Official Title of Study:

An Open-Label Exploratory Phase 2/3 Study of Nivolumab with Standard of Care Therapy vs Standard of Care Therapy for First-Line Treatment of Metastatic Colorectal Cancer (CheckMate 9X8: CHECKpoint pathway and nivoluMab clinical Trial Evaluation 9X8)

NCT Number: NCT03414983

Document Date (Date in which document was last revised): November 13, 2020

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Clinical Protocol CA2099X8

An Open-Label Exploratory Phase 2/3 Study of Nivolumab with Standard of Care Therapy vs Standard of Care Therapy for First-Line Treatment of Metastatic Colorectal Cancer (CheckMate 9X8: CHECKpoint pathway and nivoluMab clinical Trial Evaluation 9X8)

Protocol Amendment 07

Incorporates Administrative Letter 05

[redacted]

24-hr Emergency Telephone Number

[redacted]

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 07	13-Nov-2020	[redacted]
Administrative Letter 05	28-Sep-2020	
Revised Protocol 06	02-Jun-2020	Major change: Clarifies study treatment duration for standard of care (SOC) SOC may continue, after the maximum treatment duration of 24 months for nivolumab, until progression, unacceptable toxicity, withdrawal of consent, or the end of the study, whichever comes first.
Revised Protocol 05	19-Dec-2019	This revised protocol removes Interim Analysis 2 (IA2).
Revised Protocol 04	07-Dec-2018	Clarifies the infusion days for fluorouracil, updates Appendix 3, and aligns Appendix 4 with contraceptive guidance for nivolumab and other components of study treatment.
Revised Protocol 03	13-Sep-2018	Incorporates Administrative Letter 03, and reinstates exclusion criteria 2j.
Administrative Letter 03	11-Sep-2018	Adding Appendix 11 back into the document
Revised Protocol 02	06-Aug-2018	Incorporates Administrative Letter 02 and updates to be consistent with SmPC and label information. Revises prohibited and/or restricted treatments; laboratory tests, assessments, and other analyses; dose modification criteria; urinalysis [redacted] sample collection requirements. [redacted] clarifies eligibility criteria. [redacted] Minor changes and corrections including revisions to reflect the most recent language for BMS studies.
Administrative Letter 02	23-Apr-2018	[redacted]
Revised Protocol 01	02-Feb-2018	Incorporates Administrative Letter 01, revisions to laboratory tests exclusion criteria, revisions to dose modification criteria, urinalysis [redacted] sample collection requirements. [redacted] Addition of a definition of DILI for participants with elevated liver function tests at baseline. Updated rationale for the 2-year treatment duration, in addition of a number of other minor changes and corrections.
Administrative Letter 01	07-Dec-2017	[redacted]
Original Protocol	13-Oct-2017	Not applicable

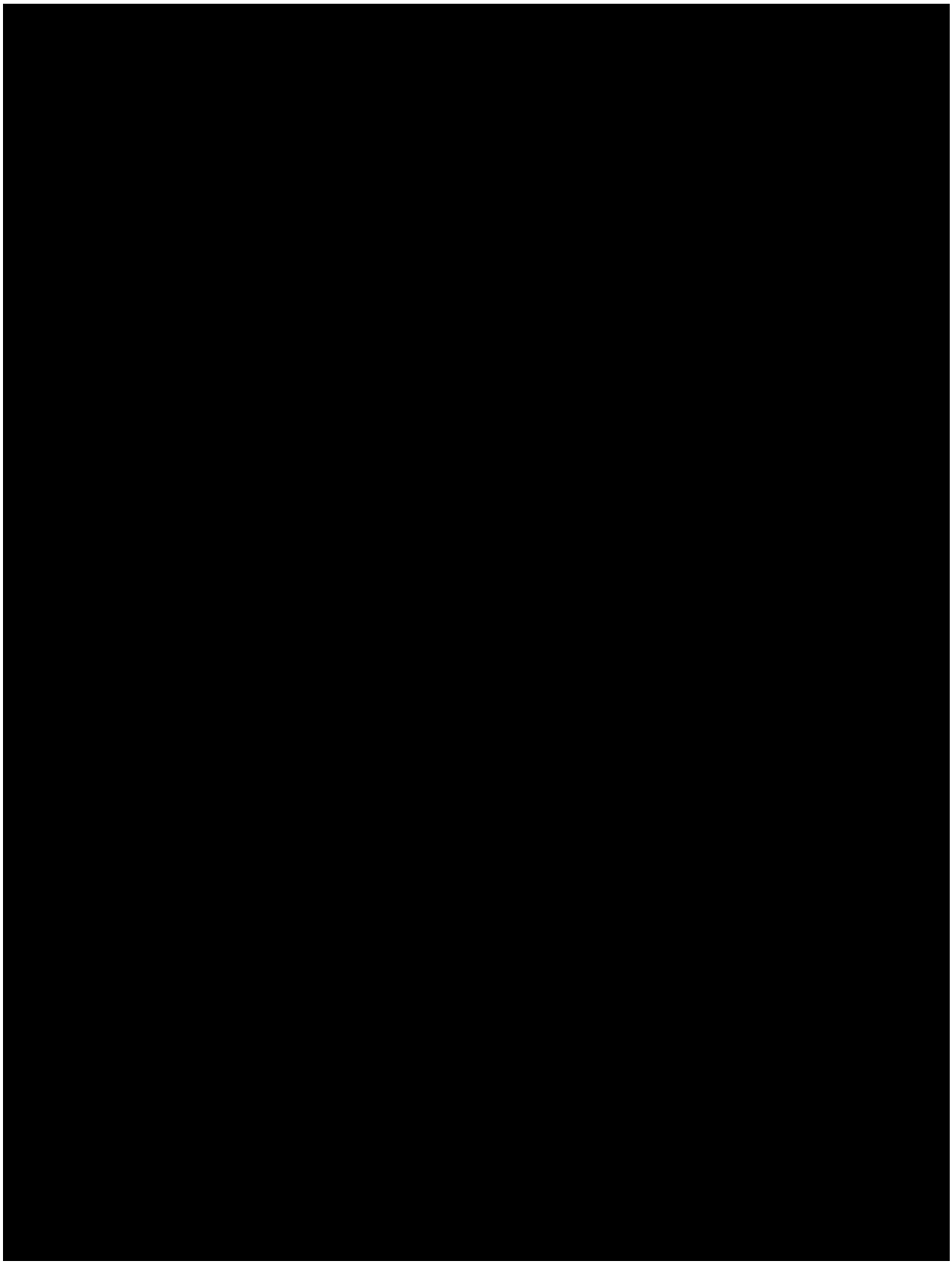


TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: An Open-Label Exploratory Phase 2/3 Study of Nivolumab with Standard of Care Therapy vs Standard of Care Therapy for First-Line Treatment of Metastatic Colorectal Cancer

