetrexed) in participants with advanced NSCLC (non-squamous histology) have been reported.[34] The chemotherapy-immunotherapy combination showed a significant improvement in ORR with a median follow up of 19 months: 57% in the pembrolizumab plus chemotherapy regimen group versus 32% in the chemotherapy regimen group. Median PFS was 19 months for the pembrolizumab plus chemotherapy arm and 8.9 months for chemotherapy alone. Although sample size for individual PD-L1 subgroups were small, there was a higher proportion of responses in patients with PD-L1 expression of ≥ 50%. A trend toward improvement in OS was observed in the pembrolizumab plus chemotherapy arm: the combination was associated with a 41% reduction in the risk of death (HR=0.59). The median OS was not reached in the pembrolizumab plus chemotherapy group, compared to 20.9 months in the chemotherapy group.[35]

The incidence of ≥ Grade 3 treatment-related adverse events was higher in the pembrolizumab plus chemotherapy group (39%), compared with the chemotherapy group (26%), but this had no impact on the discontinuation rate (10% and 13%, respectively). The most common ≥ Grade 3 treatment-related adverse events in the pembrolizumab plus chemotherapy group were anemia and decreased neutrophil count. In the chemotherapy alone group, the most common ≥ Grade 3 events were anemia and decreased neutrophil count, pancytopenia, and thrombocytopenia. There were 3 treatment-related deaths: 1 in the pembrolizumab plus chemotherapy group and with 2 in the chemotherapy group. The incidence of potentially immune-mediated adverse events in the pembrolizumab plus chemotherapy group (22%) was comparable to that noted for pembrolizumab monotherapy in other studies. Most immune-mediated adverse events were of Grade 1 or 2 severity and were manageable without treatment discontinuation.[36]

[redacted]

3.1 Study Rationale

Both PD-1 and IDO1 have been shown to suppress T-cell–mediated antitumor immunity, and IDO1 and the PD-1 ligand PD-L1 have been shown to be co-expressed in multiple cancer types and to correlate with poor prognosis. Targeting PD-1 assumes that the T cells are essentially exhausted and thus tolerant of the tumor and that this exhaustion may be reversed by blocking PD-1 signaling. Targeting IDO1 may concurrently decrease infiltration of regulatory CD4+ cells and immune suppressive cytokines. This novel combination strategy has strong biologic rationale for a number of solid tumors, including NSCLC, and may augment clinical efficacy above that demonstrated by these agents individually. Combined inhibition of both pathways may therefore lead to greater suppression of anti-tumor immunity and to increased efficacy.

Based on evolving data, it is hypothesized that chemotherapy may modify the immune response to tumours by influencing multiple mechanisms, including inducing of immunogenic cell death, stimulating release of tumour antigens and/or depletion of immuno-suppressive regulatory T-cells.[37,38,39] Therefore, the combination of agents that inhibit PD-1 and IDO1 with chemotherapy

has the potential to provide significantly improved anti-tumor activity, thereby potentially improving the overall prognosis in patients with advanced stage cancers.

Based on the above rationale and the available safety and efficacy data, the proposed phase 3 study will evaluate the combination of nivolumab with epacadostat and chemotherapy compared with chemotherapy as a first-line treatment for treatment naïve, Stage 4 or recurrent NSCLC. A third arm of nivolumab plus placebo for epacadostat in combination with platinum chemotherapy will allow estimation of contribution of components.

3.1.1 Research Hypothesis

Treatment naïve, Stage 4 or recurrent NSCLC participants with PD-L1 expression of 0 to 49% will demonstrate superior PFS and OS with the administration of the combination of nivolumab, epacadostat, and platinum doublet chemotherapy, as compared with chemotherapy alone.

3.2 Background

With the availability of anti-PD-1 agents[40,41], the treatment landscape in recurrent and metastatic NSCLC has changed and future clinical investigations will focus on combinations of checkpoint inhibitors with chemotherapy to achieve improved patient outcomes in NSCLC.

3.2.1 Inhibition of PD-L1 as a Target for Cancer

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response relies on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[42,43,44] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[45] Collectively, these signals govern the balance between T-cell activation and tolerance.

The PD-1 receptor-ligand interaction is a major pathway stimulated by tumors to suppress immune control.[46] The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA 4, ICOS, and BTLA.[47] PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, interferon-γ (IFN-γ) and Bcl-xL. PD-1 expression has also been noted to inhibit T cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[48] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and

dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (EC_{50} 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 ($IC_{50} \pm 1$ nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a CMV re-stimulation assay with human PBMC, the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[49]

For a thorough discussion of chemistry, pharmacology, efficacy, and safety, see the Nivolumab IB.

3.2.2 Inhibition of Indoleamine 2,3-Dioxygenase as a Target for Cancer

Recent interest has focused on the role of IDO1 as a mechanism of induction of tolerance to malignancy.[50] IDO is a heme-containing, monomeric oxidoreductase that catalyzes the degradation of the essential amino acid tryptophan to N-formyl-kynurenine. Kynurenine can be subsequently metabolized through a series of enzymatic steps to nicotinamide adenine dinucleotide. IDO is the first rate-limiting enzyme in one of the breakdown pathways of tryptophan. In another pathway, tryptophan hydroxylase catalysis of tryptophan catabolism leads to the formation of serotonin and melatonin.

The expression and activity profiles of IDO1 are distinct from those of tryptophan dioxygenase, an enzyme predominantly expressed in liver that catalyzes the same enzymatic reaction as IDO1 and maintains proper tryptophan balance in response to dietary uptake. In contrast to tryptophan dioxygenase, IDO1 is expressed in a variety of tissues, with particularly high levels found in areas of contact with potential sources of immune challenge (eg, gut, respiratory tract, placenta, spleen), consistent with a role for regulating tryptophan metabolism in a local microenvironment.[51] Within the immune system, IDO1 activity is specifically induced in cells such as dendritic cells and macrophages at localized sites of inflammation.[52]

The biological relevance of IDO1 inhibition to immune tolerance was first demonstrated when it was shown that treating mice with a small molecule inhibitor of the IDO1 pathway, 1-methyl-tryptophan, could break the tolerogenic state that protects allogeneic concepti from the maternal immune system.[19] A critical role for IDO1 in immunomodulation has been confirmed in numerous animal models, including models of allograft tolerance, inflammation, and cancer. While IDO1 inhibition can exacerbate disease in models of autoimmune disorders, IDO1 null mice show no evidence of susceptibility to developing spontaneous autoimmunity or alterations in immune system development[12], suggesting that IDO1 inhibition, in a therapeutic setting, may produce minimal side effects in participants without pre-existing autoimmune conditions.

Within the context of cancer, there are several lines of evidence to suggest that IDO1 is a key regulator of the immunosuppressive mechanisms responsible for tumor escape from immune surveillance. Several groups have demonstrated that blockade of IDO1 activity can directly influence the ability of tumor-bearing animals to reject tumors.[16,19] In addition, studies with 1-methyl-tryptophan, demonstrate that IDO1 inhibition dramatically increases the efficacy of various chemotherapeutic agents (eg, platinum compounds, taxane derivatives, cyclophosphamide) without increased toxicity.[20] Although the specific mechanisms responsible for this potentiation remain to be fully elucidated, the effects were not observed in T-cell deficient animals, suggesting that the results may be the consequence of the disablement of immunosuppressive mechanisms that exist within the tumor microenvironment.

Based on studies examining serum levels of tryptophan and kynurenine, IDO1 appears to be chronically activated in participants with cancer, and IDO1 activation correlates with more extensive disease.[17,18]IDO1 has subsequently been found to be overexpressed by a wide variety of human tumor cell types as well as by the DCs that localize to the tumor-draining lymph nodes.[19,20] Increased expression of IDO1 in tumor cells has been shown to be an independent prognostic variable for reduced OS in participants with melanoma, ovarian cancer, colorectal, and pancreatic cancers.[21,22,23,24,25,26]

Together, these results suggest that the IDO1 pathway is a key regulatory element responsible for the induction and maintenance of tumor immune tolerance. Small molecule inhibitors of IDO1 may provide an innovative and tractable method to treat advanced malignancies either alone or in combination with chemotherapeutics and/or immunotherapy-based strategies.

Epacadostat is an inhibitor of IDO1 in development for the treatment of malignant diseases. In cell-based assays, epacadostat potently inhibits IDO1 in both human tumor cells and human dendritic cells resulting in reduced tryptophan to kyneurinie conversion (IC_{50} values = 7.1 to 12.7 nM). Epacadostat does not significantly inhibit other proteins that could impact Trp catabolism. To facilitate the clinical development of epacadostat, the pharmacology, PK, and toxicology of epacadostat have been extensively characterized in nonclinical studies. For a thorough discussion of chemistry, pharmacology, efficacy, and safety, please refer to the Epacadostat IB.

3.2.3 Combination of IDO1 and Immune Checkpoint Inhibition

Blockade of immune inhibitory pathways is emerging as an important therapeutic modality for the treatment of cancer as evidenced by the clinical responses observed with antibodies to CTLA-4 and PD-1/PD-L1. Although these single agents have antitumor activity, multiple immune inhibitory mechanisms are present concurrently within the tumor microenvironment, suggesting that combination therapies may be required for optimal therapeutic effect.[26]

As described above, IDO1 is a negative regulatory mechanism that contributes to tumor-derived immune suppression. In preclinical models, IDO1 inhibition has been shown to synergize with blockade of either anti–CTLA-4 or anti–PD-1/PD-L1 in delaying tumor growth and increasing OS.[53,54] This effect was shown to be T-cell dependent, leading to enhanced T-cell proliferation

and interleukin-2 production within the tumor and to a marked increase in the effector-to-regulatory T-cell ratios in the tumor.

The ongoing phase 1/2 study of the safety, tolerability, and efficacy of epacadostat in combination with nivolumab which supports further investigation in CA2099NC is described above in Section 3.1. For additional information, see the epacadostat IB.

3.2.4 Combination of Immunotherapy with Chemotherapy

Chemotherapy may modify the immune response to tumours by influencing multiple mechanisms, including inducing of immunogenic cell death, stimulating release of tumour antigens and/or depletion of immuno-suppressive regulatory T-cells.[37,38,39] Platinum chemotherapy regimens have shown to be safely combined with immunotherapy agents, while improving the efficacy compared to the agents individually. Therefore, the combination of agents that inhibit PD-1 and IDO1 with chemotherapy has the potential to provide significantly improved anti-tumor activity, thereby potentially improving the overall prognosis in patients with advanced stage cancers.

The currently available data on the combination of immunotherapy with platinum chemotherapy is presented in Section 3.

3.3 Benefit/Risk Assessment

3.3.1 Risks From Nivolumab

Extensive details on the safety profile of nivolumab are available in the Investigator Brochure.

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

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

[redacted]

3.3.3 Risks for the Combination of Nivolumab plus Epacadostat in Combination with Chemotherapy

In a phase 1, CheckMate 012 study (n = 56), nivolumab in combination with platinum doublet chemotherapy in chemotherapy-naive NSCLC noted ≥ Grade 3 treatment related AEs were observed in 45% of participants. The safety profile of nivolumab plus platinum doublet chemotherapy was consistent with that expected for individual agents; however, treatment discontinuation related to AEs was greater with the combination. The most commonly reported (≥ 30% of patients) AEs of any grade were fatigue, nausea, decreased appetite, and alopecia. The most common (≥ 5% of patients) treatment-related Grade 3 or 4 AEs were pneumonitis, fatigue, and acute renal failure. No treatment-related deaths were reported.[33] All select AEs were effectively managed with corticosteroids, and none resulted in death. This study shows that immunotherapy agents may be safely combined with platinum based chemotherapy agents to provide an improvement in efficacy irrespective of the PD-L1 status.

Results from an open label cohort of a phase 2 study (KEYNOTE-021) to investigate the efficacy of the combination of first-line PD-1 inhibition and platinum doublet chemotherapy (carboplatin-pemetrexed) in participants with advanced NSCLC have also been reported.[34] The incidence of ≥ Grade 3 treatment-related adverse events was similar between groups (39% in the pembrolizumab plus chemotherapy group and 26% in the chemotherapy alone group). The most common ≥ Grade 3 treatment-related adverse events in the pembrolizumab plus chemotherapy group were anemia and decreased neutrophil count. In the chemotherapy alone group, the most common ≥ Grade 3 events were anemia and decreased neutrophil count, pancytopenia, and thrombocytopenia. The incidence of potentially immune-mediated adverse events in the pembrolizumab plus chemotherapy group (22%) was comparable to that noted for pembrolizumab monotherapy in other studies.

[redacted]

[redacted]

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary Objective	
• To compare overall survival (OS) and progression-free survival (PFS) per blinded independent central review (BICR) of nivolumab plus epacadostat in combination with chemotherapy (Arm A) to chemotherapy (Arm B) in treatment naïve, Stage 4 or recurrent NSCLC participants whose tumors express PD-L1 at 0 to 49%.	• OS • PFS assessed by BICR
Secondary Objective	
• To compare objective response rate (ORR) and to estimate of duration of response (DOR) as assessed by BICR of nivolumab plus epacadostat in combination with chemotherapy (Arm A) to chemotherapy (Arm B) in treatment naïve, Stage 4 or recurrent NSCLC participants whose tumors express PD-L1 at 0 to 49%.	• ORR and DOR assessed by BICR
• To estimate OS, and PFS, ORR, and DOR per BICR assessment, of nivolumab and placebo for epacadostat in combination with chemotherapy (Arm C) in treatment naïve, Stage 4 or recurrent NSCLC participants whose tumors express PD-L1 at 0 to 49%.	• OS • PFS, ORR, and DOR per BICR assessment

[redacted]

Table 4-1: Objectives and Endpoints	
Objectives	**Endpoints**
[redacted]	

5 STUDY DESIGN

5.1 Overall Design

CA2099NC/INCB 24360-309 is a phase 3, randomized, 3-arm trial in participants with treatment naïve, Stage 4 or recurrent NSCLC ≥ 18 years old. The study will enroll participants with PD-L1 levels from 0 to 49%. Patients with PD-L1 levels of ≥ 50% are excluded, as pembrolizumab monotherapy is approved as first line treatment in this population.

The primary objectives of the study are to compare PFS and OS in participants treated with nivolumab plus epacadostat in combination with platinum doublet chemotherapy versus platinum doublet chemotherapy alone. A third arm of nivolumab plus placebo for epacadostat in combination with platinum doublet chemotherapy will allow estimation of the contribution of components. The study arms, specific doses, and treatment frequency for each arm are described in Figure 5.1-1 and Table 7.1-1.

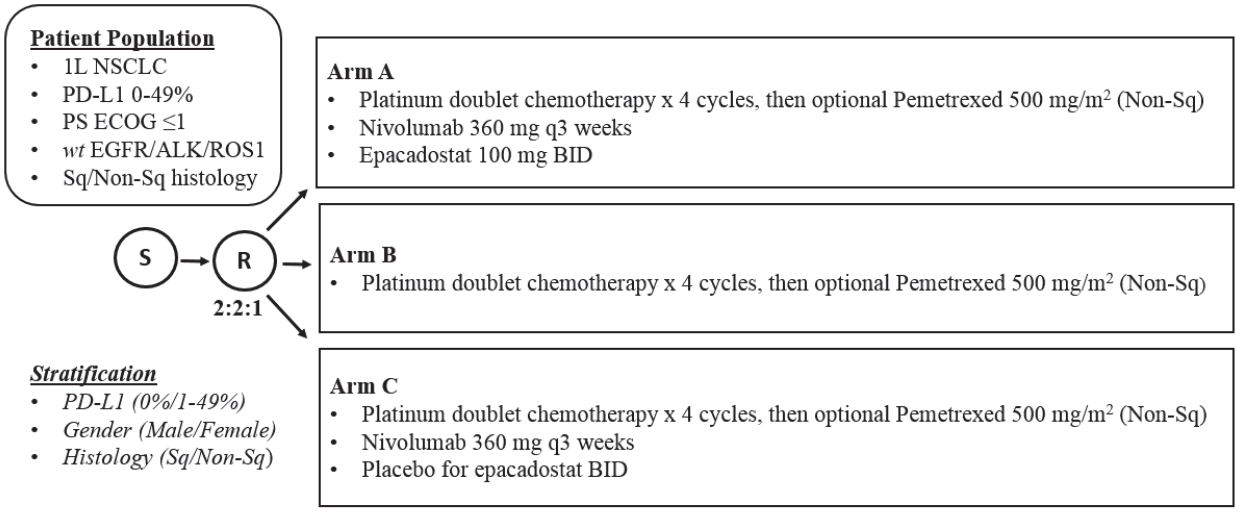
Approximately 900 participants will be screened and 630 participants will be randomized in the 3 treatment arms in a 2:2:1 ratio in the study:

- Arm A: nivolumab plus epacadostat in combination with platinum doublet chemotherapy (n = 252)
- Arm B: platinum doublet chemotherapy (n = 252)
- Arm C: nivolumab plus placebo for epacadostat in combination with platinum doublet chemotherapy (n = 126)

Participants will be stratified by PD-L1 levels (0% and 1 to 49%), gender (male and female), and tumor histology (squamous and non-squamous).

The study design schematic is presented in Figure 5.1-1.

Figure 5.1-1: Study Design Schematic



Sufficient, recent or archival tumor tissue obtained within 3 months prior to enrollment from a metastatic tumor lesion or from an unresectable primary tumor lesion which has not been previously irradiated. For randomization, 25 FFPE slides or adequate tissue block for 25 FFPE slides from core biopsy, punch biopsy, excisional biopsy or surgical specimen must be submitted to the analyzing laboratory. Specimens should contain a minimum of 100 evaluable tumor cells. Participants should not have received any systemic anticancer therapy after the date that the submitted tumor tissue was obtained. Enrollment of participants with less than the requested amount of tumor tissue must be approved by the Medical Monitor.

Tumor progression or response endpoints will be assessed by the investigator and by BICR using RECIST 1.1 criteria. Treatment with study medication will continue until RECIST 1.1-defined progression, unacceptable toxicity, withdrawal of consent, or a maximum treatment duration of 24 months. In specific circumstances, participants may be treated beyond progression as described in Section 8.1.3.

[redacted] The study will end once survival follow-up has concluded.

Physical examinations, vital sign measurements, and clinical laboratory evaluations will be performed at selected times throughout the treatment period. Participants will be closely monitored for adverse events throughout the study. [redacted]

Screening Phase

The screening phase begins by establishing the participant's initial eligibility and signing of the informed consent form (ICF). Tumor tissue (archival or recent tumor biopsy) must be submitted by the site to the analyzing lab for determination of PD-L1 status. A communication (e-mail) will

be sent by the analyzing laboratory to site for confirmation upon receiving tumor tissue. Participants must have the result of PD-L1 IHC testing from the analyzing laboratory available in order to randomize into the study. Patients with tumors unevaluable for PD-L1 will not be enrolled. Additional tumor tissue may be required by the Medical Monitor or the analyzing laboratory if initial testing is unevaluable. See Section 2 for additional information. All screening assessments and procedures must be performed prior to randomization.

Treatment Phase

The treatment phase begins with randomization after confirming all eligibility criteria have been met. Treatment should begin within 3 calendar days of randomization. Figure 5.1-1 and Table 7.1-1 describes the study arms. Each treatment cycle lasts for 21 days.

Follow-up Phase

The post-treatment follow-up begins when the decision to discontinue a participant from all treatment is made. Participants who discontinue treatment will continue to have tumor assessments (if clinically feasible) according to the schedule in Table 2-3.

Participants will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after the last dose of study medication.

After completion of the first 2 follow-up visits, participants will be followed every 3 months for survival. Survival follow-up visits may be performed by phone contact or office visit. BMS/Incyte may request that survival data be collected on all randomized participants outside of the protocol-defined window. At the time of this request, each participant will be contacted to determine their survival status unless the participant had withdrawn consent for all contact.

5.1.1 Data Monitoring Committee and Other External Committees

5.1.1.1 Independent Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be utilized to provide general oversight and safety considerations for this study, CA2099NC/INCB 24360-309. The DMC will provide recommendations to BMS/Incyte regarding actions the committee deems necessary for the continuing protection of participants enrolled in this study. The DMC will review safety data after the first 10 participants in each arm have been on-treatment for at least 4 weeks; enrollment will not be paused during this review. Additionally, relevant available data from the ongoing ECHO-204 study, which includes a cohort assessing the safety and tolerability of the Arm A treatment regimen in the same population, may be provided to the DMC. Efficacy and safety data will be reviewed every 6 months thereafter. The DMC will be charged with assessing such actions in light of an acceptable risk/benefit profile for the nivolumab arms. The DMC will act in an advisory capacity to BMS and Incyte and will monitor participant safety data for the study. The DMC will be advisory to the clinical study leadership team. The clinical study leadership will have responsibility for overall conduct of the study including managing the communication of study data. The clinical trial leadership team will be responsible for promptly reviewing the DMC recommendations, for providing guidance regarding the continuation or termination of the study,

and for determining whether amendments to the protocol or changes to the study conduct are required. Details of the DMC responsibilities and procedures will be specified in the DMC charter.

When required, adjudicated events will be submitted to the DMC and Health Authorities for review on a specified timeframe in accordance with the adjudication documentation.

5.2 Number of Participants

Approximately 900 participants will be screened and approximately 630 participants will be randomized for study treatment.

5.3 End of Study Definition

The start of the trial is defined as the first participant's first visit. End of trial is defined as the last participant's last study visit or last survival assessment. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for Chemotherapy in NSCLC

First-line treatment of advanced NSCLC is histology specific and consists of platinum-based chemotherapy doublets. For example, pemetrexed is approved in first-line in combination with cisplatin for locally advanced or metastatic non squamous NSCLC. This approval was based on a phase 3, randomized study that showed improved survival and decreased toxicity for pemetrexed combined with cisplatin in patients with non-squamous histology, in comparison to gemcitabine combined with cisplatin.[57] Pemetrexed has also been approved as continuation maintenance therapy in patients with non-squamous histology, who have not had progressive disease after four cycles of a first-line pemetrexed/platinum regimen. In contrast, gemcitabine in combination with cisplatin has been demonstrated to yield improved overall survival compared to pemetrexed/cisplatin in participants with squamous NSCLC. In squamous NSCLC, carboplatin plus paclitaxel is an alternative standard of care preferred in some geographies.

Although some but not all meta-analyses and randomized studies have demonstrated that cisplatin-based regimens may produce improved survival compared to carboplatin-based regimens, many participants are not ideal candidates for cisplatin due to its higher toxicity.[58]

Prior data from CheckMate 012 suggest similar efficacy and safety when combining nivolumab with chemotherapy, regardless of the chemotherapy backbone.

5.4.2 Rationale for PD-1 Inhibitor and IDO1 Inhibitor in Combination with Chemotherapy

While chemotherapy has largely been thought to be immunosuppressive and exert its effect via direct cytotoxicity, an emerging body of evidence suggests that some chemotherapies may influence an immune response to tumors via induction of immunogenic cell death (ICD), elimination of immunosuppressive cells, or sensitization of tumor cells to immune effector cells. Given these findings, the combination of chemotherapy with immunotherapy is a rational choice, especially in participants for whom these chemotherapies are the accepted standard of care.

PD-1/PD-L1 blockage is being investigated in combination with chemotherapeutic agents in NSCLC. A phase 1 study (n = 56) of nivolumab in combination with platinum doublet chemotherapy in chemotherapy-naive NSCLC showed ORR ranging from 33% to 47% and PFS from 4.8 to 7.1 months. Treatment-related ≥ Grade 3 AEs were observed in 45% of participants.[33] Promising efficacy signals have been observed in the KEYNOTE-021 study of pembrolizumab in combination with platinum doublet chemotherapy from open-label cohorts (n = 74, ORR 48%-71%, PFS ~10 months, ≥ Grade 3 treatment-related AEs 56%-71%) and a randomized cohort of pembrolizumab/platinum doublet chemotherapy versus platinum doublet chemotherapy (n = 123, ORR 57% vs 32%, PFS 19 months vs 8.9 months, ≥ Grade 3 treatment-related AEs 39% vs 26%). Confirmatory phase 3 clinical studies in advanced/metastatic NSCLC are ongoing for these therapies.

The IDO pathway inhibitor indoximod has been evaluated in combination with chemotherapy in clinical studies. In a phase 1 study (n = 27), indoximod in combination with docetaxel in pretreated participants with metastatic solid tumors was well-tolerated with no unexpected toxicities and had a modest ORR of 18%.[59] Based on encouraging activity observed in participants with breast cancer from this study, a phase 2 study of indoximod in combination with docetaxel or paclitaxel was initiated. Preliminary safety data showed AEs were similar to those typically seen with taxanes, and no unexpected AEs were observed.[60] Indoximod in combination with gemcitabine and paclitaxel in participants with metastatic pancreatic cancer was also well-tolerated in a phase 1/2 study, and preliminary efficacy showed durable responses in 42% of participants.[61]

Overall, the data suggest that combining the IDO1 inhibitor epacadostat, a PD-1 inhibitor, and chemotherapy may result in a further increase of immunomodulatory effects in the tumor microenvironment, and ultimately improve the overall clinical benefit in participants with advanced or metastatic solid tumors without overlapping toxicity profiles.

For additional information on nivolumab and epacadostat, see the Nivolumab IB and Epacadostat IB, respectively.

5.4.2.1 Rationale for Overall Survival and Progression-free Survival as Co-Primary Endpoints

Overall survival is a universally accepted direct measure of benefit endpoint in oncology trials, including NSCLC. Since treatments which may otherwise be administered sequentially are being combined in this study, demonstration of survival benefit is considered necessary in order to demonstrate clinical relevance. PFS is included as a co-primary endpoint based on its acceptability as an endpoint in first line treatment of NSCLC[10], particularly if there is large magnitude of the effect and favorable risk-benefit. Inclusion of PFS also addresses potential confounding of OS by effective subsequent therapies and provides an opportunity for earlier assessment of efficacy that could benefit patients.

5.4.3 Rationale for Participant Selection

As first-line standard of care for participants with EGFR mutations and ALK/ROS1 translocations is targeted therapy[3] rather than chemotherapy. Participants known to have these abnormalities will be excluded from this study.

In addition, patients with EGFR mutations have a better prognosis, even in the absence of EGFR inhibitor therapy and may have an improved response to chemotherapy compared to patients without EGFR mutations.[62] Excluding these participants will help to reduce the potentially confounding effects of these mutations on the study endpoints.

Patients with PD-L1 levels of ≥ 50% are eligible to receive pembrolizumab monotherapy as first line treatment for their disease and are therefore excluded from participation in this study.

5.5 Justification for Dose

5.5.1 Justification for Nivolumab Dose

Nivolumab 360 mg will be administered as an IV infusion over 30 minutes every 3 weeks (Q3W). Nivolumab has been shown to be safe and well tolerated up to a dose level of nivolumab 10 mg/kg Q2W. As population PK (PPK) analyses have shown that the PK of nivolumab are linear over a dose range of 0.1 to 10 mg/kg with no differences observed in PK across ethnicities and tumor types, the PPK model was used to simulate exposures at different dosing regimens, including nivolumab 360 mg Q3W. The simulated steady-state average concentration (Cavgss) following administration of nivolumab 360 mg Q3W are expected to be similar to those following administration of nivolumab 240 mg Q2W and nivolumab 3 mg/kg Q2W administered to participants weighing 80 kg. It should be noted that the steady-state peak concentrations (Cmaxss) following nivolumab 360 mg Q3W are predicted to be less than those following the administration of nivolumab 10 mg/kg Q2W, providing sufficient safety margins. Finally, nivolumab 360 mg Q3W in combination with platinum-doublet chemotherapy dosing is currently being studied for the treatment of NSCLC and gastric cancer in a phase 3 study.

[redacted]

5.5.3 Rationale for Shorter Infusion Times for Nivolumab

Long infusion times place a burden on patients and treatment centers. Previous clinical studies of nivolumab monotherapies have used a 60-minute infusion duration for nivolumab. A shortened infusion duration of 30 minutes has been implemented across all approved indications and future planned indications based on a thorough review of safety data from participants who have received nivolumab 3 mg/kg over 30 minutes Q2W in study CA209153 and 480 mg over 30 minutes Q4W in study CA209511, and clinical experience with nivolumab up to 10 mg/kg. Using a shorter infusion time will reduce a patient's chair time and part of the distress associated with cancer treatment, and ultimately allow for a more efficient utilization of resources in cancer care.

Nivolumab has been administered safely at doses ranging up to 10 mg/kg over these infusion durations. Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across multiple clinical studies, and all have been managed by following established safety algorithms. Differences in exposure using a 30-minute infusion are not expected to have a clinically meaningful effect on safety since dose/exposure-response relationships were predicted to be relatively flat.

Based on the data from CA209153, nivolumab can be safely infused over 30 minutes. Specifically, the overall safety profile was similar between 30-minute and 60-minute infusion groups, even taking into consideration the substantially longer exposure in the 30-minute infusion group in the CA209153 study. Despite the longer exposure for participants in the 30-minute infusion group, there were no clinically meaningful differences in the frequency of hypersensitivity/infusion-related reactions compared to those reported for participants in the 60-minute infusion group. Hypersensitivity/infusion reactions were generally manageable using dosing interruptions, with only a limited impact on the total dose received for that cycle. Additionally, nivolumab 10 mg/kg infused over 60 minutes, which corresponds to a higher infusion rate than 3 mg/kg or 240 mg infused over 30 minutes, was found to be well tolerated in 2 studies: CA209003 (MDX1106-03) and CA209010. Furthermore, interim results from study CA209511 support the safety of a 30-minute infusion time with a dose of 480 mg nivolumab. Overall, no new safety events were identified in participants administered nivolumab over 30 minutes. Similarly, 30 minute infusion with a dose of 360 mg nivolumab is not expected to present any new safety concerns compared to the prior experience.

5.5.4 Rationale for the Duration of Treatment with Nivolumab and Epacadostat/Placebo for Epacadostat

The optimal duration of immunotherapy is currently unknown. However, because immunotherapy engages the immune system to control the tumor, continuous treatment as is required with targeted agents or cytotoxic therapy may not be necessary.

Accumulating evidence from different clinical trials in different tumor types with nivolumab or nivolumab combined with ipilimumab indicates that most of the responses are generally occurring early, with a median time to response of 2-4 months.[8,63,64,65,66] A recent analysis in a melanoma study suggests the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment.[67]

For these reasons, treatment with nivolumab and epacadostat/placebo for epacadostat will be given for up to 24 months in the absence of disease progression or unacceptable toxicity.

5.5.5 Rationale for Permitting Continued Treatment in Select Cases of Progressive Disease

Accumulating clinical evidence indicates some participants treated with immune system stimulating agents may develop progression of disease (by conventional response criteria) before demonstrating clinical OR and/or SD. This phenomenon was observed in approximately 10% of participants in the phase 1 study of nivolumab and also with ipilimumab monotherapy.[49] Two hypotheses have been put forth to explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. Therefore participants will be allowed to continue study therapy after initial investigator-assessed RECIST 1.1 defined progression if they are assessed to be deriving clinical benefit and tolerating study drug. Such participants must discontinue study therapy upon evidence of further progression found in Section 8.1.1.

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Participants must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal participant 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) Recurrent or histologically confirmed stage IV NSCLC per 8th IASLC[68] of squamous or non-squamous histology that is not amenable to therapy with curative intent (surgery or radiation therapy with or without chemotherapy).

b) No prior treatment with systemic anti-cancer therapy for Stage IV disease.

i) Prior adjuvant or neoadjuvant chemotherapy is permitted as long as the last administration of the prior regimen occurred at least six months prior to randomization.

ii) Prior definitive chemoradiation for locally advanced disease is also permitted as long as the last administration of chemotherapy or radiotherapy (whichever was given last) occurred at least six months prior to randomization.

c) ECOG Performance Status of 0 to1

d) Measureable disease by CT or MRI per RECIST 1.1 criteria radiographic tumor assessment performed within 28 days prior to randomization

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

e) Documentation of PD-L1 status of 0 to 49% by IHC performed by the central lab prior to randomization. Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or 15 unstained tumor tissue sections, obtained within 3 months prior to enrollment, with an associated pathology report, must be submitted to the core laboratory for inclusion. Central lab must provide Interactive Response Technology (IRT) with confirmation of receipt of evaluable tumor tissue prior to randomization. Biopsy should be excisional, incisional or core needle. Fine needle aspiration is unacceptable for submission.

f) All toxicities or safety issues attributed to prior cancer therapy (systemic anti-cancer therapy, radiation or surgery), other than alopecia and fatigue, must have resolved or returned to baseline values recorded prior to those cancer therapies at least 2 weeks before randomization for the current study.

3) Age and Reproductive Status

a) Males and Females, ≥ 18 years or age of majority

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

c) Women must not be breastfeeding

d) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with study treatments and after the last dose of study treatment (ie, 30 days [duration of ovulatory cycle] plus the time required for the investigational drug to undergo approximately 5 half-lives. WOCBP receiving nivolumab must agree to follow instructions for method(s) of contraception for 5 months after the last dose of study treatment.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with study treatments and after the last dose of study treatment (ie, 90 days [duration of sperm turnover] plus the time required for the investigational drug to undergo approximately 5 half-lives). Males who are sexually active with WOCBP receiving nivolumab must agree to follow instructions for method(s) of contraception for 7 months after the last dose of study treatment. In addition, male participants must be willing to refrain from sperm donation during this time.

f) Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

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

6.2 Exclusion Criteria

1) Medical Conditions

a) Participants with known 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. All participants with non-squamous histology must have been tested for EGFR mutation status. EGFR test should be done locally. Participants of non-squamous histology with unknown or indeterminate EGFR status are excluded.

b) Participants with known ALK or ROS1 rearrangements which are sensitive to available targeted inhibitor therapy are excluded. All participants with non-squamous histology must have been tested for ALK/ROS1 rearrangement status. ALK/ROS1 tests should be done locally. Participants of non-squamous histology with indeterminate ALK and/or ROS1 status may enroll.

c) Participants with untreated CNS metastases. Participants are eligible if CNS metastases have been adequately treated and have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to randomization.

d) Unevaluable PD-L1 status or PD-L1 status of ≥ 50% by IHC performed by a central laboratory

e) Participants with carcinomatous meningitis

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

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

h) Participants with a history of significant cardiac disease or presence of an abnormality in electrocardiograms (ECG) that, in the investigator's opinion, is medically exclusionary or clinically meaningful.

   i) Screening QTc interval > 480 msec (corrected by Fridericia or Bazett formula) is an exclusion criteria. In the event that a single QTc is > 480 msec, the participant may enroll if the average QTc for 3 ECGs is ≤480 msec.

i) Participants with interstitial lung disease or active, non-infectious pneumonitis (symptomatic and/or requiring treatment) that may interfere with the detection or management of suspected drug-related pulmonary toxicity

j) Other active malignancy

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

l) Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally.

m) 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.

n) Participants with serious or uncontrolled medical disorders

2) Prior/Concomitant Therapy

a) Prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, IDO1 targeted agent or any other antibody or drug targeting T cell co-stimulation or checkpoint pathways

b) Participants using UGT1A9 inhibitor or inducer from screening through follow-up period (see Appendix 9)

c) Participants receiving MAOIs (see Appendix 8) or melatonin supplement within the 21 days before screening.

d) 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.

e) Any history of serotonin syndrome after receiving 1 or more serotonergic drugs.

3) Physical and Laboratory Test Findings

a) WBC < 2000/μL

b) Neutrophils < 1500/μL

c) Platelets < 100 x 10^3/μL

d) Hemoglobin < 9.0 g/dL

e) Serum creatinine >1.5 x ULN or calculated creatinine clearance < 40 mL/min (using the Cockcroft-Gault formula)

f) AST/ALT: > 2.5 x ULN

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

h) Has known history of or is positive for active Hepatitis B (HBsAg reactive) or has active Hepatitis C (HCV RNA). Note: Testing must be performed to determine eligibility.

i) HBV DNA must be undetectable and HBsAg negative at screening visit.

ii) Hepatitis C antibody testing is allowed for screening purposes in countries where HCV RNA is not part of SOC. In these cases, HCV antibody positive participants will be excluded.

iii) Participants who have had definitive treatment for HCV are permitted if HCV RNA is undetectable at screening.

i) International normalized ratio (INR) or prothrombin time (PT) > 1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or INR is within therapeutic range of intended use of anticoagulants.

j) Activated partial thromboplastin time (aPTT) > 1.5 × ULN unless participant is receiving anticoagulant therapy, as long as PTT is within therapeutic range of intended use of anticoagulants.

4) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to platinum-containing compounds or study drug components

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and BMS/Incyte approval is required.)

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

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

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently [randomized/entered in the study/included in the analysis population]. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4.1 Retesting During Screening or Lead-In Period

Participant Re-enrollment: This study permits the re-enrollment of a participant that has discontinued the study as a pre-treatment failure (ie, participant has not been randomized). If re-enrolled, the participant must be re-consented.