(CheckMate 9X8: CHECKpoint pathway and nivoluMab clinical Trial Evaluation 9X8)

Study Phase: 2/3

[redacted]

CA209-9X8 (CHECKpoint pathway and nivoluMAB clinical trial evaluation 9X8) is a Phase 2/3, open-label, multi-center trial to evaluate nivolumab in combination with standard of care (SOC) therapy (mFOLFOX6) with bevacizumab for the treatment of first-line metastatic colorectal cancer (mCRC)[1]. [redacted]

Study Population:

Male and female participants of 18 years of age or more with first-line histologically confirmed metastatic colorectal cancer, not amenable to curative resection.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare the efficacy of nivolumab plus SOC chemotherapy with bevacizumab (Nivo+SOC) with SOC chemotherapy with bevacizumab (SOC) in participants with mCRC	• Progression Free Survival (PFS) by BICR
Secondary	
• To evaluate preliminary efficacy in all randomized participants	• ORR, DCR, DoR, TTR by BICR per RECIST v1.1 • ORR, PFS, DCR, DoR, TTR by investigator per RECIST v1.1 • OS
• To characterize the safety and tolerability of nivolumab in combination with standard therapy with bevacizumab	• Safety (including but not limited to): Incidence of AEs, SAEs, deaths, and clinical abnormalities per CTCAE (Version 4)
[redacted]	

Objectives	Endpoints
[redacted]	

AEs, adverse events; BICR, blinded independent central review; DCR, disease control rate; DoR, duration of response; [redacted] OS, overall survival; ORR, objective response rate; [redacted] SOC, standard of care; [redacted] TTR, time to response; [redacted].

Overall Design:

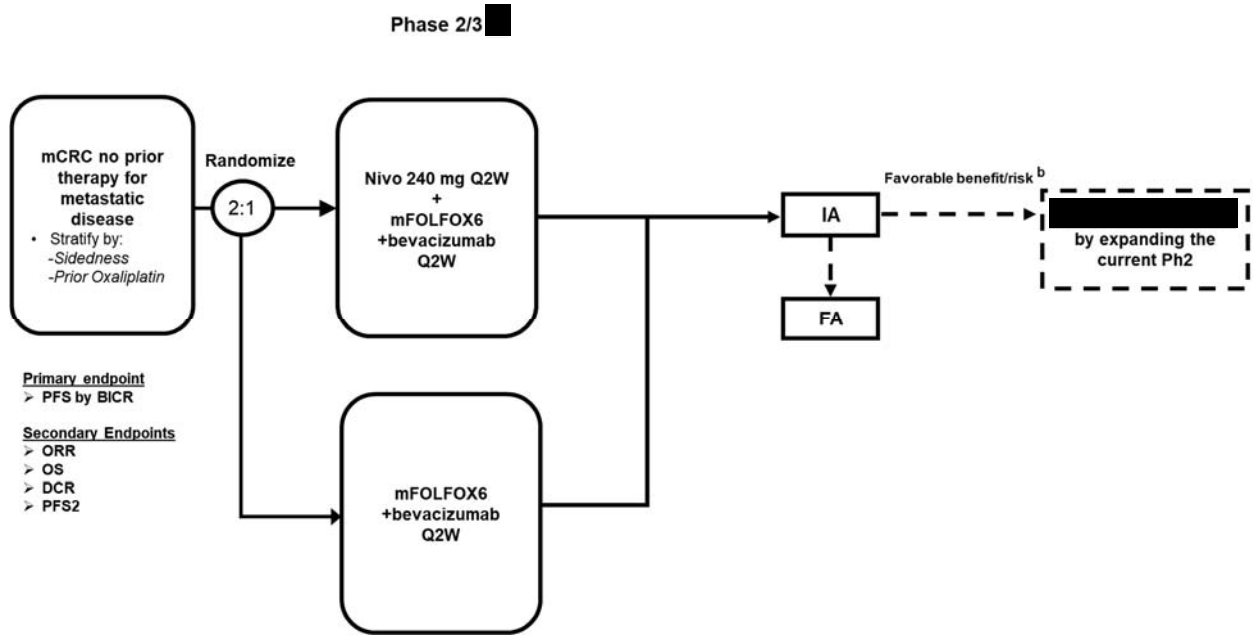
This is a Phase 2/3 open-label, multi-center trial of nivolumab in combination with SOC first-line chemotherapy with bevacizumab to evaluate the safety profile and clinical activity of this regimen in participants with treatment-naive metastatic colorectal cancer (mCRC).

In Phase 2, participants will be randomized to treatment with mFOLFOX6 + bevacizumab with or without nivolumab. [redacted]

Participants will be treated until progression, unacceptable toxicity, withdrawal of consent, or the end of the study, whichever comes first. Nivolumab will be given for a maximum of 24 months.

[redacted]

Figure 1: Study Design



DCR, disease control rate; FA; final analysis; IA, interim analysis; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

[redacted]