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

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

7 TREATMENT

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

Study treatment includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP):

In this protocol, investigational product(s) is/are:

- Nivolumab
- Epacadostat
- Epacadostat matching placebo
- Carboplatin
- Cisplatin
- Gemcitabine
- Paclitaxel
- Pemetrexed

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

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

The selection and timing of dose for each participant is as follows in Table 7-1:

Table 7-1: Study treatments for CA2099NC / INCB 24360-309

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Nivolumab Injection[a]	10 mg/mL	IP	Open Label	Vials	Refer to the label or container and/or pharmacy manual.
Cisplatin Concentrate for solution for infusion [b]	1 mg/mL	IP	Open Label	Vials	Refer to the label or container and/or pharmacy manual.
Carboplatin Solution for IV Injection[b]	10 mg/mL	IP	Open Label	Vials	Refer to the label or container and/or pharmacy manual.
Epacadostat Tablets[c]	100 mg and 25 mg	IP	Blinded	Bottles	Refer to the label or container and/or pharmacy manual.
Epacadostat Matching Placebo	Not applicable	IP	Blinded	Bottles	Refer to the label or container and/or pharmacy manual.
Gemcitabine Concentrate for Solution for Infusion or Gemcitabine Powder for Solution for Infusion[b]	1000 mg / vial	IP	Open Label	Vials	Refer to the label or container and/or pharmacy manual.
Paclitaxel Solution for Injection[b]	100 mg/vial (6 mg/mL)	IP	Open Label	Vials	Refer to the label or container and/or pharmacy manual.
Pemetrexed Powder for Concentrate for Solution for Infusion[b]	500 mg/ vial	IP	Open Label	Vials	Refer to the label or container and/or pharmacy manual.

[a] May be labeled as either “BMS-936558-01” or nivolumab.

[b] 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).

[c] For participants who cannot swallow tablets but can eat and/or drink, epacadostat/placebo for epacadostat tablets may be crushed and dissolved in water or dispersed in a medium such as applesauce, or a nutritional supplement such as Ensure® and administered orally. In the case of participants who are unable to eat or drink by mouth, the epacadostat/placebo for epacadostat tablet(s) may be crushed and dissolved in water and delivered to the participant through a feeding tube. Detailed information is provided in the Pharmacy Manual.

7.1 Treatments Administered

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

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
Nivolumab	360 mg	Q3W	IV
Epacadostat[a]	100 mg	Twice daily	Oral
Epacadostat Matching Placebo[a]		Twice daily	Oral
Doublet Chemotherapy[b]			
Squamous histology			
Gemcitabine + Cisplatin	1000 or 1250 mg/m^2 75 mg/m^2	Q3W up to 4 cycles (Gemcitabine on days 1,8)	IV
Gemcitabine + Carboplatin	1000 mg/m^2 AUC 5	Q3W up to 4 cycles (Gemcitabine on days 1,8)	IV
Paclitaxel + Carboplatin	200 mg/m^2 AUC 6	Q3W up to 4 cycles	IV
Non-squamous histology			
Cisplatin + Pemetrexed	75 mg/m^2 500 mg/m^2	Q3W up to 4 cycles	IV
Carboplatin + Pemetrexed	AUC 5 or 6 500 mg/m^2	Q3W up to 4 cycles	IV
Optional Maintenance Treatment Non-squamous histology			
Pemetrexed	500 mg/m^2	Q3W	IV

[a] For participants who cannot swallow tablets but can eat and/or drink, epacadostat/placebo for epacadostat tablet(s) may be crushed and dissolved in water or dispersed in a medium such as applesauce, or a nutritional supplement and administered orally. In the case of participants who are unable to eat or drink by mouth, the epacadostat/placebo for epacadostat tablet(s) may be crushed and dissolved in water and delivered to the participant through a feeding tube. Detailed information is provided in the Pharmacy Manual.

[b] Information on investigator's selection of chemotherapeutic regimen may be collected, as applicable.

7.1.1 All Arms

Study treatment should begin within 3 calendar days of randomization and the maximum duration of study treatment is 24 months.

It is important to note that some chemotherapy-related AEs may overlap with suspected immune-related AEs potentially related to nivolumab or epacadostat/placebo for epacadostat. In these cases, both the treatment management algorithm (Appendix 6 and Section 7.4) for nivolumab/epacadostat/placebo for epacadostat and local prescribing guidelines for chemotherapy should be reviewed to determine the most appropriate management of study medications (see Section 7.4 for dose modification guidance for the study drugs).

7.1.2 Nivolumab

Participants should receive nivolumab at a dose of 360 mg as a 30-minute infusion on Day 1 of each treatment cycle every 3 weeks until progression, unacceptable toxicity, withdrawal of consent, completion of 24 months of treatment, or the study ends, whichever occurs first.

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. When the dose is fixed (eg, 360 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 120 mL. Nivolumab infusion must be promptly followed by a saline flush to clear the line. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

There will be no dose escalations or reductions of nivolumab allowed. Participants may be dosed no less than 18 days from the previous dose during Q3W cycles. Premedications are not recommended for the first dose of nivolumab.

Participants should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.4.

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed. See Section 7.4.2.1 and Section 8.1.1 for additional information on dose delay or dose discontinuation, respectively.

7.1.3 Epacadostat/Placebo for Epacadostat

The starting dose of epacadostat is 100 mg BID daily continuously during Q3W cycles. Epacadostat/placebo for epacadostat will be continued until progression, unacceptable toxicity, withdrawal of consent, permanent discontinuation of nivolumab, completion of 24 months of treatment, or the study ends, whichever occurs first.

On Day 1 of each cycle, epacadostat or placebo for epacadostat is administered orally in the clinic first followed by IV infusion of nivolumab (see Table 2-2). All other doses should be self-administered. All BID doses of epacadostat or placebo for epacadostat will be taken orally, in the morning and evening, approximately 12 hours apart without regard to food. If the morning or evening dose is missed by more than 4 hours, that dose should be skipped, and the next scheduled dose should be taken at the usual time. On days when epacadostat or placebo for epacadostat and nivolumab are administered, epacadostat or placebo for epacadostat should administered first, and the nivolumab infusion should be started no later than 10 minutes after epacadostat/placebo for epacadostat administration.

Epacadostat or placebo for epacadostat will be given twice daily in combination with nivolumab as long as participants are receiving benefit from treatment and have not met any criteria for study withdrawal (Section 8.1). Intra-participant dose escalation of epacadostat/placebo for epacadostat is not permitted.

Epacadostat/placebo for epacadostat dose may be dose reduced (to -1 dose level [50 mg BID]), delayed, or discontinued depending on how well the participant tolerates the treatment (see Section 7.4.2.2 for dose modification guidance for epacadostat/placebo for epacadostat). If the nivolumab dose is delayed because of an AE), epacadostat/placebo for epacadostat should also be delayed (see Section 7.4.2 for exceptions to this guidance). If nivolumab is permanently discontinued for any reasons, epacadostat/placebo for epacadostat will be permanently discontinued. Participants may complete chemotherapy as prescribed in Section 7.1.4.

7.1.4 Platinum Doublet Chemotherapy

Refer to Table 7.1-1 for specific doses of specific chemotherapy products. Follow the local prescribing information of each respective agent for information on administration. Platinum doublet chemotherapy will be continued for a maximum of 4 cycles every 3 weeks (± 3 days). In Arm A and Arm C, chemotherapy agents should be given after the nivolumab infusion. There is a 30-minute (60 minutes if required for pre-medication) delay before the start of the chemotherapy infusion to monitor the participant for signs of possible nivolumab infusion reactions. Chemotherapy agents should be administered according to standard of care or instructional practice.

All participants who will be receiving 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 carboplatin treatment for the remainder of the platinum doublet cycles (up to 4 cycles in total).

Carboplatin dose will be calculated using the Calvert formula as follows:

- Carboplatin dose (mg) = Target AUC x [(CrCl (ml/min) + 25]
- Creatinine clearance (CrCl) calculation is based on the Cockroft-Gault formula) and should include the most recent serum creatinine and most recent weight. NOTE: If calculation of the CrCl by the Cockroft-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.

Investigators must indicate, at the time of randomization, whether or not a participant will be treated with pemetrexed continuation maintenance if eligible to do so. If the investigator subsequently decides that a participant should not be treated with pemetrexed continuation maintenance, even though eligible, or decides to treat a participant for whom the investigator had indicated at randomization that maintenance would not be used, this decision must be discussed with the Medical Monitor.

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.

Administration of chemotherapy may be interrupted, delayed, reduced, or discontinued depending on how well the participant tolerates the treatment. See Sections 7.4.3, 7.4.5.2, and 8.1.2 for more details regarding dose delays, reductions, retreatment, and discontinuations.

Premedication for use with pemetrexed: Oral corticosteroid 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. Intramuscular (IM) injection of vitamin B12 1000 mcg should be given approximately one 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. Participants with non-squamous histology may begin folic acid and vitamin B12 prior to randomization in anticipation of pemetrexed.

Premedications for use with paclitaxel: Oral or IV corticosteroid should be given prior to paclitaxel according to local standard. Such premedication may consist of oral dexamethasone 20 mg 12 hours and 6 hours prior to paclitaxel administration. Oral or IV diphenydramine 50 mg (or its equivalent) and an H2-blocker (per local standards) should be administered 30 to 60 minutes prior to paclitaxel infusion. All participants should be carefully monitored for infusion reactions during the paclitaxel administration. Participants should be treated in a facility with the necessary medical-resuscitation equipment and medications on hand to manage serious acute infusion reactions.

7.1.4.1 Cisplatin /Gemcitabine

Participants will receive gemcitabine at a dose of 1000 or 1250 mg/m^2 for a 30-minute IV infusion on days 1 and 8 with cisplatin at a dose of 75 mg/m^2 as a 30 to 120-minute IV infusion 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 following the end of the gemcitabine infusion. Pretreatment hydration for cisplatin can follow local standard of care, or 1 to 2 liters of fluid (per local standards) infused IV for 8 to 12 hours prior to cisplatin infusion is 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.

7.1.4.2 Carboplatin/ Gemcitabine

Participants will receive gemcitabine at a dose of 1000 mg/m^2 as a 30-minute IV infusion on Days 1 and 8 with carboplatin at a dose of AUC 5 as a 30-minute IV infusion, on Day 1 of a 3-week cycle, for up to 4 cycles, or at doses per the local prescribing information. Gemcitabine 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 gemcitabine on Day 1 of each cycle, and the carboplatin dose will be calculated using the Calvert formula.

7.1.4.3 Cisplatin/Carboplatin and Pemetrexed with or without Pemetrexed Continuation Maintenance

Cisplatin/ Pemetrexed with or without Pemetrexed Continuation Maintenance

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/m² as a 120-minute IV infusion on Day 1 of a 3-week treatment cycle for up to 4 cycles. (Note: calculated CrCl must be ≥ 45 mg/min for pemetrexed to be dosed.) After cycle 4, participants with stable disease or response will discontinue cisplatin and may continue pemetrexed at the same dose and schedule as continuation maintenance until progression, unacceptable toxicity, withdrawal of consent, or a maximum treatment duration of 24 months. In participants who required pemetrexed dose reduction due to toxicity during the cisplatin/pemetrexed combination cycles, the dose of pemetrexed may be escalated to 500 mg/m^2 after the discontinuation of cisplatin, at the investigator's discretion and according to local standards, if the prior toxicity was thought to be related mainly to cisplatin. 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 standards, or use 1 to 2 liters of fluid (per local standards) infused IV for 8 to 12 hours prior to cisplatin infusion is 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.

Carboplatin/Pemetrexed with or without Pemetrexed Continuation Maintenance

Participants will receive pemetrexed at a dose of 500 mg/m2 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. After cycle 4, participants with stable disease or response will discontinue carboplatin and may continue pemetrexed at the same dose and schedule as continuation maintenance until progression, unacceptable toxicity, withdrawal of consent, or a maximum treatment duration of 24 months. In participants who required pemetrexed dose reduction due to toxicity during the pemetrexed/carboplatin combination cycles, the dose of pemetrexed may be escalated to 500 mg/m^2 after the discontinuation of carboplatin, at the investigator's discretion and according to local standards, if the prior toxicity was thought to be related mainly to 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% weight used to calculate the previous dose. The carboplatin dose will be calculated using the Calvert formula.

7.1.4.4 Carboplatin/Paclitaxel

Participants will receive paclitaxel at a dose of 200 mg/m^2 as a 180-minute IV infusion, followed by carboplatin at a dose of AUC 6 as a 30 to 60-minute IV infusion, both on Day 1 of a treatment cycle every 3 weeks for 4 cycles. Paclitaxel 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 s participant's weight is within 10% of the weight used to calculate the previous dose.

The carboplatin dose will be calculated using the Calvert formula.

7.2 Method of Treatment Assignment

After the participant's initial eligibility is established and informed consent has been given, the participant will be enrolled into the study and assigned a participant number using the centralized IRT system. Every person that signs the informed consent form must be assigned a participant number by the IRT. Before the study is initiated, each user will receive log in information and directions on how to access the IRT. Exact procedures for using the IRT will be detailed in the IRT manual.

Enrolled participants that have met all eligibility criteria will be randomized centrally via the IRT system. PD-L1 status will be transferred directly from the analyzing lab to the IRT system.

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

Participants will be stratified by PD-L1 status, gender, and histology for randomization into Arms A, B, or C in 2:2:1 ratio.

7.3 Blinding

In this study, participants and investigators are blinded to the epacadostat treatment in Arm A and Arm C.

Blinding of treatment assignment of epacadostat for Arm A and Arm C 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 investigational product 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 if 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 investigational product, the problem may be properly managed by assuming that the participant is receiving active product. 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 Principal Investigator should only call in for emergency unblinding AFTER the decision to discontinue the participant has been made.

For this study, the method of unblinding for emergency purposes is the IRT system.

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.

In case of an emergency, the investigator(s) has unrestricted access to randomization information via the Interactive Response Technology (IRT) and is capable of breaking the blind through the IRT system without prior approval from sponsor. Following the unblinding, the Investigator shall notify the Medical Monitor and/or Study Director.

This information, including the reason for the blind being broken, must be recorded on the appropriate study page of the source document.

7.4 Dosage Modifications

Dosing of nivolumab/epacadostat/placebo for epacadostat may be modified or discontinued without delay of chemotherapy dosing if the drug-related toxicity is determined by the investigator to be immune-related and clearly not related to chemotherapy. Conversely, dosing of one or all of the chemotherapy drugs may be dose-modified or discontinued without delay of nivolumab/epacadostat/placebo for epacadostat dosing if drug-related toxicity is determined to be related to only to chemotherapy drugs and clearly not related to immunotherapy. Refer to the below sub-sections, Section 7.4.2, Appendix 6, and Appendix 7 for guidance on dose modifications and discontinuation for individual components.

However, if drug-related toxicity could be attributable to either immunotherapy or chemotherapy or if the investigator is unable to determine which study drug is the cause, then drug-related AE is considered to be related to both immunotherapy and chemotherapy. In the above scenario where the investigator is unable to determine the causality of the AE, except in the case of emergency, the Medical Monitor should be consulted before interrupting or restarting therapy.

In the cases where the AE is considered to be related to both immunotherapy and chemotherapy, all the guidance for dose modification and discontinuation for both immunotherapy and

chemotherapy should be reviewed to determine the most appropriate management of study medication (Section 7.4.2, Appendix 6, and Appendix 7).

A dose of chemotherapy given more than 3 days after the intended dose date will be considered a dose delay. A maximum delay of 8 weeks between doses is allowed. Longer delays will require approval from the Medical Monitor.

7.4.1 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab and epacadostat are considered immuno-oncology agents in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

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

The above algorithms are found in the nivolumab Investigator Brochure, as well as in Appendix 6.

7.4.2 Dose Modifications for Immunotherapy (Nivolumab and Epacadostat/Placebo for Epacadostat) (Arms A and C)

Refer to Appendix 6 and Appendix 7 for the detailed toxicity management algorithm for nivolumab and epacadostat/placebo for epacadostat.

In most cases of immune-related toxicities, decision on dose delay or permanent discontinuation will be implemented consistently for both nivolumab and epacadostat/placebo for epacadostat. If nivolumab is delayed or permanently discontinued for immune-related toxicity, then epacadostat/placebo for epacadostat will be delayed or permanently discontinued as well, and vice-versa. The following are exceptions to the above guidance:

- Nivolumab dosing may continue as planned in cases of epacadostat/placebo for epacadostat dose delays or discontinuation due to Serotonin Syndrome (See Section 7.4.2.3 for details).
- Epacadostat/placebo for epacadostat dosing may continue in cases of nivolumab dosing delays due to Grade 1-2 immune-mediated dermatitis, except in the cases of suspected Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) where both the drugs will be dose delayed. In cases of confirmed SJS/TEN diagnosis and in cases of Grade 3-4 immune-related dermatitis requiring permanent nivolumab discontinuation, epacadostat/placebo for epacadostat should also be discontinued. Refer to Appendix 6, Appendix 7, and Section 8.1.1 for additional details. If the rash is Grade 3 by BSA and otherwise mild, temporarily hold epacadostat/placebo for epacadostat may occur, use topical steroids, and resume dose when resolved to < Grade 1.

- Epacadostat/placebo for epacadostat dosing may continue if nivolumab dosing is interrupted or delayed due to nivolumab-related infusion reactions. However, if nivolumab is permanently discontinued, epacadostat/placebo for epacadostat will be discontinued as well.
- In cases requiring occasional short-term interruptions of one of the two drugs, for reasons other than AEs, the dosing for the other drug may continue as planned, eg. nivolumab dosing may continue if epacadostat/placebo for epacadostat dose is temporarily interrupted due to patient non-compliance. Similarly, epacadostat/placebo for epacadostat dosing may continue if nivolumab is temporarily delayed due to scheduling issues.

7.4.2.1 Dose Delay Criteria for Nivolumab and Epacadostat/Placebo for Epacadostat (Arms A and C)

This section should be reviewed in conjunction with Appendices 6 and 7. Nivolumab and epacadostat/placebo for epacadostat administration should be delayed for the following:

- Grade 2 non-skin, drug-related adverse event, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related adverse event
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade 3 AST, ALT, Total Bilirubin will require dose discontinuation (see Section 8.1.1
- Serotonin Syndrome will require a delay of epacadostat. Nivolumab dosing can be continued (see Section 7.4.2.3 for Serotonin Syndrome management).
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of nivolumab/epacadostat/placebo for epacadostat.

Participants who require delay of nivolumab or epacadostat/placebo for epacadostat should be re-evaluated weekly or more frequently if clinically indicated and resume dosing of nivolumab/epacadostat/placebo for epacadostat when re-treatment criteria are met. Treatment delay up to 8 weeks for nivolumab/epacadostat/placebo for epacadostat is allowable (any dose delays greater than 8 weeks will require approval from the Medical Monitor).

If nivolumab is delayed, epacadostat/placebo for epacadostat should also be delayed. There will be no dose reductions for nivolumab. The criteria for dose discontinuation is provided in Section 8.1.1.

7.4.2.2 Dose Modification Criteria for Nivolumab and Epacadostat/Placebo for Epacadostat (Arms A and C)

No dose reduction for nivolumab are allowed.

In case of drug-related AEs that may be attributable to epacadostat/placebo for epacadostat, the dose can be reduced to -1 dose level (50 mg BID). The criteria for dose reduction, dose delay, and dose discontinuation is provided in Appendix 7. Intra-participant dose escalations are not permitted. Participants will remain on their assigned dose or a lower dose of epacadostat/placebo for epacadostat (if required) because of an AE.

7.4.2.3 Recommended Management for Serotonin Syndrome

As noted in Section 3.3.2 there is a theoretical chance that epacadostat could cause an increase in serotonin levels in the brain that might trigger serotonin syndrome when administered in combination with other serotonergic agents.[55] This syndrome has been most closely associated with use of MAOIs, meperidine/pethidine, linezolid, or methylene blue; all of these agents are prohibited during the study. Serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) are permitted in the study. The following procedures will be implemented if participants exhibit the signs/symptoms of serotonin syndrome, including tremor, hyperreflexia, spontaneous, ocular, or inducible clonus, together with agitation, fever, diaphoresis, or muscle rigidity:

- Immediately interrupt epacadostat/placebo for epacadostat administration. Administration of nivolumab may continue.
- Immediately interrupt any SSRI or SNRI administration.
- Provide appropriate medical management of the participant until all signs/symptoms are resolved (eg, IV fluids and/or sympathomimetic amines for hypotension, benzodiazepines for agitation, administration of 5-hydroxytryptamine antagonists such as cyproheptadine).
- If participant chooses to remain in the study, restart treatment with epacadostat/placebo for epacadostat after the SSRI or SNRI has been discontinued, no sooner than 5 half-lives have elapsed for the specific SSRI or SNRI in question and after resolution of signs/symptoms of serotonin syndrome. The SSRI or SNRI treatment MAY NOT be restarted.
- If the SSRI/SNRI cannot be stopped, the epacadostat/placebo for epacadostat can be discontinued and the participants can continue on-study nivolumab treatment. In this circumstance, the study blind will not need to be broken.
- If participant chooses to withdraw from the study, or must restart treatment with SSRI or SNRI, the participant should be scheduled for a follow-up visit. Treatment with SSRI or SNRI may be initiated 2 weeks after resolution of signs and symptoms of serotonin syndrome.

7.4.3 Dose Modifications for Chemotherapy

This section includes guidance on dose modifications for gemcitabine, pemetrexed, cisplatin, carboplatin, and paclitaxel treatment-related toxicities. Investigators should confirm that the local prescribing guidelines for individual drugs are also reviewed to determine the most appropriate management of study medications.

Dose Delay: Dosing of both drugs in the platinum doublet chemotherapy regimen should be delayed for any of the following on the Day 1 of each cycle:

- Presence of febrile neutropenia or neutropenia < 1500 cells/mm^3 for greater than one week despite the use of growth factors
- Any Grade ≥ 2 non-skin, drug-related adverse event, except for alopecia, fatigue or laboratory abnormalities
- Any Grade 3 skin drug-related AE
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia does not require a dose delay

  - Delay if total bilirubin >1x ULN or if AST and/or ALT > 1.5 x ULN occurs concomitant with alkaline phosphatase > 2.5x ULN
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants skipping the dose of study medication.

A dose given more than 3 days after the intended dose date will be considered a dose delay. A maximum delay of 8 weeks between doses is allowed. Longer delays may be allowed following discussion with the Medical Monitor. Subsequent dose reductions may be required as described below. Participants may receive growth factors (including G-CSF and erythropoietin) at the discretion of the investigator.

Dose Reduction: Dose reductions of chemotherapy may be required, and will be performed according to Table 7.4.3-1. 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 platinum doublet chemotherapy regimen are not linked and may be adjusted independently as summarized below.

Table 7.4.3-1: Dose Modifications of Chemotherapeutic Agents

Dose Level	Gemcitabine	Pemetrexed	Cisplatin	Carboplatin	Carboplatin	Paclitaxel
Starting dose	1000 or 1250 mg/m² (with cisplatin) or 1000 mg/m² (with carboplatin)	500 mg/m²	75 mg/m²	AUC 5 or 6 with pemetrexed/ or AUC 5 with gemcitabine	AUC 6 with paclitaxel	200 mg/m^2
First dose reduction	750 or 950 mg/m² (with cisplatin) or 750 mg/m² (with carboplatin	375 mg/m²	56 mg/m²	AUC 4 or 5 with pemetrexed or AUC 4 with gemcitabine	AUC 5 with paclitaxel	150 mg/m^2
Second dose reduction	500 or 625 mg/m² (with cisplatin) or 500 mg/m² (with carboplatin)	250 mg/m²	38 mg/m²	AUC 3 or 4 with pemetrexed or AUC 3 with	AUC 4 with paclitaxel	100 mg/m^2
Third dose reduction	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue

Any participants with two prior dose reductions for one agent who experiences a toxicity that would cause a third dose reduction must be discontinued from that agent.

7.4.3.1 Recommended Chemotherapy Dose Reductions for Hematologic Toxicity

Dose modifications for hematologic toxicities (according to CTCAE version 4) are summarized in Table 7.4.3.1-1. Dose adjustments are based on nadir blood counts (assessed as per local standards) since the preceding drug administration. Dose level adjustments for doublet chemotherapy are relative to that of the preceding administration. Generally, both chemotherapy agents in the doublet chemotherapy regimen should be dose reduced together for hematologic toxicity. After the first cycle, growth factors may be used to assist hematologic recovery. Local standards of care should be applied in the use of these supportive measures. Additionally, prophylactic antibiotics may be used according to local standards. Antibiotic or growth factor use should be reported on the eCRF.

Table 7.4.3.1-1: Dose Modifications for Hematologic Toxicity (Based on Nadir Counts)

Toxicity	Gemcitabine	Pemetrexed	Cisplatin	Carboplatin	Paclitaxel
Neutrophils Count Decreased					
Grade 4 (< 500/mm^3 or < 0.5 x 10^9/L)	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level
Platelet count Decreased					
Grade 3 (25,000 - < 50,000/mm^3; 25.0 < 50.0 x 10^9/L)	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level
Grade 4 (< 25,000/mm^3; < 25.0 x 10^9/L)	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level

7.4.3.2 Chemotherapy Dose Reductions for Non-Hematologic Toxicities

Dose adjustments for chemotherapy for non-hematologic toxicities during treatment are described here. All dose reductions should be made based on the worst grade toxicity. Participants experiencing any of the toxicities during the previous cycle should have their 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 two drugs in the doublet chemotherapy regimen are not linked and may be reduced independently, as summarized in Table 7.4.3.2-1.

Table 7.4.3.2-1: Dose Modifications for Non-Hematologic Toxicity

Toxicity	Gemcitabine	Pemetrexed	Cisplatin	Carboplatin	Paclitaxel
Febrile Neutropenia Grade ≥ 3	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level
Diarrhea Grade ≥ 3	Reduce one dose level	Reduce one dose level	No change	No change	Reduce one dose level
Allergic reaction[a] Grade ≥ 3	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue
Neuropathy Grade 2	No change	No change	Reduce one dose level	No change	Reduce one dose level
Neuropathy Grade ≥ 3	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue
Calculated creatinine clearance < 50 mL/min	No change	No change	Discontinue	Discontinue if creatinine clearance < 20 ml/min	No change
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	Adjust as medically indicated

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

7.4.4 Treatment of Nivolumab-related Infusion Reactions

Since nivolumab contains 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) common terminology criteria for adverse event (CTCAE, Version 4) 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 nivolumab administrations.

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

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 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 nivolumab 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 electronic case report form (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 nivolumab. 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 nivolumab. Begin an IV infusion of normal saline and treat the participant t 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. Nivolumab 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).

7.4.5 Criteria to Resume Dosing

7.4.5.1 Criteria to Resume Nivolumab/Epacadostat/Placebo for Epacadostat Dosing

Participants may resume treatment with nivolumab when the drug-related AE(s) resolve(s) to Grade ≤ 1 or baseline, with the following exceptions:

- Participants may resume treatment in the presence of Grade 2 fatigue.
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- For participants with Grade 2 AST, ALT and/or Total Bilirubin Abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete. Participants with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters (Section 8) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the Medical Monitor.
- Participants who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the Medical Monitor/designee. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
- Dose delay of nivolumab which results in treatment interruption of > 8 weeks requires treatment discontinuation, with exceptions as noted in Section 8.
- Participants who delay study treatment due to any Grade 3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis, which is assessed by the investigator not to be related to nivolumab, may resume nivolumab and epacadostat/placebo for epacadostat when the amylase or lipase abnormality has resolved to Grade < 3. The Medical Monitor should be consulted prior to resuming nivolumab in such participants.

7.4.5.2 Criteria to Resume Treatment with Chemotherapy

- Participants may resume treatment with chemotherapy when the ANC returns to 1500/µl. the platelet count returns to 100,000/mm^3, 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 8 weeks from the last dose given should discontinue the drug(s) that caused the delay.

- When resuming chemotherapy treatment, follow the dose reduction recommendations in Section 7.4.3.1.

7.5 Preparation/Handling/Storage/Accountability

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

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

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

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

- Infusion-related supplies (eg, IV bags, in-line filters,0.9%NaCl solution) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.
- For nivolumab, please refer the current version of the Investigator Brochure and/or pharmacy reference sheet for ongoing storage, handling, dispensing and infusion information.
- Epacadostat should be stored at ambient conditions 15°C-30°C or 59°F-86°F.
- Further guidance and information for final disposition of unused study treatment are provided in Appendix 2.

7.5.1 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

7.6 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the participant's medical record and eCRF.

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 adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 7.7.4)

- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of NSCLC)
- Any botanical preparation (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care.
- Administration of live attenuated vaccines within 30 days before the first dose of study treatment and while participating in the study is prohibited. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines are live attenuated vaccines which are not allowed.
- Any melatonin supplements.
- Any MAOI or drug associated with significant MAO inhibitory activity agents is prohibited from 21 days before Day 1 through 2 weeks after the final dose of epacadostat has been taken (see Appendix 8).
- Any UGT1A9 inhibitor or inducer (see Appendix 9)

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. Participants may receive other medications that the investigator deems to be medically necessary.

The exclusion criteria (Section 6.2) describe other medications that are prohibited during this study. There are no prohibited therapies during the post-treatment follow-up phase.

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.

Use of coumarin-based anticoagulants (eg, warfarin [Coumadin], fluindione [Previscan]), and vitamin K antagonists are discouraged. Low-dose coumarin-based anticoagulants, eg, warfarin 1 mg is acceptable; however, doses that increase the INR are discouraged. If an alternative cannot be used, the INR should be monitored closely (weekly for the first 4 weeks after initiation of therapy and upon discontinuation of epacadostat or matching placebo for epacadostat)

Use of the anticonvulsant carbamazepine (a UGT1A9 inducer) is discouraged. Because there is a potential interaction that could result in lower epacadostat exposures, an alternative to carbamazepine should be used, if possible.

7.7.3 Imaging Restriction and Precaution

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each participant. Imaging contraindications and contrast risks should be considered in

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

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

7.7.3.1 Radiation Restriction

Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with the Medical Monitor.

7.7.4 Permitted Therapy

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

7.7.4.1 Supportive Care Guidelines

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator, including, but not limited to, the items outlined below:

- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Participants should be strongly encouraged to maintain liberal oral fluid intake.
- Anti-infectives: Participants with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.
- Immune-related AEs: See Section 7.4.1, Section 7.4.2, Appendix 6, and Appendix 7 regarding diagnosis and management of adverse experiences of a potential immunologic etiology.
- Management of infusion reactions from nivolumab (Section 7.4.4)

7.8 Treatment After the End of the Study

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

BMS/Incyte reserves the right to terminate access to BMS/Incyte supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of the nivolumab or epacadostat 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/Incyte will follow local regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

Participants MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator and based on toxicity management algorithm, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by Bristol-Myers Squibb (BMS) and Incyte Corporation
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Additional protocol specified reasons for discontinuation (see Section 8.1.1 and Section 8.1.2)
- Progressive disease, unless the participant is eligible for treatment through progression as determined by the investigator.

If a participant in Arms A or C meets criteria for discontinuation due to drug-related AE and the investigator, based on best clinical judgement, is unable to determine whether it is immune-related or chemotherapy-related, the participant should discontinue both immunotherapy and chemotherapy and be taken off the treatment phase of the study. In these instances, unless in the case of emergency, the investigator should consult with the Medical Monitor prior to the treatment discontinuation.

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

In the case of pregnancy, the investigator must immediately notify the Sponsor/designee of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the Sponsor/designee within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the Medical Monitor/designee must occur.

All participants who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 2. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

8.1.1 Nivolumab and Epacadostat/Placebo for Epacadostat Dose Discontinuation (Arms A and C)

Nivolumab/Epacadostat/Placebo for Epacadostat treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Grade ³ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN

* In most cases of Grade 3 AST or ALT elevation, study drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug(s), a discussion between the investigator and the Medical Monitor/designee must occur.

- Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset

  - Grade 4 drug-related endocrinopathy adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor/designee.
- Any event that leads to delay in dosing lasting > 8 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  - Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the medical monitor/designee.
- Serotinin Syndrome that does not resolve on treatment would require discontinuation of epacadostat/placebo for epacadostat (Section 8.1.1).

Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks, the medical monitor/designee must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

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

8.1.2 Chemotherapy Dose Discontinuation

Chemotherapy treatment should be permanently discontinued for the following:

- Any drug-related Grade 4 toxicity including laboratory abnormalities the participant will be discontinued from the relevant study drug, with the following exceptions:
  - Isolated Grade 4 electrolyte abnormalities not associated with clinical sequelae and are adequately managed and corrected within 72 hours of onset
  - Grade 4 neutropenia or lymphopenia ≤ 7 days
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions:
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation, except for the following scenarios:
    - Grade 3 drug-related thrombocytopenia associated with bleeding
    - Any of the following drug-related liver function test (LFT) abnormalities:
      - AST or ALT > 8 x ULN
      - Total bilirubin > 5 x ULN
      - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
      - Calculated creatinine decreases to < 50 mL/min based on Cockcroft Gault formula on participants receiving cisplatin. Switch to carboplatin is allowed at the discretion of investigator for the remaining cycles.

- Any dosing delay lasting > 8 weeks, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug related adverse events are allowed. Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks, the Medical Monitor must be consulted. Tumor assessments should continue as per protocol event if dosing is delayed.
  - Dosing delays > 8 weeks that occur for non-drug-related reasons may be allowed if approved by the Medical Monitor. Prior to reinitiating treatment in a participant with a dosing delay lasting > 8 weeks, the Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued treatment.

8.1.3 Nivolumab and Epacadostat/ Placebo for Epacadostat Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[49]

Participants treated with nivolumab and epacadostat/ placebo for epacadostat (Arms A and C) will be permitted to continue nivolumab and epacadostat/ placebo for epacadostat treatment beyond initial RECIST 1.1 defined PD, assessed by the investigator, as long as they meet the following criteria:

- Investigator-assessed clinical benefit.
- Tolerance of study drug
- 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 nivolumab and epacadostat/ placebo for epacadostat treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

Chemotherapy treatment will not be permitted to continue beyond initial RECIST 1.1 defined PD.

A radiographic assessment/ scan should be performed within 6 weeks of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab and epacadostat/ placebo for epacadostat.

If the investigator feels that the nivolumab and epacadostat/placebo for epacadostat-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 Time and Events Schedule, Table 2-2.

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

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

8.1.4 Post Study Treatment Study Follow-up

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

BMS may request that survival data be collected on all randomized participants outside of the protocol defined window (Table 2-3). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contacts or is lost to follow-up.

8.2 Discontinuation from the Study

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

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

8.3 Lost to Follow-Up

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

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
  - EGFR, ALK, and ROS-1 will be assessed locally at screening (refer to Table 2-1)
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on site/local labs until all study 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 adverse events, the participant should be immediately

evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the BMS-936558 (nivolumab) and INCB 024360 (epacadostat) Investigator Brochures.

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

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

Participants will be followed for survival every 3 months via in person or by telephone contact after the participants have discontinued study drug treatment. All randomized participants will be followed for survival.

Images will be submitted to an imaging core lab. Sites should be trained prior to scanning the first study participant. Image acquisition guidelines and submission process will be outlined in the CA2099NC/INCB 24360-309 Imaging Manual to be provided by the core lab.

9.1.1 Imaging Assessments for the Study

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

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

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

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

CT and MRI scans should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging timepoints.

Use of CT component of a PET-CT scanner: Combined modality scanning such as with PET-CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined PET-CT are of limited use in anatomically-based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically-based RECIST measurements. However, if a site can document that the CT performed as part of a PET-CT is of

identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the FDG 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.

Participants should undergo tumor assessments by CT or MRI at Screening and every 6 weeks (±7 days) from the date of randomization until Week 48 and then every 12 weeks (±7 days) until disease progression (based on BICR review) or death.

MRI of the brain without and with contrast is required during screening for participants with a history of or clinical suspicion of brain metastases. All participants with a history of brain metastasis should have surveillance MRIs approximately every 12 weeks from the date of randomization or sooner if clinically indicated. Previously-treated CNS metastases are not considered measurable lesions for purposes of RECIST-determined response.

Tumor assessments must continue per protocol until RECIST 1.1 progression, confirmed by BICR, has occurred.

Participants with a history of bone metastasis may have a bone scan if clinically indicated. Bone scan or PET scan is 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.

Assessments of PR and CR must be confirmed at least 4 weeks after initial response. A Best Response of SD can only be made after the participant is on-study for a minimum of 35 days from the date of randomization. Investigators will also report the number and size of new lesions that appear while on study. The time point of tumor assessments will be reported on the eCRF based on the investigator's assessment. For participants who are treated beyond disease progression, tumor assessments will continue to be performed until discontinuation of study treatment (typically upon evidence of further progression).

Tumor assessments for all participants should continue as per protocol even if dosing is delayed or discontinued. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Change in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the Investigator using the RECIST 1.1 criteria.

Any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled time points and/or at an outside institution) should be collected for RECIST 1.1 tumor assessment and submitted to the BICR.

9.1.2 Independent Review of Progression

The clinical management of participants during the study will be based upon local radiologic tumor measurements. Tumor assessments for each participant should be submitted to the radiology vendor as they are performed, on an ongoing basis. The blinded, independent radiologists will

review all available tumor assessments for that given participant and determine if RECIST 1.1 criteria for progression have been met.

When RECIST 1.1 progression is assessed by the investigator (whether assessed before or after the start of palliative local therapy or subsequent therapy), the BICR must be requested. If clinically acceptable, subsequent therapy should begin only after RECIST 1.1 progression has been assessed by BICR. Participants who start palliative local therapy or subsequent therapy prior to BICR review must continue tumor assessments (if clinically feasible) according to the protocol-specified schedule. Scans should be submitted to the third-party radiology vendor for BICR review. Tumor assessments may be discontinued following BICR confirmed progression.

In addition, participants receiving treatment beyond progression must continue tumor assessments until such treatment has been discontinued.

Details of the Independent Review of Progression process will be specified in the BICR charter.

[redacted]

9.2 Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 3.