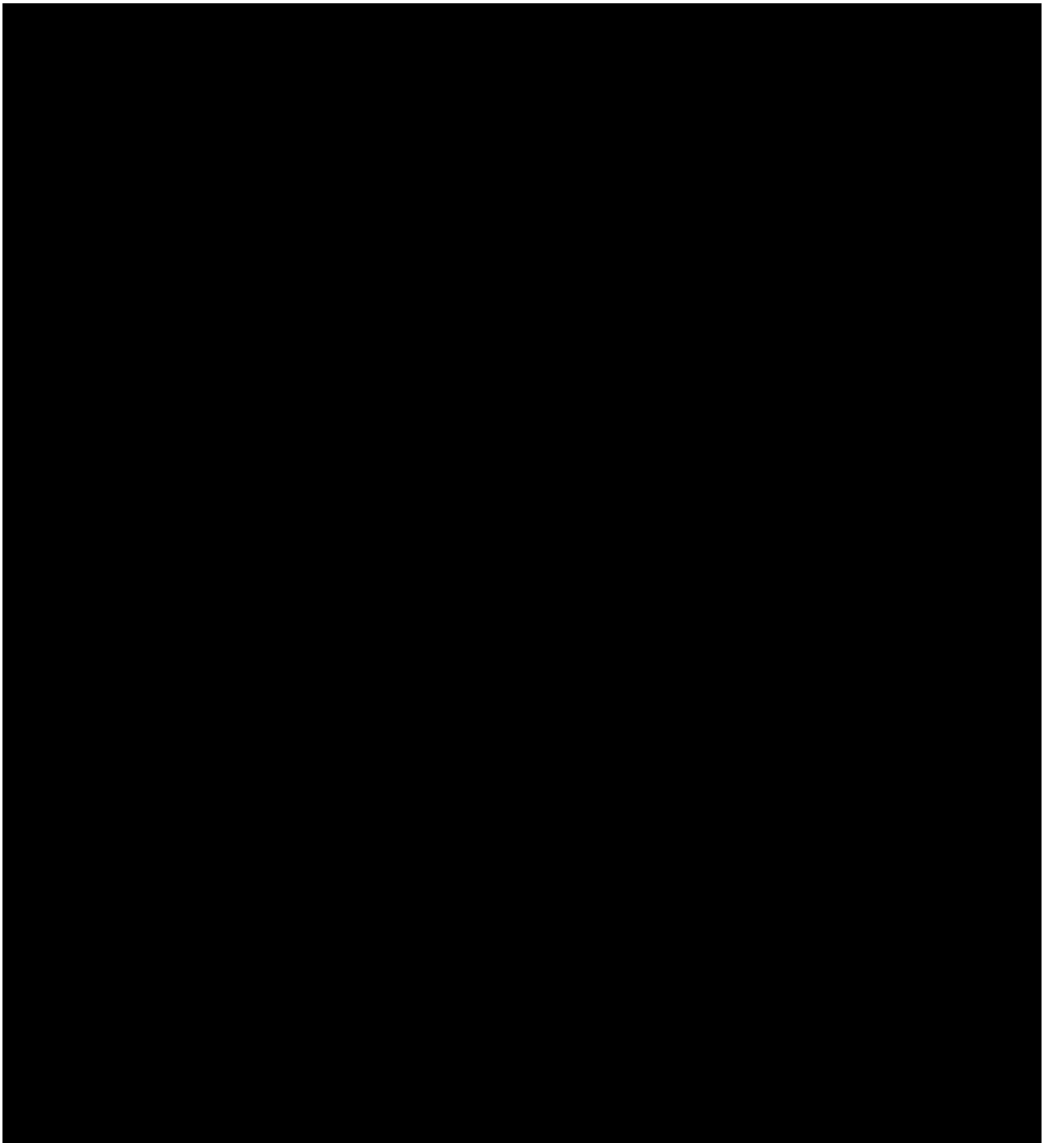
[b] Depending on the results at the time of interim analysis (IA), different possible decisions may be made as indicated by dashed arrows. If there is not enough evidence of favorable benefit/risk at IA, the Phase 2 study will continue to complete with 180 participants unless unacceptable safety concern arises.

One interim analysis (IA) is planned in Phase 2 portion of the study to [redacted].

[redacted] The interim results will guide the following decisions:

- When a strong efficacy signal is observed for all randomized participants, [redacted] is observed and no substantial differential effects by subgroups, the study will expand [redacted].
- Otherwise, the study continues as planned.

If there are not enough data to support an internal decision at the time of IA, the study will continue to 180 randomized participants.



Treatment Arms and Duration:

Study treatments:

Study Drug for CA2099X8		
Medication	**Potency**	**IP/Non-IP**
Nivolumab [a] Solution for Injection	100 mg (10 mg/ml) and 40 mg (10 mg/ml)	IP
Oxaliplatin [b]	various strengths	IP
{Leucovorin / Calcium Folinate} [b]	various strengths	IP
Fluorouracil [b]	various strengths	IP
Bevacizumab [b]	various strengths	IP

[a] May be labeled as either "BMS-936558-01" or "Nivolumab"

[b] These products may be obtained by the investigational sites as local commercial products in certain countries if allowed by local regulations.

[redacted]

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA2099X8)

Procedure[a]	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	Register in Interactive Response system to obtain participant number. Must be obtained prior to performing any protocol related screening procedures. Study allows for re-enrollment of a participant that has discontinued the study as a pre-treatment failure. If re-enrolled, the participant must be re-consented and assigned a new participant number from IRT.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening (re-enrollment if applicable) and confirmed prior to randomization.
Medical History	X	All medical history relevant to the disease under study
Baseline Tumor Submission	X	Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections (minimum 20 slides from a metastatic site or 25 from a primary colon site), obtained within 180 days prior to enrollment and after the last dose of the most recent systemic anti-cancer therapy, with an associated pathology report, must be submitted to the core laboratory for inclusion. For participants with samples outside of the above criteria, a fresh biopsy will be required. If the above sample is not from the primary colon tumor, an additional archival sample of at least 5 slides must be submitted from the primary colon tumor. These five slides may be submitted after randomization. Central lab must provide 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.
Baseline Tumor Assessment	X	Must be performed within 28 days prior to first dose. Brain imaging to be performed at screening for participants with a history or clinical symptoms of brain metastasis. Bone scan may be performed as clinically indicated. See Section 9.1.1

Table 2-1: Screening Procedural Outline (CA2099X8)

Procedure[a]	Screening Visit	Notes
Safety Assessments		
Targeted Physical Examination, Measurements, Vital Signs and Performance Status	X	Height, weight, Performance Status (ECOG, see Appendix 6), BP, HR, Temperature. Must be collected within 14 days prior to randomization.
ECG	X	Within 14 days prior to randomization.
Assessment of Signs and Symptoms	X	Must be performed within 14 days prior to randomization.
Concomitant Medication Use	X	Must be collected within 14 days prior to randomization. Vaccine use within 30 days prior to randomization.
SAE Assessment	X	Serious Adverse Event collection from time of consent.
Laboratory Tests		Includes blood and urine samples.
CBC w/differential, Chemistry, Endocrine, Viral, urinalysis	X	CBC, chemistry, urinalysis and endocrine testing must be performed within 14 days prior to randomization. Note: Laboratory tests do not need to be repeated on C1D1 if screening lab results are deemed still clinically valid by the treating investigator. Urinalysis or urine dipstick including protein, glucose, blood, leukocyte esterase, specific gravity, pH[b] Viral testing to be performed within 28 days prior to randomization. Refer to Section 9.4.3 for list of laboratory tests to conduct.
Pregnancy Test	X	For WOCBP only: Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done at screening visit and within 24 hours prior to first dose of study therapy. See Appendix 4 For females under the age of 55, FSH > 40 mIU/mL is required to confirm menopause.
MMR/Microsatellite Status	X	Confirm availability of pathology report for MMR or microsatellite-testing results. Report must contain MMR or microsatellite-testing results and should also contain specific results per markers tested by IHC or PCR. Please see inclusion criteria (Section 6.1) [redacted] for details.