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

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

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

Contacts for SAE reporting are specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment until 100 days after last dose of study treatment at the timepoints specified in the Schedule of Activities (Section 2). Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participants.

Sections 5.6.1 and 5.6.2 in the Nivolumab IB and Section 5.4 in the Epacadostat IB represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. For reference safety information on chemotherapy regimens, refer to the drug product labels. Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

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.

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

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

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

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

9.2.2 Method of Detecting AEs and SAEs

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. (In order to prevent reporting bias, participants should not be questioned regarding the specific occurrence of one or more AEs.)

9.2.3 Follow-up of AEs and SAEs

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

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

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

9.2.4 Regulatory Reporting Requirements for SAEs

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

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

9.2.5 Pregnancy

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

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

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS/Incyte or designee. In order for BMS/Incyte or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

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

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

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

9.2.7 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

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

AND

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

9.2.8 Other Safety Considerations

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

9.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 9.2).

9.4 Safety

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

9.4.1 Physical Examinations

Refer to Schedule of Activities.

9.4.2 Clinical Safety Assessments

9.4.2.1 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

Table 9.4.2.1-1: Clinical Laboratory Assessments

Hematology - CBC	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Coagulation:	
INR	
Prothrombin time	
aPTT (Screening only)	
Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin	Albumin - screening only Sodium Potassium

Table 9.4.2.1-1: Clinical Laboratory Assessments

Alkaline phosphatase (ALP) Lactate dehydrogenase (LDH) Creatinine Blood Urea Nitrogen (BUN) or serum UREA Fasting glucose	Chloride Calcium Phosphorus TSH, free T3 and free T4 - screening TSH, with reflexive fT3 and fT4 if TSH is abnormal - on treatment
Serology	
Hepatitis B/C, (HBV sAG, HBV DNA, HCV antibody or HCV RNA) - screening only HIV testing where locally mandated. See Appendix 11.	
Pregnancy test (WOCBP only minimum sensitivity 25 IU/L or equivalent units of HCG).	
Follicle stimulating hormone (FSH) screening -only required to confirm menopause in women < age 55)	

9.4.2.2 Electrocardiogram 12-lead Assessment

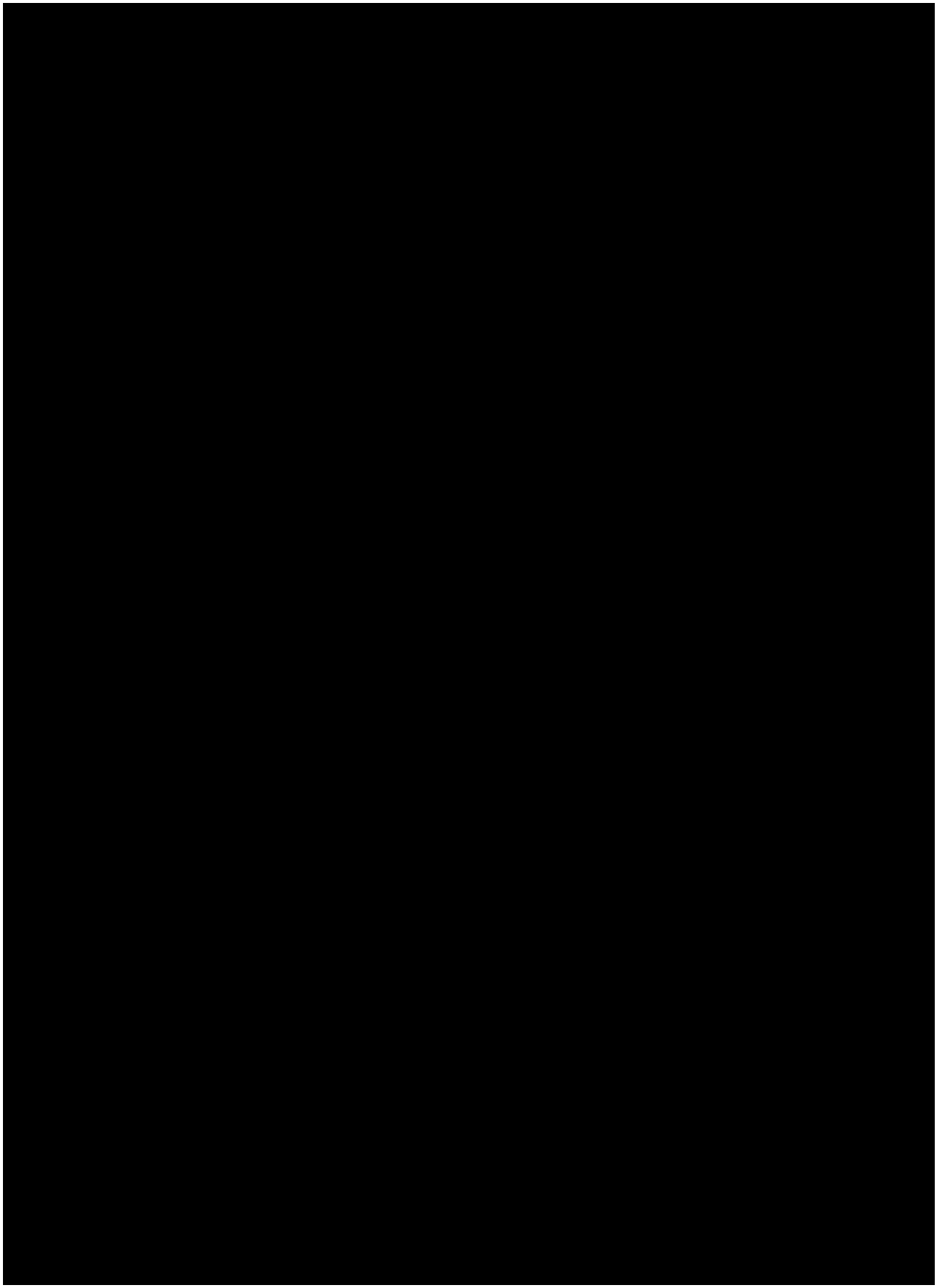
Pre-dose 12-lead ECGs will be obtained at screening, Cycle 1 Day 1, Cycle 2 Day 1 and at the end of treatment. If clinically indicated, additional ECGs may be obtained during the study.

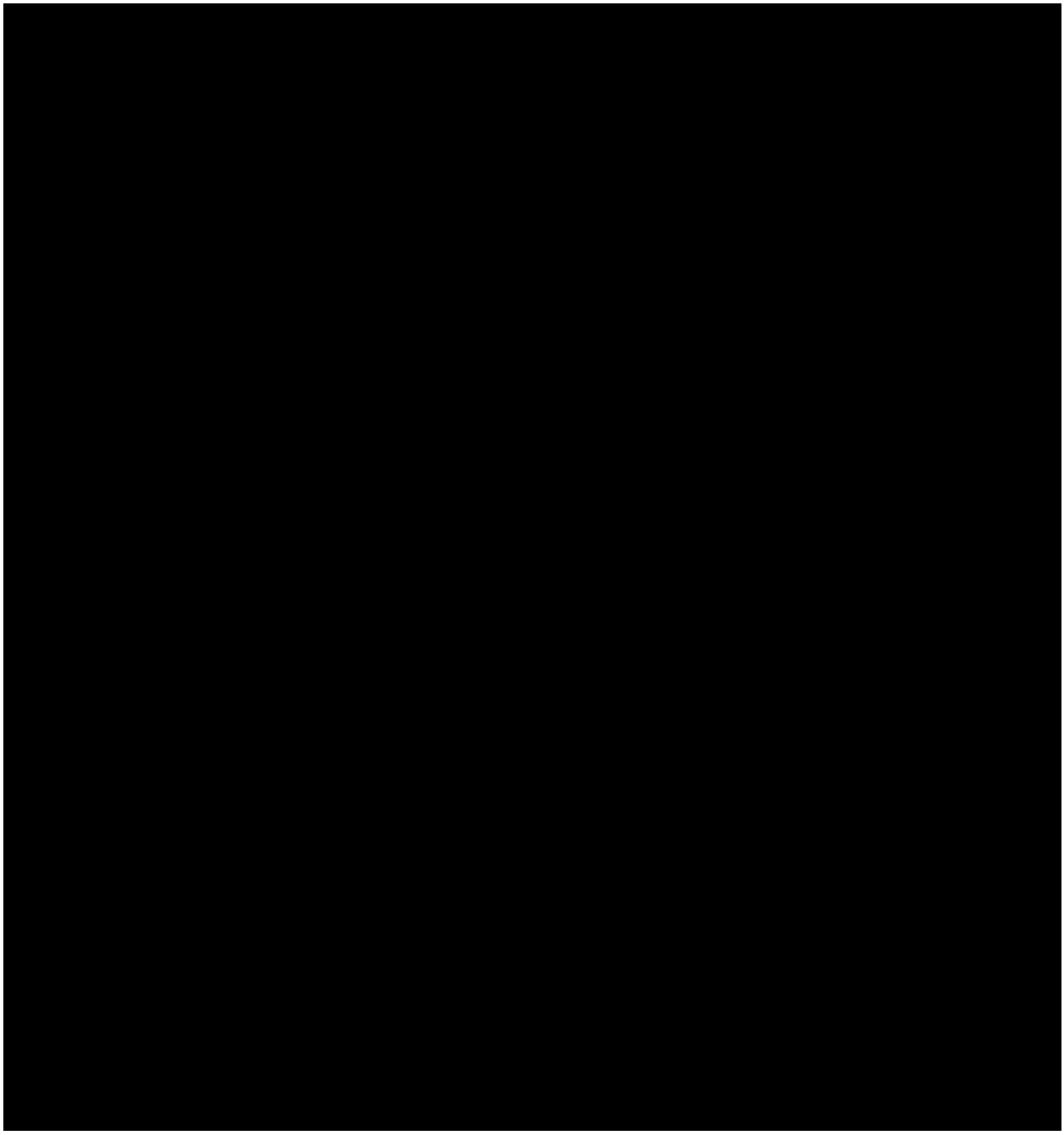
All 12-lead ECGs will be performed with the participant in a recumbent or semirecumbent position after 5 minutes of rest. The ECG readings will be interpreted by the investigator at the site to be used for eligibility and for immediate participant management. The decision to include or exclude a participant or to withdraw a participant from the study treatment based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the Medical Monitor, as appropriate. Clinically significant abnormal findings, as determined by investigator, will require a triplicate ECG. In the event that a single QTc is > 480 msec at screening, the participant may enroll if the average QTc for 3 consecutive ECGs is ≤ 480 msec or with approval from the Medical Monitor/designee. Prolonged QTc intervals must be read by a cardiologist. For participants with an intraventricular conduction delay (QRS interval > 120 msec) at screening, the JTc interval may be used in place of the QTc with Medical Monitor/designee approval. In addition, the JTc interval should be used for all subsequent assessments.

Clinically significant abnormal ECG findings at screening will be recorded as medical history. Clinically significant abnormal ECG findings after the first dose of study treatment should be recorded as an AE.

9.4.3 Imaging Safety Assessment

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





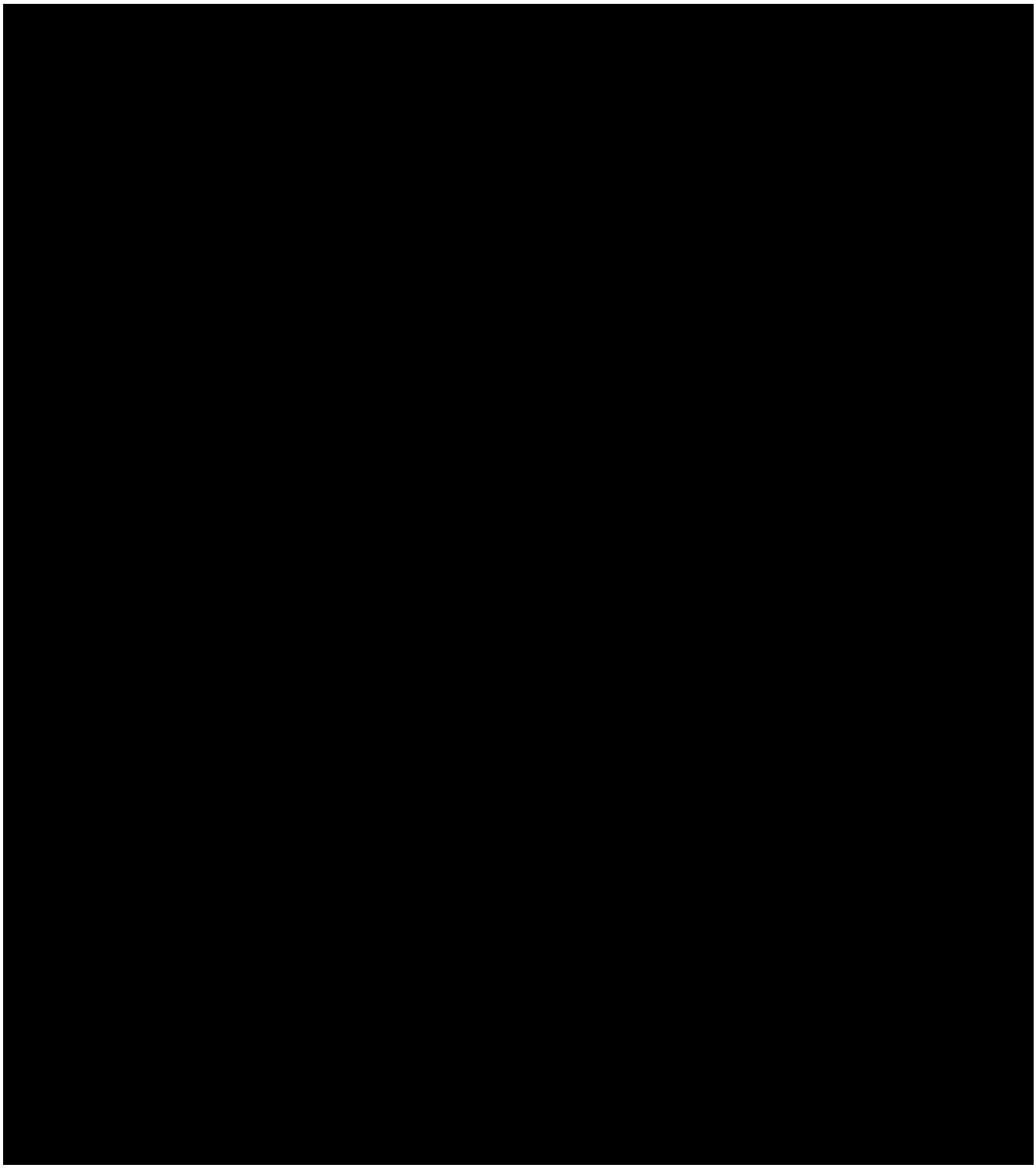
9.6 Pharmacodynamics

See Section [redacted] for additional information.

9.7 Pharmacogenomics

See Section [redacted] for additional information.

[redacted]



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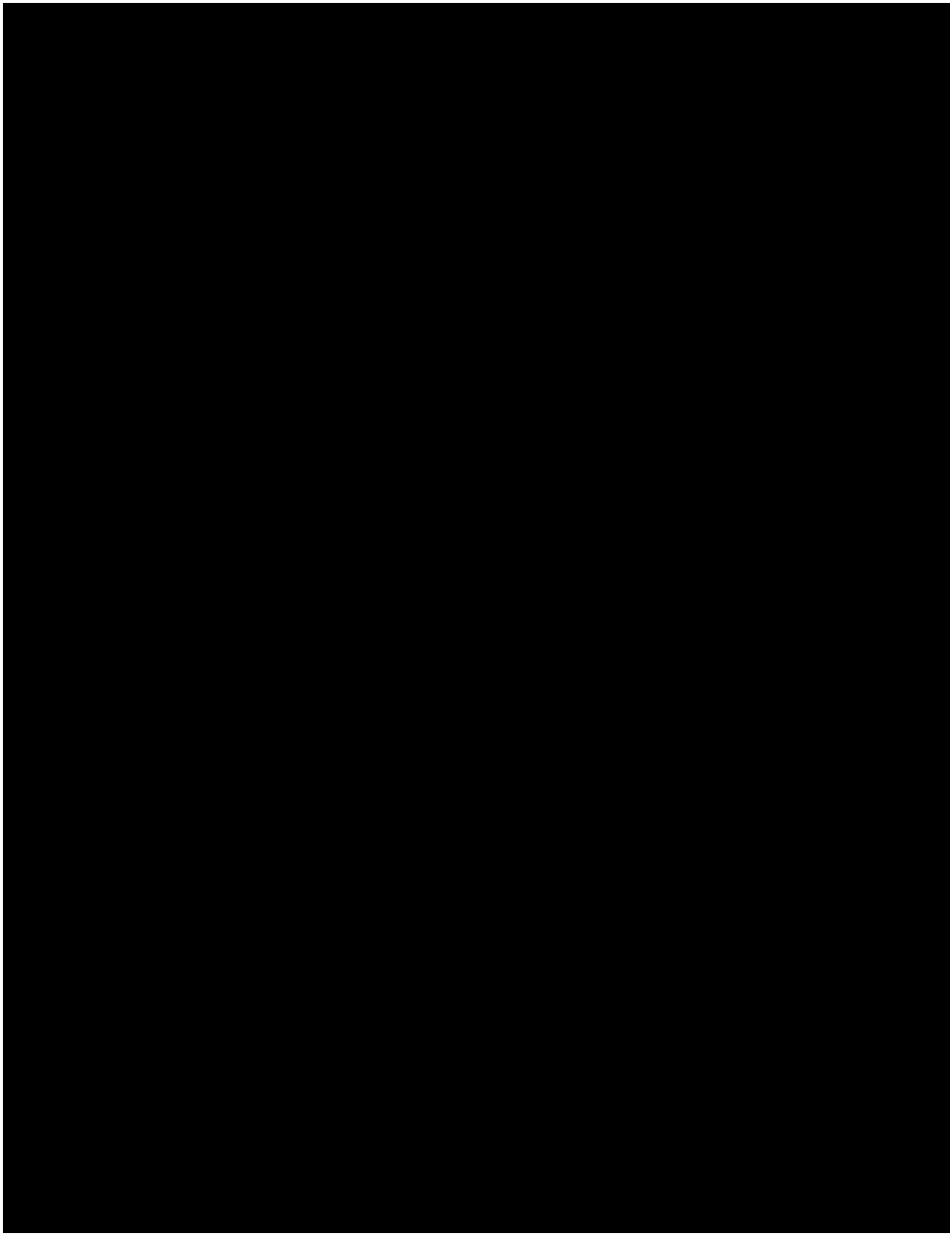

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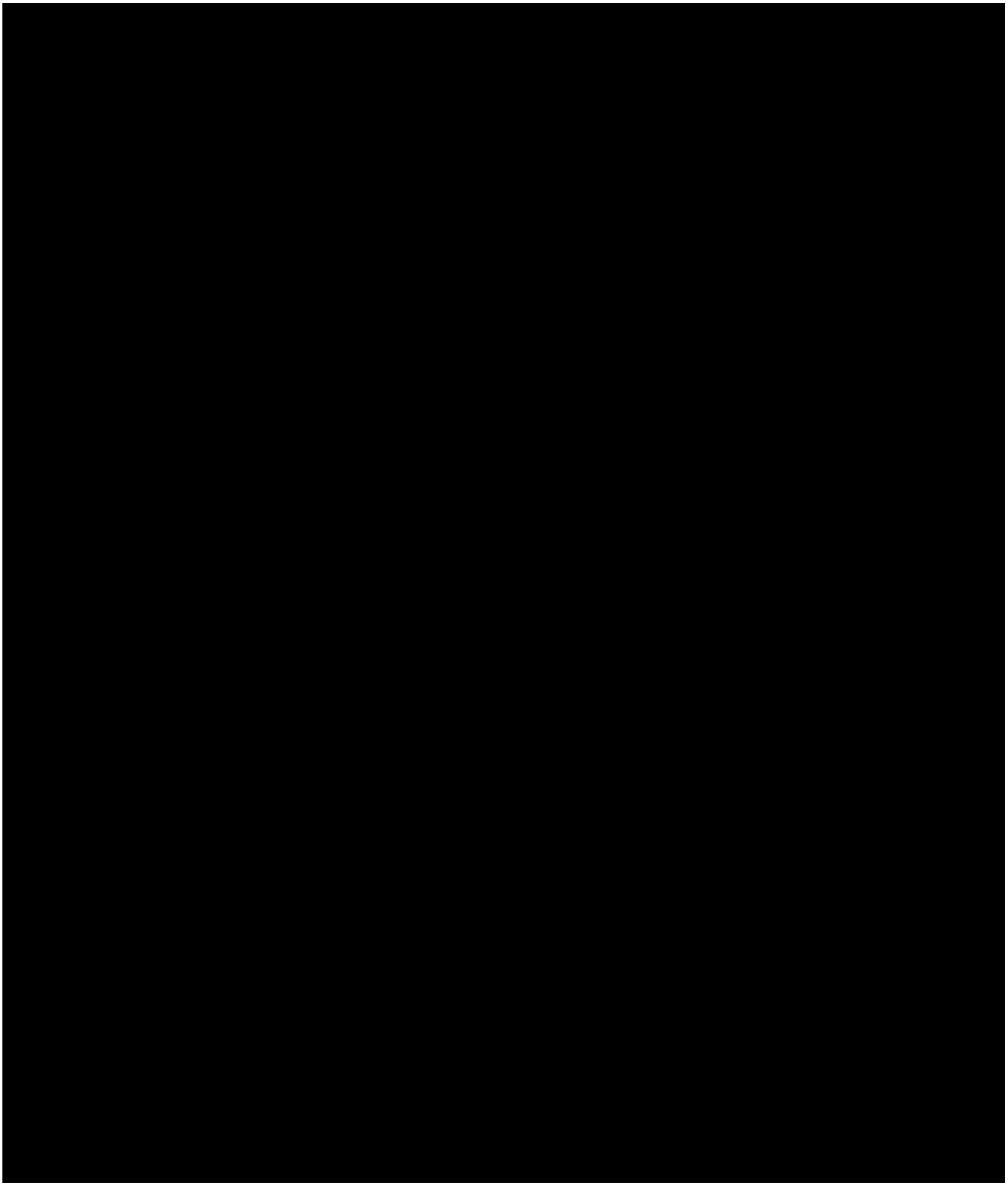

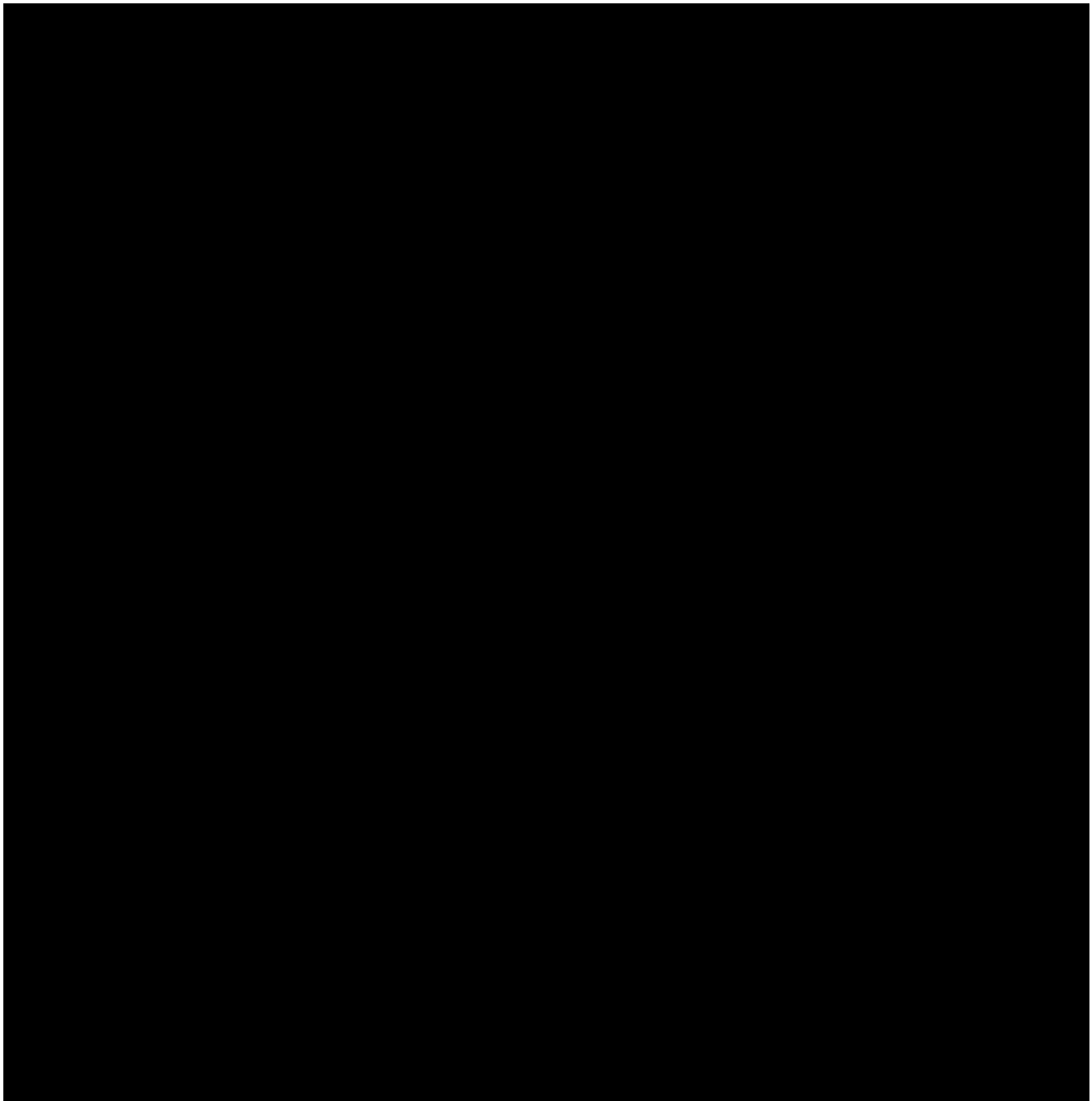

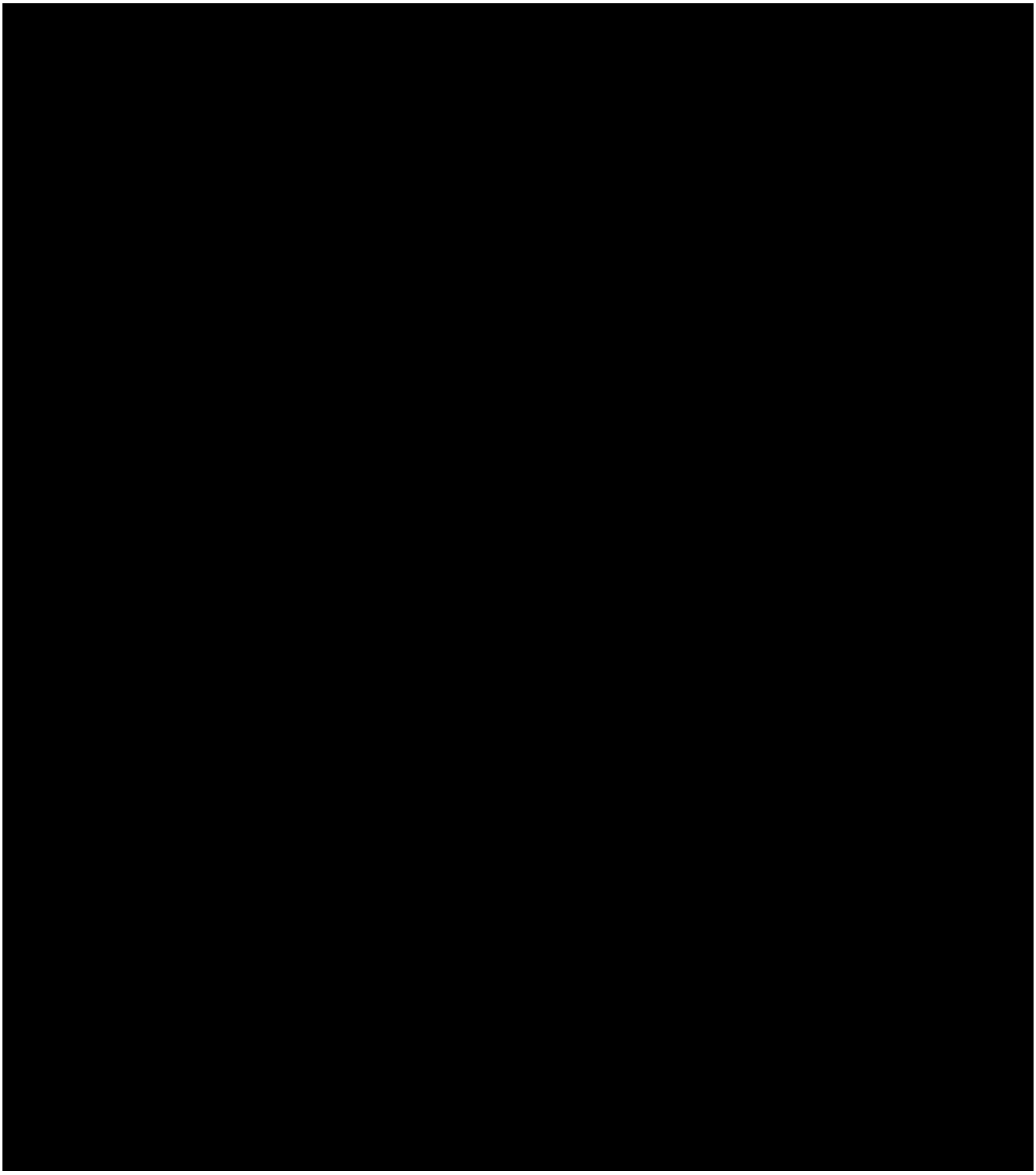

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ADA	Anti-drug antibodies
AE	adverse event
AIDS	autoimmunity deficiency syndrome
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AR	additional research
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
BICR	Blinded independent central review
BID, bid	bis in die, twice daily
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CFR	code of federal regulations
CI	confidence interval
CLcr	creatinine clearance
Cmax, CMAX	maximum observed concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRF	case report form, paper or electronic
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte–associated protein-4
DMC	data monitoring committee

Term	Definition
DOR	duration of response
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4th Edition)
ECG	electrocardiogram
ECHO	Epacadostat Clinical Development in Hematology and Oncology
EOI	End of Infusion
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	estimated glomerular filtration rate
egfr	epidermal growth factor receptor
FDA	Food and Drug Administration
FISH	fluorescent in-situ hybridization
FFPE	formalin-fixed, paraffin-embedded
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
G-CSF	growth colony stimulating factor
GFR	glomerular filtration rate
GI	gastrointestinal
HBsAg	hepatitis b surface antigen
HBV	hepatitis b virus
HCG	human chorionic gonadotropin
HCV	hepatitis c virus
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
IASLC	International Association for the Study of Lung Cancer
IB	Investigator Brochure
ICD	immunogenic cell death
ICH	International Conference on Harmonisation
IDO1	indoleamine-2,3-dioxygenase 1
IEC	Independent Ethics Committee
Ig	immunoglobin
IMP	investigational medicinal products

Term	Definition
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	international unit
IV	intravenous
LDH	lactate dehydrogenase
MAOI	monoamine oxidase inhibitors
MRI	magnetic resonance imaging
N	number of subjects or observations
N/A	not applicable
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
NSQ	nonsquamous
OR	objective response
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD-1	program death-1
PD-L1	program death ligand-1
PD	pharmacodynamics
PFS	progression-free survival
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PR	partial response
PRO	patient reported outcome
PS	performance status
PVC	polyvinyl chloride
PT	prothrombin time
QoL	quality of life

Term	Definition
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SCC	squamous cell carcinoma
SD	standard deviation
SNP	
SNRI	serotonin/norepinephrine reuptake inhibitor
SQ	
SSRI	selective serotonin reuptake inhibitor
TAO	Trial Access Online, the BMS implementation of an EDC capability
TCR	T-cell receptor
TEAE	Treatment emergent AE
TIL	tumor infiltrating lymphocytes
T-HALF	half life
[redacted]	[redacted]
TSH	thyroid stimulating hormone
ULN	upper limit of normal
[redacted]	[redacted]
WBC	white blood cell
WOCBP	women of childbearing potential
wt	wild type

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

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

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.

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

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

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

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

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

Subjects unable to give their written consent (e.g., stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The participant must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this participant become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a participant who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

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

SOURCE DOCUMENTS

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

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

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

STUDY TREATMENT RECORDS

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

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

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

CASE REPORT FORMS

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

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

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

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

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

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

MONITORING

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

Representatives of BMS/Incyte must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable .Certain CRF pages and/or electronic files may serve as the source documents:

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

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

RECORDS RETENTION

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

investigator (or head of the study site in Japan) must contact BMS/Incyte/designee prior to destroying any records associated with the study.

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

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

RETURN OF STUDY TREATMENT

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

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

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

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

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

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

CLINICAL STUDY REPORT AND PUBLICATIONS

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

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

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

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

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

ADVERSE EVENTS

Adverse Event Definition:
An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

SERIOUS ADVERSE EVENTS

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

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

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study treatment is an SAE.

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

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

EVALUATING AES AND SAES

Assessment of Causality
The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following: Related: There is a reasonable causal relationship between study drug administration and the AE. Not related: There is not a reasonable causal relationship between study drug administration and the AE. The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Follow-up of AEs and SAEs
If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

Follow-up of AEs and SAEs
All SAEs must be followed to resolution or stabilization.

Reporting of SAEs to Sponsor or Designee

- SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms).
- The preferred method for SAE data reporting collection is through the eCRF.
- The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning.
  - In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

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

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

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

Highly Effective Methods That Are User Independent

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b]
- Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c]
- Intrauterine device (IUD)[c]
- Bilateral tubal occlusion

- Vasectomized partner

A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

- Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence

NOTES:

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

[b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Unacceptable Methods of Contraception

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus).
- Spermicide only
- Lactation amenorrhea method (LAM)

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

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

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

COLLECTION OF PREGNANCY INFORMATION

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

APPENDIX 5 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

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

APPENDIX 6 MANAGEMENT ALGORITHMS

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

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

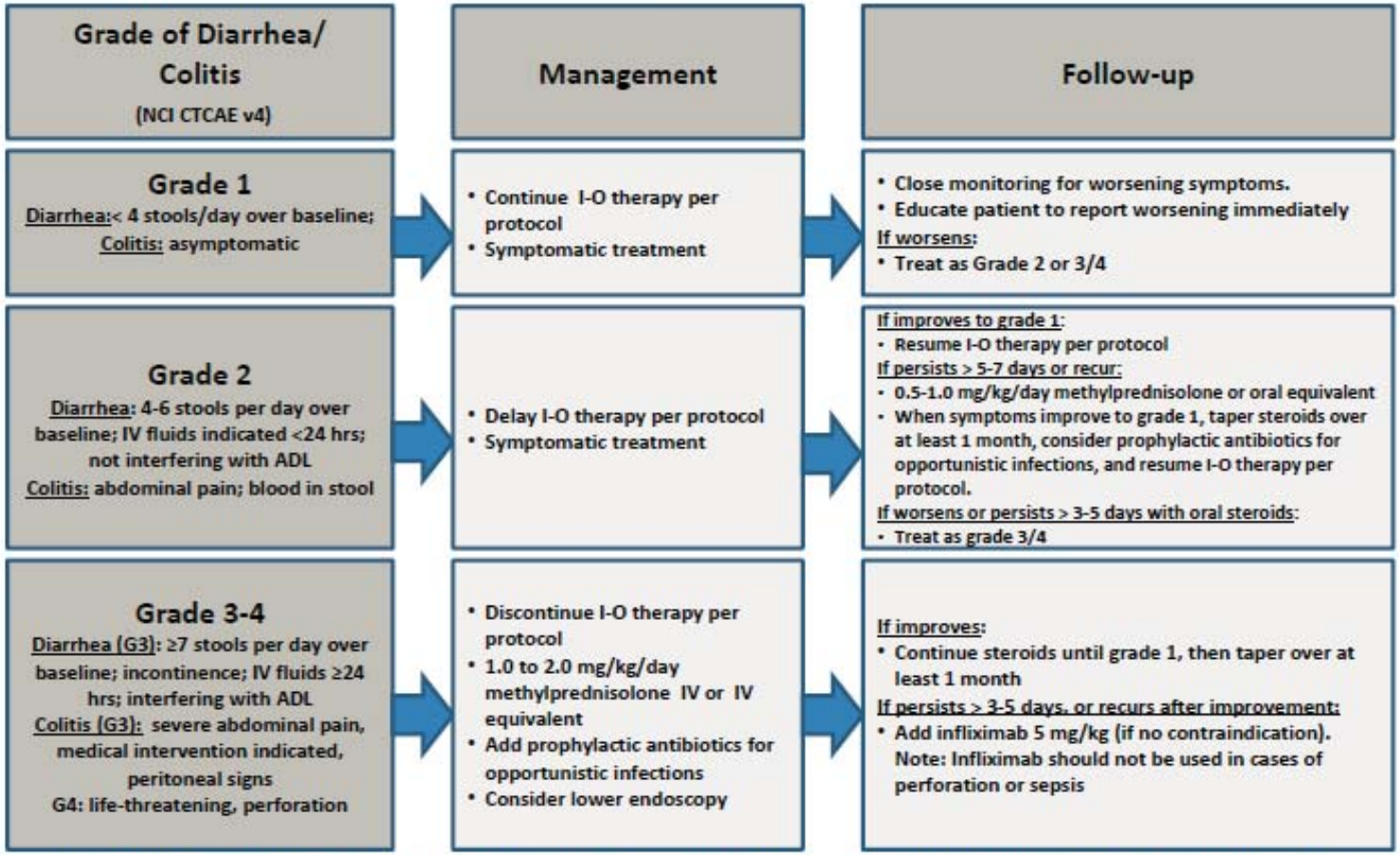
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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