Table 2-1: Screening Procedural Outline (CA2099X8)

Procedure[a]	Screening Visit	Notes
RAS and BRAF mutation Status	X	Verify RAS and BRAF mutation status, including Kirsten Rat Sarcoma (KRAS) and Neuroblastoma Rat Sarcoma (NRAS), based on local testing [redacted]
CEA (and CA19-9) Assessment	X	CEA tumor marker will be assessed at screening. If CEA is within normal limits, a CA19-9 tumor marker will be checked. If the CA19-9 is elevated, this patient will be followed with the CA19-9 AND CEA tumor markers. However, if the CA19-9 is within normal limits, this patient will be followed with CEA tumor marker only.

BP, blood pressure; CA19-9, cancer antigen 19-9; CBC, complete blood count; CEA, carcino embryonic antigen; HR, heart rate; MMR, mismatch repair; SAEs, serious adverse events.

[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

[b] Urinalysis or urine dipstick. If blood, protein, or leukocytes esterase are positive on the dipstick, microscopic examination of the sediment is required. If urine protein is ≥ 2+ from urine dipstick or equivalent from random urinalysis, results from a 24-hour urine collection or urine protein to creatinine ratio (UPCR) are required to determine eligibility (refer to exclusion criteria).

Table 2-2: On-Treatment Procedural Outline (CA2099X8)

Procedure [a]	Cycle 1 (1 cycle = 4 weeks)[b]				Each Subsequent Cycle (cycle = 4 weeks)				Notes
	D1	D2	D15	D16	D1	D2	D15	D16	
Safety Assessments									
Targeted Physical Examination, Measurements, Vital Signs, Performance Status	X		X		X		X		Weight, BP, HR, Temperature and Performance Status
Adverse Events Assessment (including SAEs)	Continuously								Record at each visit
Concomitant Medication	Continuously								Record at each visit
Laboratory Tests									
Pregnancy Test	X	See notes							Serum or urine pregnancy test to be done within 24 hours prior to first dose, and then every 4 weeks (± 7 days) regardless of dosing schedule. See Appendix 4.
CBC w/differential, Chemistry panel and urinalysis	X		X		X		X		Laboratory assessments should be performed within 72 hours prior to each infusion. Urinalysis or urine dipstick including protein, glucose, blood, leukocyte esterase, specific gravity, pH to be performed within 72 hrs prior to each bevacizumab infusion[d]. Refer to Section 9.4.3
Thyroid Testing	X				X				Refer to Section 9.4.3
CEA (and CA19-9) Assessment	X	See notes							Selected tumor marker(s) at screening (CEA alone or CEA and CA19-9) will be assessed every 2 weeks (±7 days) until Week 12, then every 8 weeks (±7 days) thereafter, prior to each restaging.

Table 2-2: On-Treatment Procedural Outline (CA2099X8)

Procedure [a]	Cycle 1 (1 cycle = 4 weeks)[b]				Each Subsequent Cycle (cycle = 4 weeks)				Notes
	D1	D2	D15	D16	D1	D2	D15	D16	
Efficacy Assessments									
Tumor assessments	Imaging will begin at Week 12 (± 7 days) from randomization, and then every 8 weeks (± 7 days) thereafter until confirmed progression, withdrawal of consent, or the study ends, whichever occurs first. This schedule should be followed even if treatment delay occurs.								
Brain Imaging	See Section 9.1.1								
[redacted]									

Table 2-2: On-Treatment Procedural Outline (CA2099X8)

Procedure [a]	Cycle 1 (1 cycle = 4 weeks)[b]				Each Subsequent Cycle (cycle = 4 weeks)				Notes
	D1	D2	D15	D16	D1	D2	D15	D16	
[redacted]									
IRT Vial Assignment									

Table 2-2: On-Treatment Procedural Outline (CA2099X8)

Procedure [a]	Cycle 1 (1 cycle = 4 weeks)[b]				Each Subsequent Cycle (cycle = 4 weeks)				Notes
	D1	D2	D15	D16	D1	D2	D15	D16	
Randomization	X								Randomization after eligibility is confirmed. First treatment should occur within 3 calendar days of randomization.
Dispense Study Treatment:									
Nivolumab 240 mg flat dose (Arm A) IV	X		X		X		X		ONLY in ARM A (Nivolumab + SOC)
Oxaliplatin 85 mg/m^2 IV	X		X		X		X		
Leucovorin 400 or 350 mg/m^2 IV[c]	X		X		X		X		
Fluorouracil 400 mg/m^2 IV	X		X		X		X		
Fluorouracil 1200 mg/m^2 IV[c]	X		X		X		X		Continuous infusion over 24 hours. Day 1 (or Day 15) through Day 2 (or Day 16) of each cycle (total dose of 2400 mg/m^2 over 48 hours)
OR									
Fluorouracil 2400 mg/m^2 IV[c]	X		X		X		X		Continuous infusion over 46 to 48 hours. Day 1 (or Day 15) through Day 2 (or Day 16)
Bevacizumab 5 mg/kg IV	X		X		X		X		

BP, blood pressure; CA19-9, cancer antigen 19-9; CBC, complete blood count; CEA, carcino embryonic antigen; HR, heart rate; [redacted] IRT, interactive response technology; [redacted] SAEs, serious adverse events.

Note: All scheduled clinic visits are to occur within ± 3 days of scheduled day.

[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

[b] If a dose is delayed, the procedures schedule for that same timepoint should also be delayed to coincide with when that timepoint's dosing actually occurs. If dose is delayed, CEA (and CA19-9) schedule should be kept regardless of dosing.

[c] Regimen for FOLFOX6 may be used as per local standards

[d] If urine protein is ≥ 2+ from urine dipstick or equivalent from random urinalysis a 24 hour urine collection or UPCR should be performed and results obtained before the next treatment with bevacizumab. See Section 7.4.4 for bevacizumab dose modification criteria.

Table 2-3: Follow-up Procedural Outline (CA2099X8)

Procedure [a]	Safety Follow-up visits 1 and 2[b]	Survival Follow-up[c]	Notes
Safety Assessments			
Targeted Physical Examination, Vital Signs	X		
Adverse Events Assessment (including SAEs)	X		Participants will be followed for treatment 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 last dose. (See Appendix 3)
Concomitant Medication Review	X		
Review of Subsequent Cancer Therapies	X	X	Additional subsequent cancer therapy details such as regimen, setting of the regimen, line of therapy, start date and end date of each regimen, best response to the regimen and date of progression after second line therapy will be collected.
Laboratory Tests			
Pregnancy Test	X		
CBC w/differential, Chemistry panel, Thyroid testing, and urinalysis	X		To be done at safety follow-up visit 1. To be repeated at safety follow-up visit 2 if study related toxicity persists. FU visit 1 ONLY: Urinalysis or urine dipstick including protein, glucose, blood, leukocyte esterase, specific gravity, pH[d] Refer to Section 9.4.3 Clinical Safety Laboratory Assessments for list of laboratory tests.
Efficacy Assessments			
Tumor assessments	Participants who enter the follow-up period without tumor progression will continue to have tumor imaging assessments as per on-treatment schedule (at Week 12 from randomization, and then every 8 weeks thereafter until confirmed progression, withdrawal of consent, or the study ends, whichever occurs first).		

Table 2-3: Follow-up Procedural Outline (CA2099X8)

Procedure [a]	Safety Follow-up visits 1 and 2[b]	Survival Follow-up[c]	Notes
Brain Imaging	See Section 9.1.1		
[redacted]			
Participant Status			
Survival status	X	X	Every 3 months after safety follow-up visit 2; may be accomplished by visit, phone contact or email, to assess subsequent anti-cancer therapy for up to 3 years after completing safety follow up visit in all cohorts.

CBC, complete blood count; SAEs, serious adverse events; [redacted].

Note: All scheduled clinic visits are to occur within ± 3 days of scheduled day.

[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

[b] Participants must be followed for at least 100 days after last dose of study treatment. Follow-up visit 1 (FU1) = 30 days from the last dose (± 7 days) or coincides with the date of discontinuation (± 7 days) if date of discontinuation is greater than 42 days after last dose, Follow-up visit 2 (FU2) = 100 days (± 7 days) from last dose. Both Follow Up visits should be conducted in person.

[c] 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 may request that survival data be collected on all treated participants outside of the 3 month specified window. At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact.

[d] Urinalysis or urine dipstick. If blood, protein, or leukocytes esterase are positive on the dipstick, microscopic examination of the sediment is required. If urine protein is ≥ 2+ from urine dipstick or equivalent from random urinalysis, 24-hour urine collection or UPCR may be performed if deemed clinically indicated by the investigator.

3 INTRODUCTION

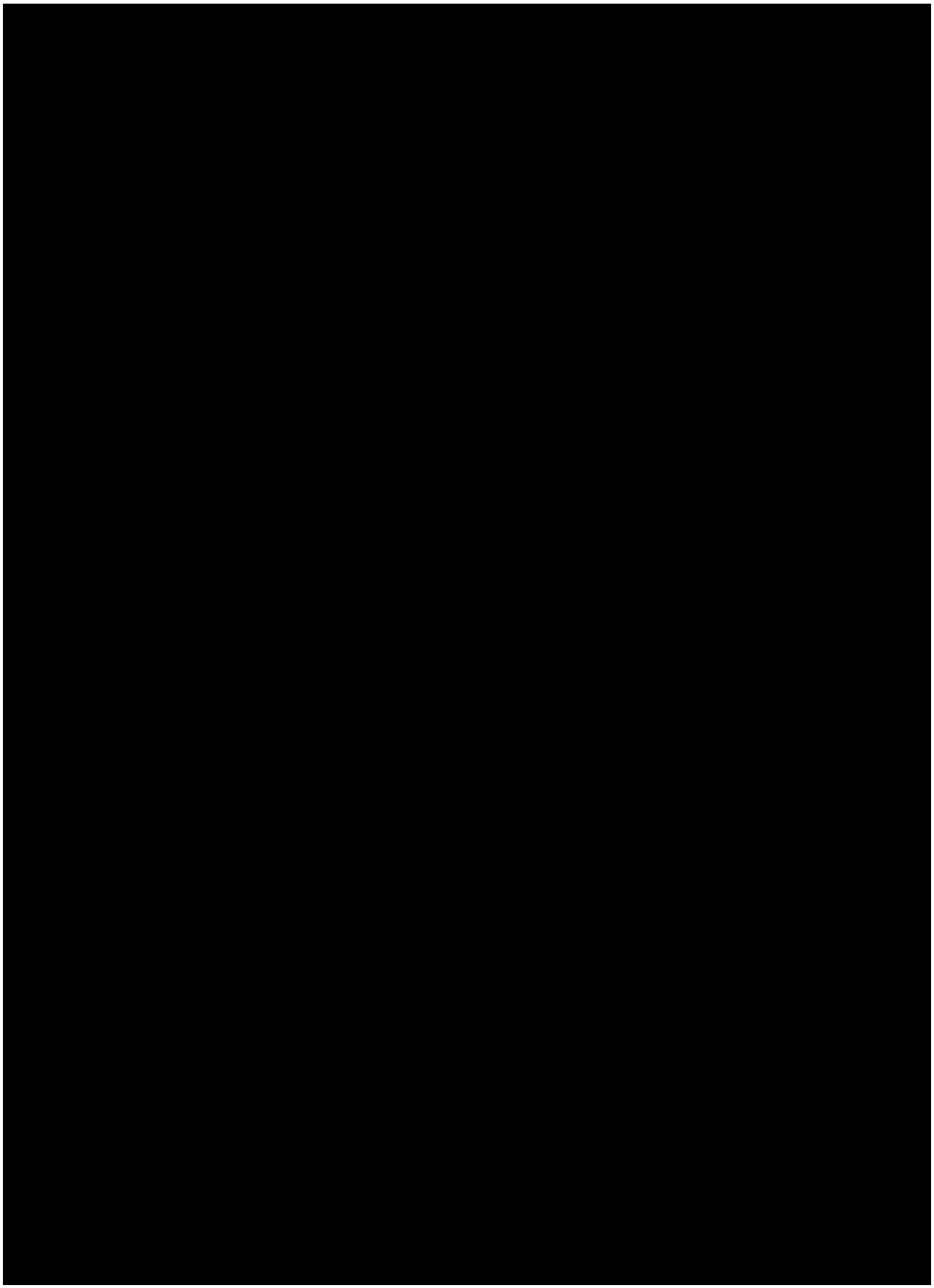
[redacted]