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

GI Adverse Event Management Algorithm

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

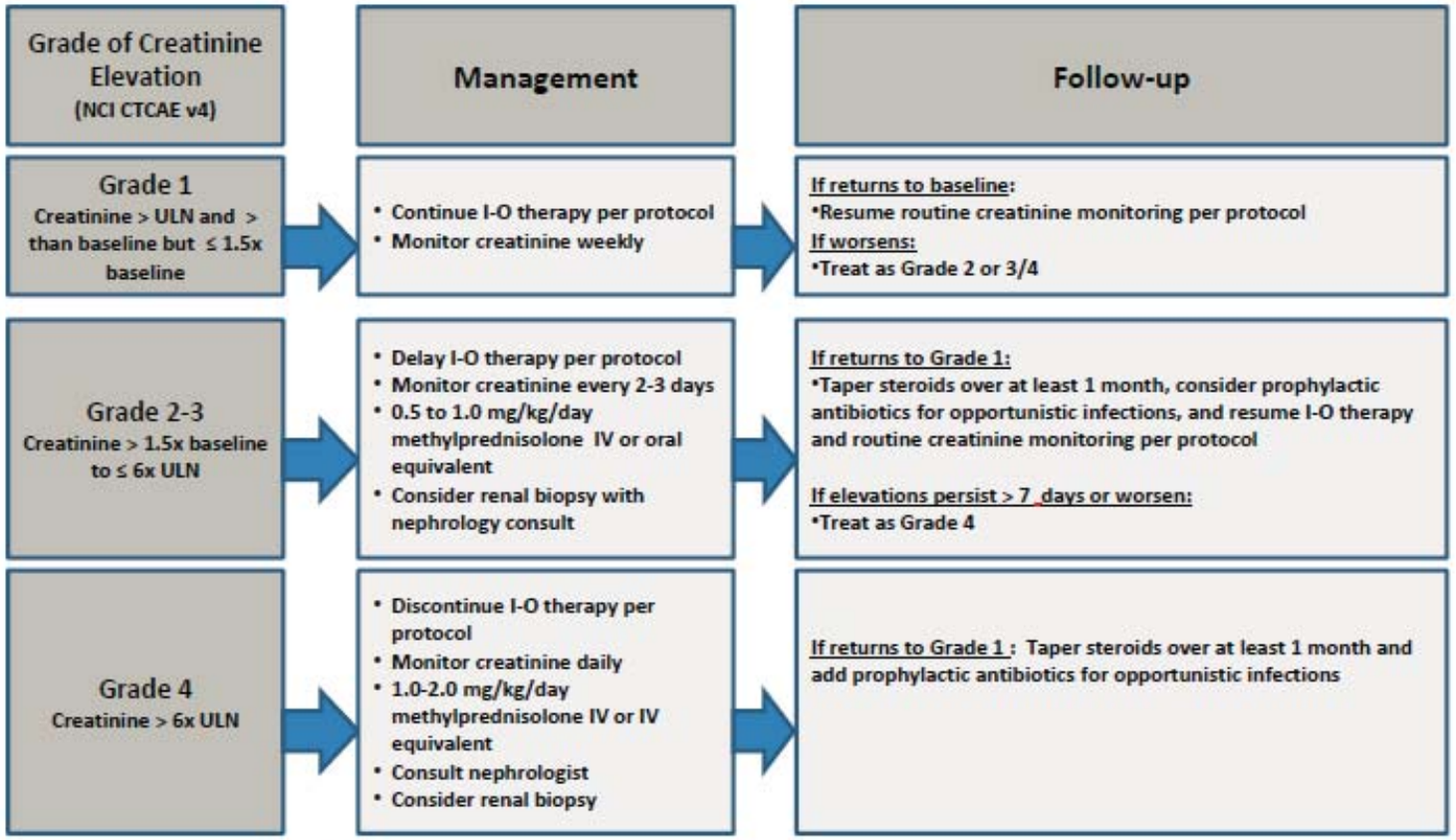


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

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

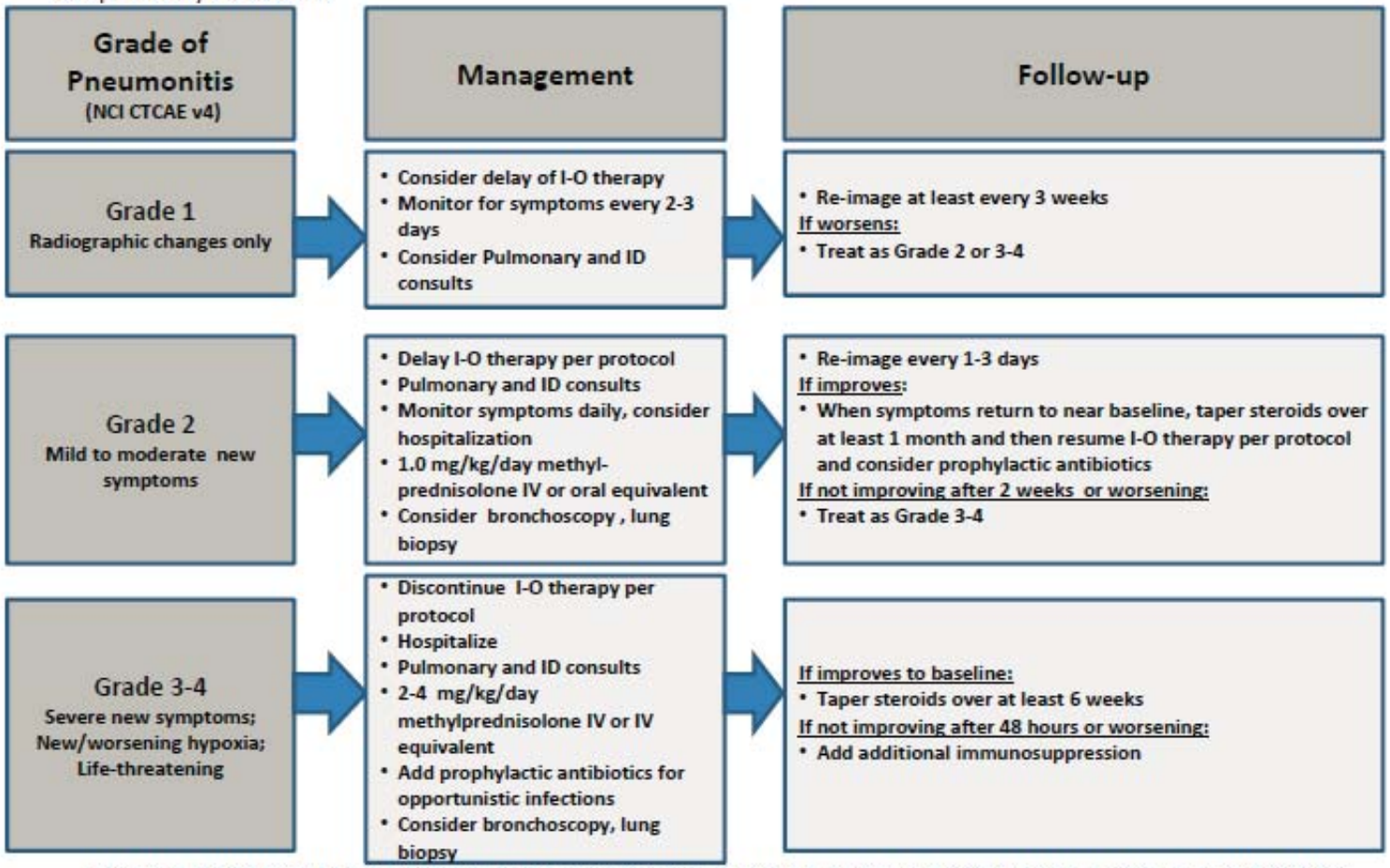


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Pulmonary Adverse Event Management Algorithm

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

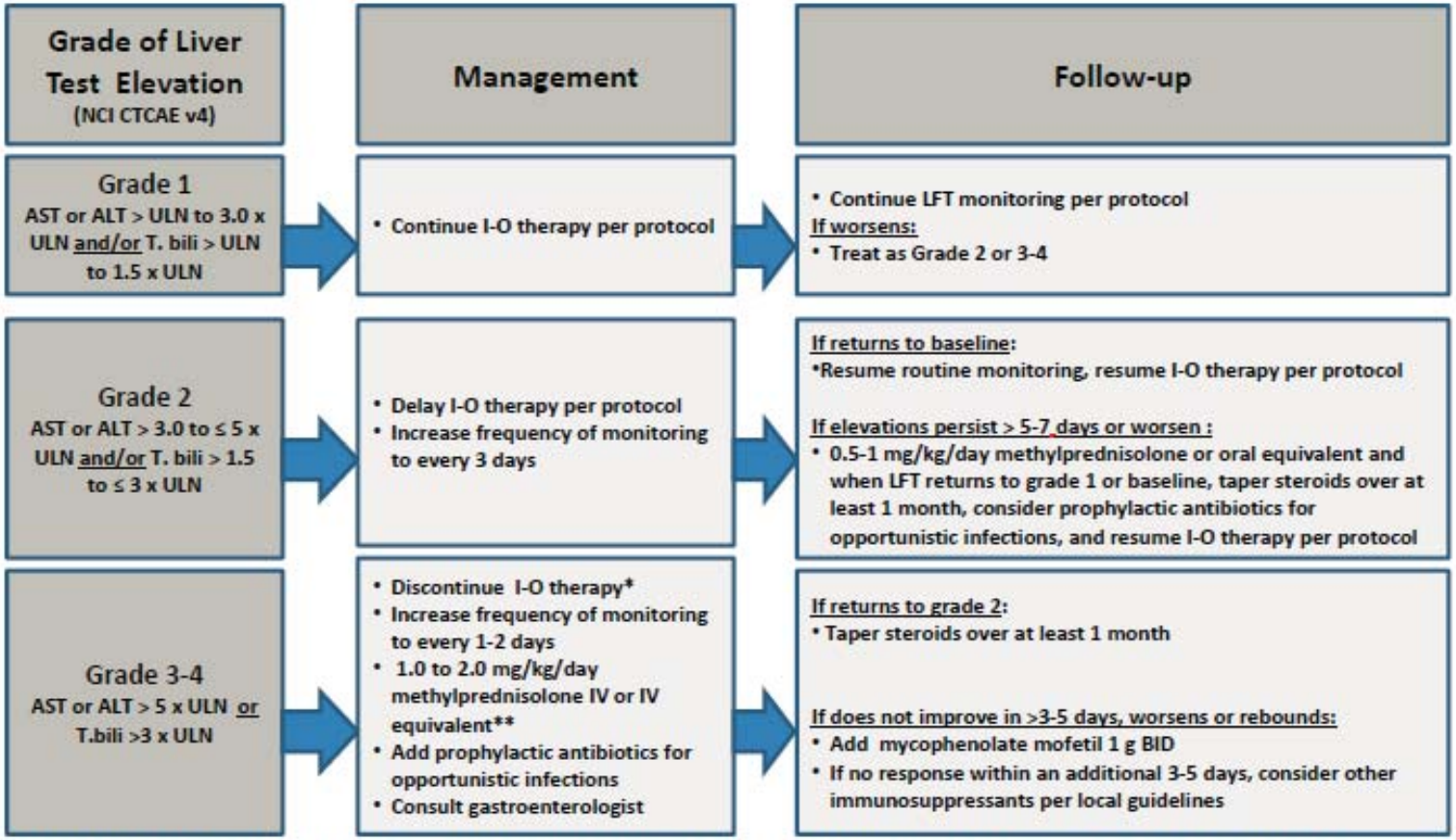


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Hepatic Adverse Event Management Algorithm

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



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

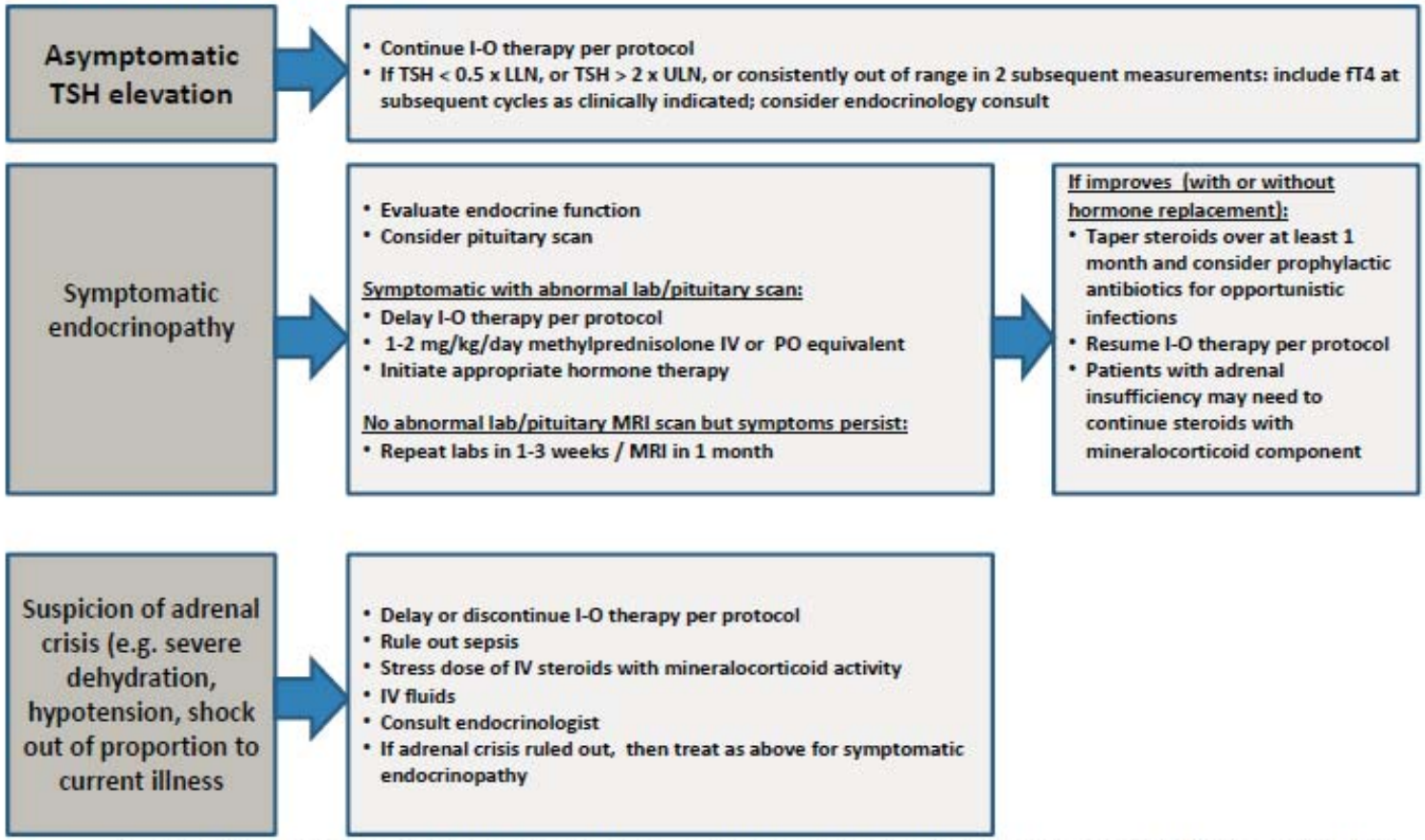
*I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.

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

Updated 05-Jul-2016

Endocrinopathy Management Algorithm

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

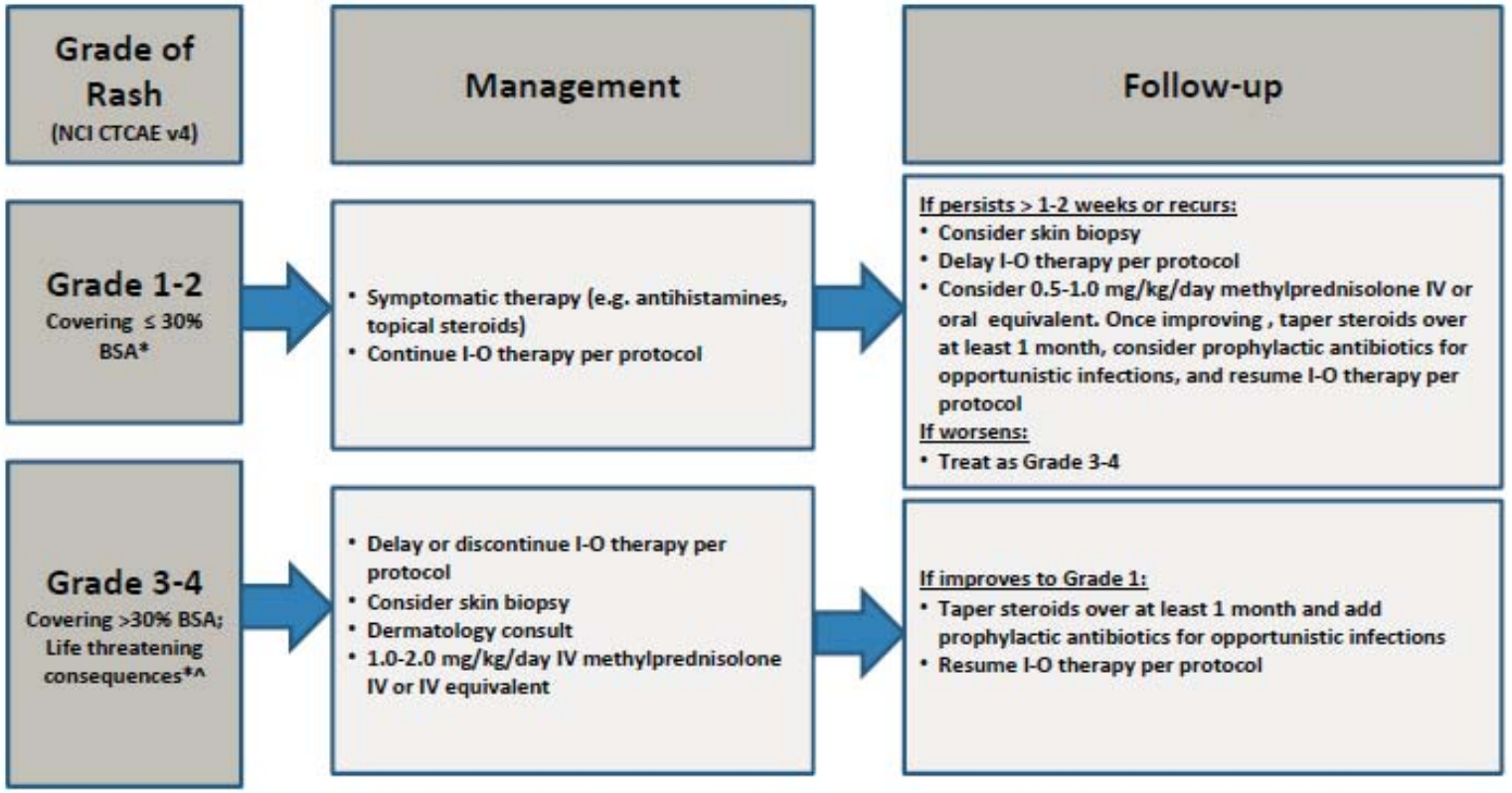


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Skin Adverse Event Management Algorithm