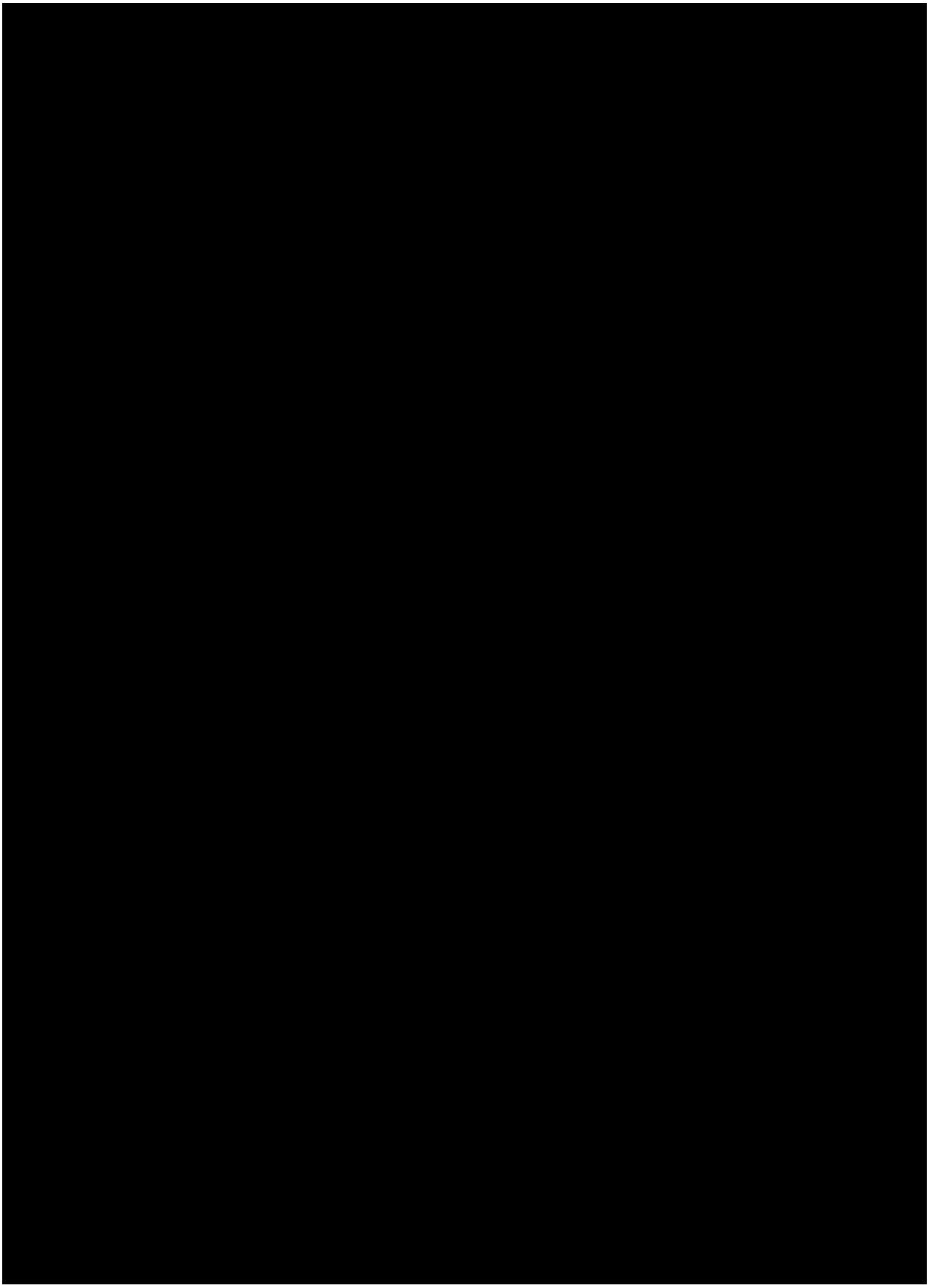
CA209-9X8 (CHECKpoint pathway and nivoluMAB clinical trial evaluation 9X8) is a Phase 2/3, open-label, multi-center trial to evaluate nivolumab (BMS-936558) in combination with standard of care (SOC) chemotherapy (mFOLFOX6) with bevacizumab for the treatment of first-line metastatic colorectal cancer (mCRC)[1]. [redacted]

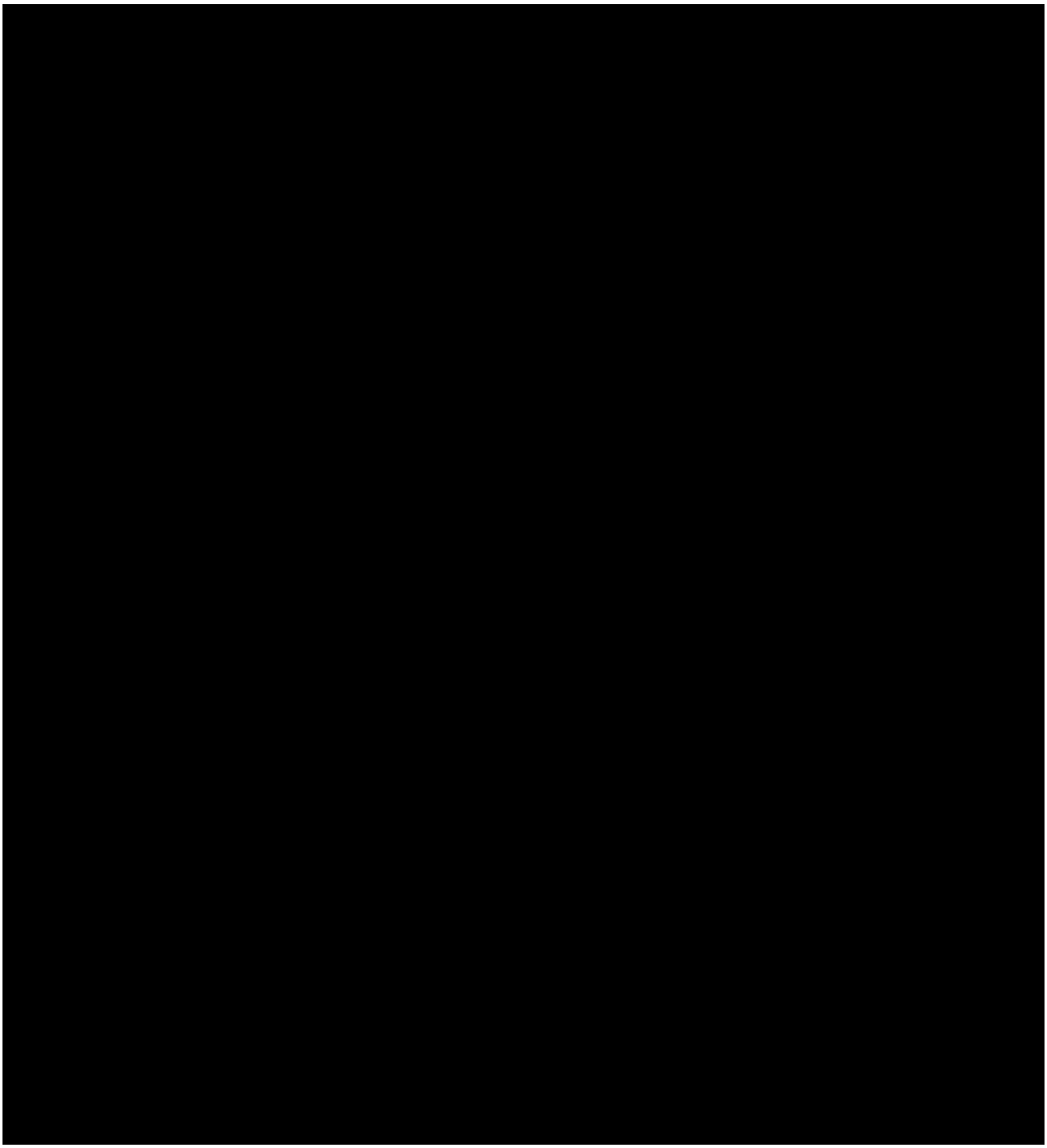
[redacted]

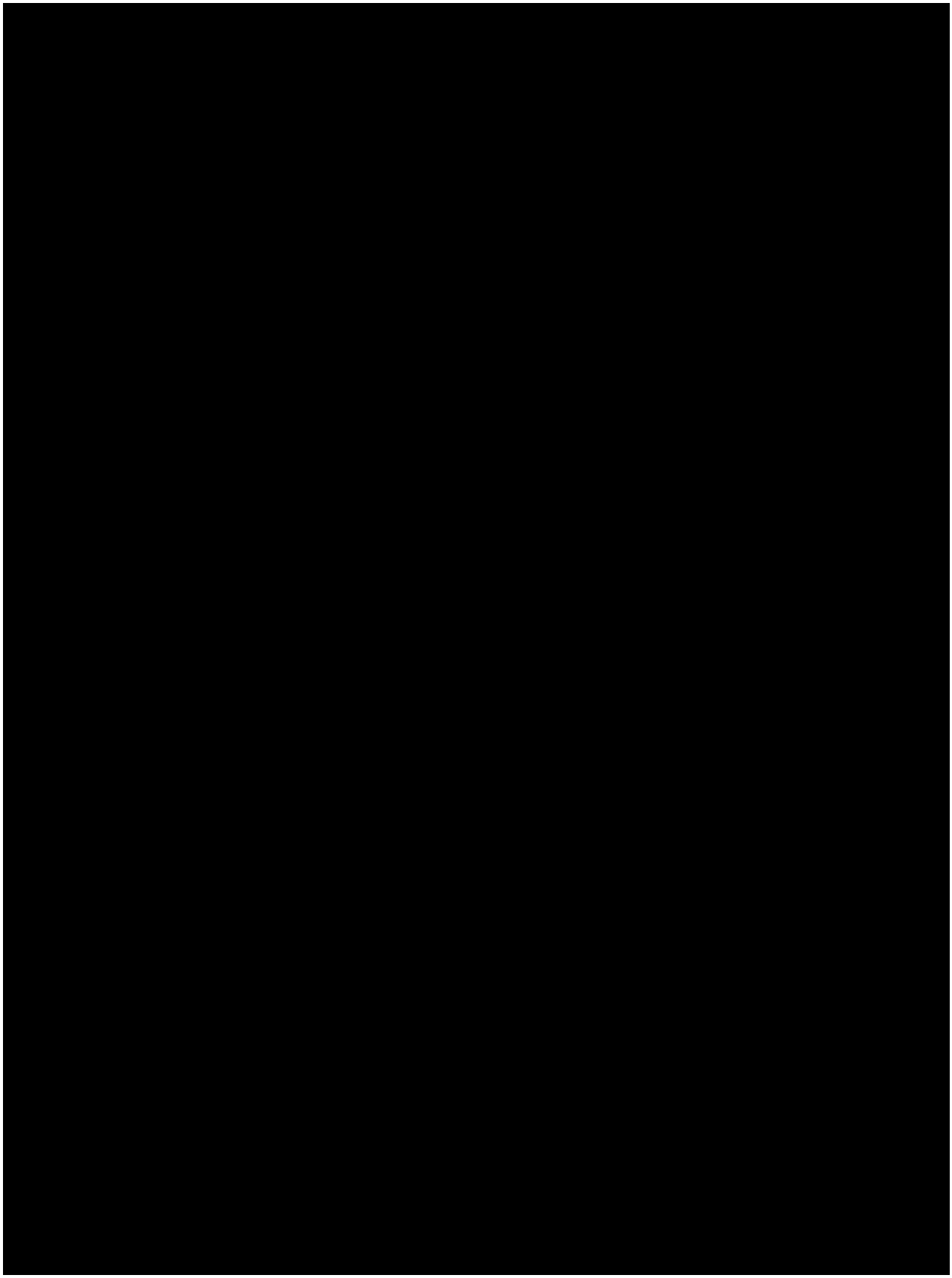
3.1.1 Research Hypothesis

Nivolumab plus SOC chemotherapy with bevacizumab (Nivo + SOC) will demonstrate superior efficacy (defined as progression-free survival [PFS]) compared to SOC chemotherapy with bevacizumab alone in participants with previously untreated mCRC. [redacted]