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

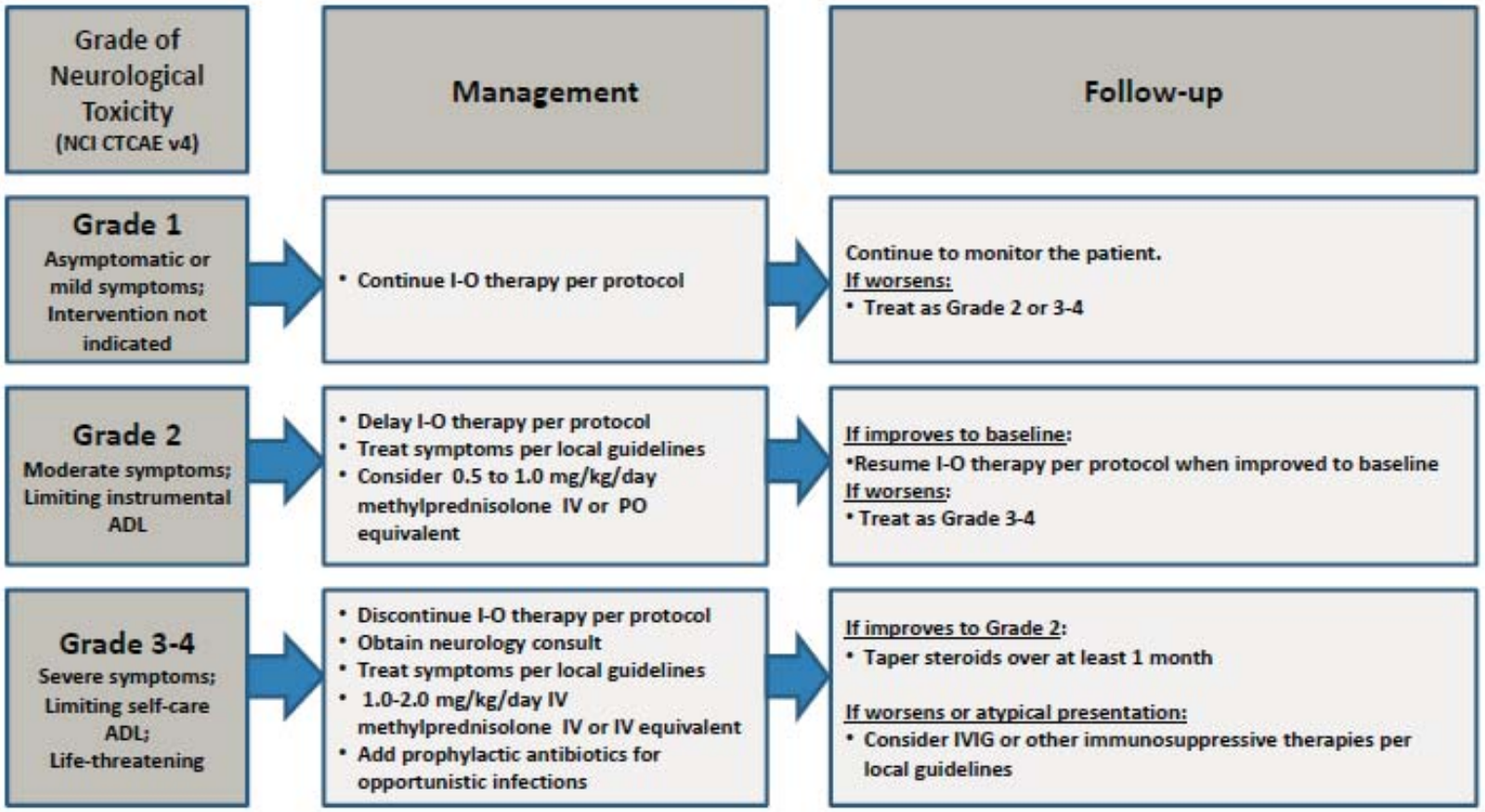


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Updated 05-Jul-2016

Neurological Adverse Event Management Algorithm

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



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

Updated 05-Jul-2016

APPENDIX 7 DOSE MODIFICATIONS FOR EPACADOSTAT/PLACEBO FOR EPACADOSTAT

The following dose modification criteria should be reviewed in conjunction with the immune-related adverse events management algorithm provided in Appendix 6.

In cases of potential overlapping chemotherapy/immunotherapy-related toxicities, irrespective of investigator's attribution, the Medical Monitor should be consulted prior to continuing dosing or restarting therapy.

Table 12-1: Dose Modifications for Epacadostat

Type of Adverse Events	Grade	Criteria	Guidance for dose modification
Pulmonary Adverse Events	Grade 2	AE resolves to near baseline in 0-2 weeks	Resume at -1 dose level
		AE does not resolve to near baseline in > 2 weeks	Treat as Grade 3/4. Permanently discontinue
		Second episode after re-challenge	Permanently discontinue
GI Adverse Events	Grade 2	AE resolves to ≤ Grade 1 or baseline in 0-4 weeks	Resume at the same dose level
		AE resolves to baseline between 4-6 weeks	Resume at -1 dose level
		AE does not resolve to baseline in > 6 weeks	Permanently discontinue
Hepatic Adverse Events	Grade 2	AE resolves to ≤ Grade 1 or baseline in 0-4 weeks	Resume at the same dose level
		AE resolves to baseline between 4-6 weeks	Resume at -1 dose level
		AE does not resolve to baseline in > 6 weeks	Permanently discontinue
Skin Adverse Events	Grade 3-4	AE resolves to baseline in 0-4 weeks	Resume at the same dose level
		AE resolves to baseline between 4-6 weeks	Resume at -1 dose level
		AE does not resolve to baseline in > 6 weeks	Permanently discontinue
Neurological Adverse Events	Grade 2	AE resolves to baseline in 0-4 weeks	Resume at the same dose level
		AE resolves to baseline between 4-6 weeks	Resume at -1 dose level
		AE does not resolve to baseline in > 6 weeks	Permanently discontinue

Table 12-1: Dose Modifications for Epacadostat

Type of Adverse Events	Grade	Criteria	Guidance for dose modification
Endocrine Adverse Events	Grade 2-3[a]	AE resolves to ≤ Grade 1 or baseline in 0-4 weeks	Resume at the same dose level
		AE resolves to baseline between 4-6 weeks	Resume at -1 dose level
		AE does not resolve to baseline in > 6 weeks	Permanently discontinue[a]
Hematological Adverse Events	Grade 4	Grade 4 neutropenia lasting ≤ 7 days Grade 4 lymphopenia or leukopenia that resolved to ≤ Grade 1 or baseline	Resume at -1 dose level
		All Grade 4 hematological AEs not included above	Permanently discontinue

[a] Grade 2-3 drug-related endocrinopathy adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Medical Monitor/designee.

APPENDIX 8 MONOAMINE OXIDASE INHIBITORS AND DRUGS ASSOCIATED WITH SIGNIFICANT MONOAMINE OXIDASE INHIBITORY ACTIVITY

Monoamine Oxidase Inhibitors	Drugs Associated With Significant Monoamine Oxidase Inhibitory Activity
Hydrazines (eg, phenelzine)	Meperidine
Caroxazone	Linezolid
Echinopsidine	Methylene blue
Furazolidone	
Tranylcypromine	
Brofaromine	
Metralindole	
Minaprine	
Moclobemide	
Pirlindole	
Toloxatone	
Lazabemide	
Pargyline	
Rasagiline	
Selegiline	

APPENDIX 9 UGT1A9 INHIBITORS AND INDUCERS

Any UGT1A9 inhibitors and inducers include aceclofenac, acitretin, amitriptyline, androsterone, cyclosporine, dasatinib, diclofenac, diflunisal, efavirenz, erlotinib, estradiol (17-beta), flutamide, gefitinib, gemfibrozil, glycyrrhetinic acid, glycyrrhizin, imatinib, imipramine, ketoconazole, lamotrigine, linoleic acid supplements, mefenamic acid, mycophenolic acid, niflumic acid, nilotinib, oxcarbazepine, phenobartital, phenylbutazone, phenytoin, probenecid propofol*, quinidine, rifampin, ritonavir, sorafenib, sulfinpyrazone, valproic acid, and verapamil.

*__Note__: Propofol, when used for short-term sedation during surgical/biopsy procedures, is allowed after consultation with the medical monitor. The epacadostat dose may be taken on the morning of the procedure and the evening dose held following the procedure. Epacadostat may be resumed the next day.

APPENDIX 10 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) WITH BMS MODIFICATIONS

1 EVALUATION OF LESIONS

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

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

1.1 Measurable

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

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

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

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

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

1.2 Non-Measurable

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

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

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

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

1.4 Baseline Documentation Of 'Target' And 'Non-Target' Lesions

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

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

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

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

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

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

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

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

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

2.1.1.2 Target lesions that become 'too small to measure'

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

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

2.1.1.3 Lesions that split or coalesce on treatment

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

2.2 Evaluation of Non-Target Lesions

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

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

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

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

2.2.1.1 When the patient also has measurable disease

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

2.2.1.2 When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition:

if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include, an increase in lymphangitic disease from localized to widespread, or may be described as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.2.2 New Lesions

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

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

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

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up

CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

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

2.3.2 Time Point Response

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

Table 2.3.2-1: Time Point Response: Patients With Target (± Non-Target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease and NE = inevaluable

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
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.

APPENDIX 11 COUNTRY SPECIFIC REQUIREMENTS

Argentina, Czech Republic, France, Germany, Italy, Spain

Criterion to exclude HIV positive participants including, but not limited to, the countries listed above if required by local regulatory authorities.

	Country-specific language
Section 2 Flow Chart/Time and Events Schedule, Table 2-1: Screening Assessments- Laboratory Tests	Add "HIV" to the list of laboratory tests
Section 6.2 Exclusion Criteria, Exclusion criterion 1.l	"Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)"to be replaced with "Positive test for HIV".

APPENDIX 12 EXPECTED TOXICITIES FOR NIVOLUMAB, EPACADOSTAT, CARBOPLATIN, CISPLATIN, GEMCITABINE, PACLITAXEL, AND PEMETREXED

The table entitled Expected Toxicities for Nivolumab, Epacadostat, Carboplatin, Cisplatin, Gemcitabine, Paclitaxel, and Pemetrexed lists the expected toxicities for each study drug in the CA2099NC/INCB 24360-309 study. Additional information can be found on each respective study drug's Investigational Brochure and/or Prescribing Information.

EXPECTED TOXICITIES FOR NIVOLUMAB, EPACADOSTAT, CARBOPLATIN, CISPLATIN, GEMCITABINE, PACLITAXEL, AND PEMETREXED

Expected Toxicities	**Immuno-Oncology AGENTS**		**Chemotherapy AGENTS**				
System Organ Class Preferred Term	**Nivolumab**	**Epacadostat**	**Carboplatin**	**Cisplatin**	**Gemcitabine**	**Paclitaxel**	**Pemetrexed**
Blood and Lymphatic System Disorders							
Anaemia		X	X	X	X	X	X
Leukopenia			X	X		X	X
Neutropenia			X	X	X	X	X
Thrombocytopenia			X	X	X	X	X
Cardiac Disorders							
Bradycardia						X	
Hypotension		X				X	
Ear and Labyrinth Disorders							
Ototoxicity			X	X			
Endocrine Disorders							
Hyperthyroidism	X						
Hypothyroidism	X	X					
Eye Disorders							
Ocular toxicity				X			
Gastrointestinal Disorders							
Abdominal distension		X					
Abdominal pain	X	X					
Colitis	X						

EXPECTED TOXICITIES FOR NIVOLUMAB, EPACADOSTAT, CARBOPLATIN, CISPLATIN, GEMCITABINE, PACLITAXEL, AND PEMETREXED

Expected Toxicities	Immuno-Oncology AGENTS		Chemotherapy AGENTS				
System Organ Class Preferred Term	**Nivolumab**	**Epacadostat**	**Carboplatin**	**Cisplatin**	**Gemcitabine**	**Paclitaxel**	**Pemetrexed**
Constipation	X	X					X
Diarrhoea	X	X	X	X	X	X	X
Dry mouth	X						
Nausea	X	X	X	X	X	X	X
Small intestinal obstruction		X					
Stomatitis	X				X		X
Vomiting	X	X	X	X	X	X	X
General Disorders and Administrative Site Conditions							
Asthenia	X	X	X	X			
Chills	X						
Oedema	X						X
Fatigue	X	X					X
Mucosal inflammation			X			X	X
Pain	X	X	X				
Pyrexia	X			X	X		X
Immune System Disorders							
Hypersensitivity			X	X		X	
Infections and Infestations							
Infection		X	X	X	X	X	X
Pneumonia		X					
Injury, Poisoning and Procedural Complications							
Infusion related reaction	X		X	X		X	
Investigations							
Alanine aminotransferase increased	X	X			X		X
Amylase increased	X			X			

EXPECTED TOXICITIES FOR NIVOLUMAB, EPACADOSTAT, CARBOPLATIN, CISPLATIN, GEMCITABINE, PACLITAXEL, AND PEMETREXED

Expected Toxicities	Immuno-Oncology AGENTS		Chemotherapy AGENTS				
System Organ Class Preferred Term	**Nivolumab**	**Epacadostat**	**Carboplatin**	**Cisplatin**	**Gemcitabine**	**Paclitaxel**	**Pemetrexed**
Aspartate aminotransferase increased	X	X	X	X	X	X	X
Blood alkaline phosphatase increased	X		X		X	X	
Blood bilirubin increased			X	X	X	X	
Blood creatinine increased	X		X	X	X		X
Blood thyroid stimulating hormone increased	X						
Blood urea increased			X	X	X		
Blood uric acid increased				X			
Electrocardiogram abnormal						X	
Lipase increased	X						
Weight decreased		X					
Metabolism And Nutrition Disorders							
Decreased appetite	X	X					X
Dehydration		X		X			
Hyperglycaemia	X						
Hypocalcaemia			X	X			
Hypokalaemia		X	X	X			
Hypomagnesemia			X	X			
Hyponatraemia	X	X	X	X			
Hypophosphataemia				X			
Musculoskeletal and Connective Tissue Disorders							

EXPECTED TOXICITIES FOR NIVOLUMAB, EPACADOSTAT, CARBOPLATIN, CISPLATIN, GEMCITABINE, PACLITAXEL, AND PEMETREXED

Expected Toxicities	Immuno-Oncology AGENTS		Chemotherapy AGENTS				
System Organ Class Preferred Term	**Nivolumab**	**Epacadostat**	**Carboplatin**	**Cisplatin**	**Gemcitabine**	**Paclitaxel**	**Pemetrexed**
Arthralgia	X	X				X	
Back pain	X	X					
Myalgia	X					X	
Nervous System Disorders							
Dizziness	X	X					
Headache	X	X					
Paraesthesia					X		
Neuropathy peripheral			X	X		X	X
Somnolence					X		
Psychiatric Disorders							
Insomnia		X					
Renal and Urinary Disorders							
Haematuria					X		
Proteinuria					X		
Respiratory, Thoracic, And Mediastinal Disorders							
Cough	X	X					
Dyspnoea	X	X			X		
Pneumonitis	X	X					
Skin and Subcutaneous Tissue Disorders							
Alopecia			X	X	X	X	X
Dry skin	X						
Erythema	X						
Pruritus	X	X					X
Pruritus generalised	X	X					
Rash	X	X		X	X		X
Rash maculo-papular	X	X					
Rash papular		X					

EXPECTED TOXICITIES FOR NIVOLUMAB, EPACADOSTAT, CARBOPLATIN, CISPLATIN, GEMCITABINE, PACLITAXEL, AND PEMETREXED

Expected Toxicities	Immuno-Oncology AGENTS		Chemotherapy AGENTS				
System Organ Class Preferred Term	**Nivolumab**	**Epacadostat**	**Carboplatin**	**Cisplatin**	**Gemcitabine**	**Paclitaxel**	**Pemetrexed**
Vitiligo	X						
Vascular disorders							
Haemorrhage			X	X	X	X	

Note: MedDRA Medical Dictionary for Regulatory Activities. ICH Version 20. March 2017.

Sources:

1) Incyte Epacadostat (INCB024360) Investigator's Brochure. Version Number: 09. Report Date: 12 DEC 2016 Table 23 Expected Treatment-Emergent Adverse Events for Epacadostat Monotherapy (N = 149) and Epacadostat Risk section from Global Informed Consent.

2) Bristol-Myers Squib Investigator Brochure Nivolumab BMS-936558 MDX1106 ONO-4538. Version no.: 16 Version date: 23-Jun-2017. Table 5.6.1-1

3) Carboplatin- carboplatin injection, solution. Sanja Pharmaceutical Prescribing Information March, 2016 and National Cancer Institute Cancer Therapeutic Evaluation Program Possible Side Effects of Carboplatin (Table Version Date: March 24, 2015)

4) Cisplatin-cisplatin injection. BluePoint Laboratories. Prescribing Information April, 2016 and National Cancer Institute Cancer Therapeutic Evaluation Program Possible Side Effects of Cisplatin (Table Version Date: April 20, 2015)

5) Gemzar (gemcitabine for injection), for intravenous use. Eli Lilly. Highlights of Prescribing Information. Initial U.S. Approval: 1996. Revised: 09/2017.

6) Taxol (paclitaxel) injection. Bristol-Myers Squibb. Prescribing Information and Patient Information. Rev April 2011

7) Alimta - pemetrexed disodium heptahydrate injection, powder, lyophilized, for solution Eli Lilly and Company. Highlights of Prescribing Information. Initial US Approval: 2004. Revised 2/2015.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 01	23-Oct-2017	ALK and ROS1 testing are mandatory for participants with nonsquamous histology Table for expected toxicities from study drugs added to Appendix 12
Original Protocol	15-Sep-2017	Not applicable

Signature Manifest

Document Number: IC-DEV-PROT-AMEND-0296 **Revision:** 1

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Quick Approval

Approve Now

Name/Signature	Title	Date	Meaning/Reason
[redacted]	[redacted]	21 Nov 2017, 03:06:26 PM	Approved

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[redacted]	[redacted]	02 Feb 2018, 04:25:39 PM	Approved