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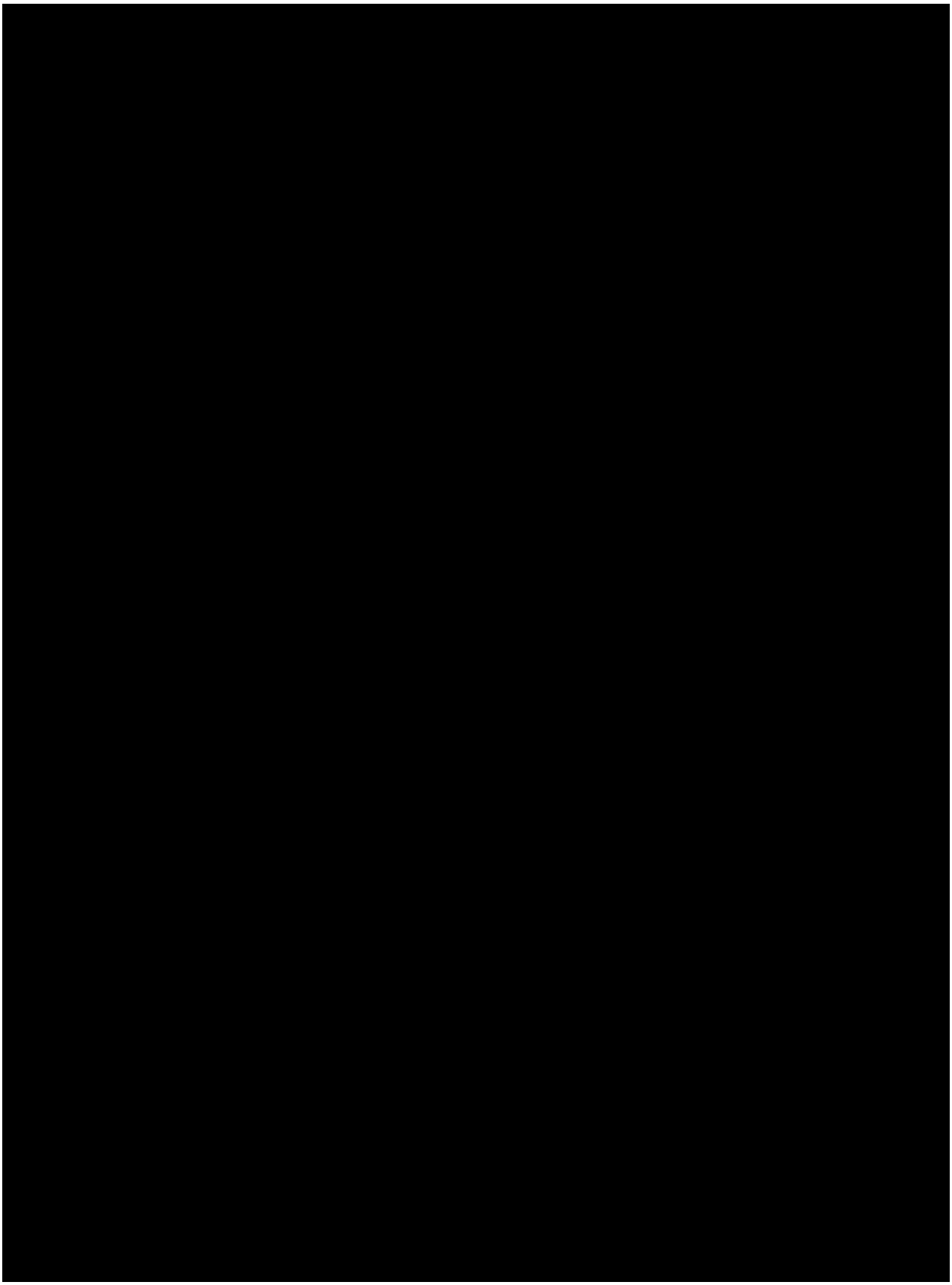
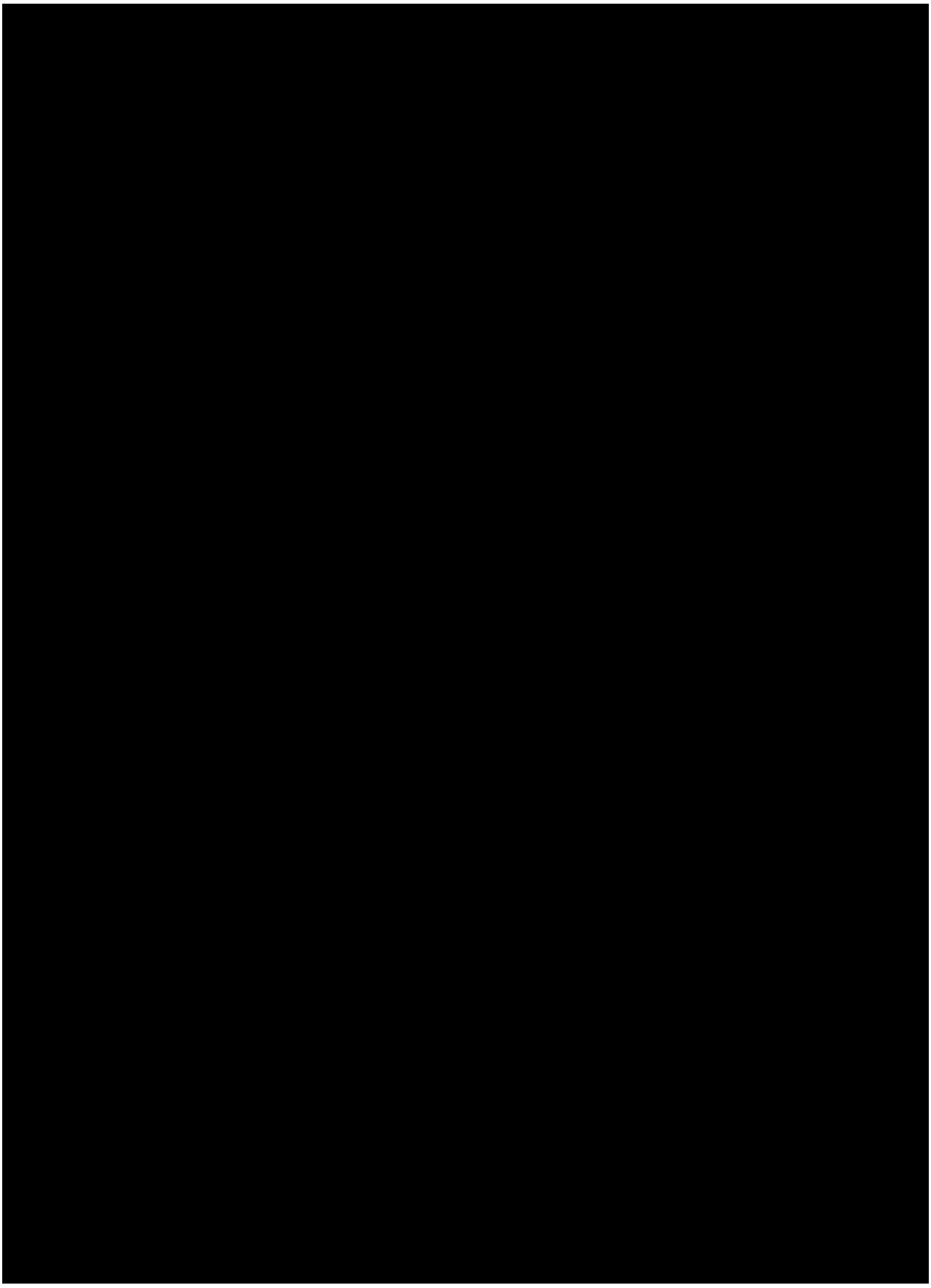




[redacted]

[redacted]

[redacted]

[redacted]

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the efficacy of nivolumab plus standard of care (SOC) chemotherapy with bevacizumab (Nivo + SOC) with SOC chemotherapy with bevacizumab in participants with mCRC	• Progression Free Survival (PFS) by BICR
Secondary	
• To evaluate preliminary efficacy in all randomized participants	• ORR, DCR, DoR, TTR by BICR per RECIST v1.1 • ORR, PFS, DCR, DoR, TTR by investigator per RECIST v1.1 • OS
• To characterize the safety and tolerability of nivolumab in combination with standard therapy with bevacizumab	• Safety (including but not limited to): incidence of AEs, SAEs, deaths, and clinical abnormalities per CTCAE (Version 4)

[redacted]

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
[redacted]	

AEs, adverse events; BICR, blinded independent central review; DCR, disease control rate; DoR, duration of response; [redacted] OS, overall survival; ORR, objective response rate; PFS, progression-free survival; SOC, standard of care; TTR, time to response; [redacted].

5 STUDY DESIGN

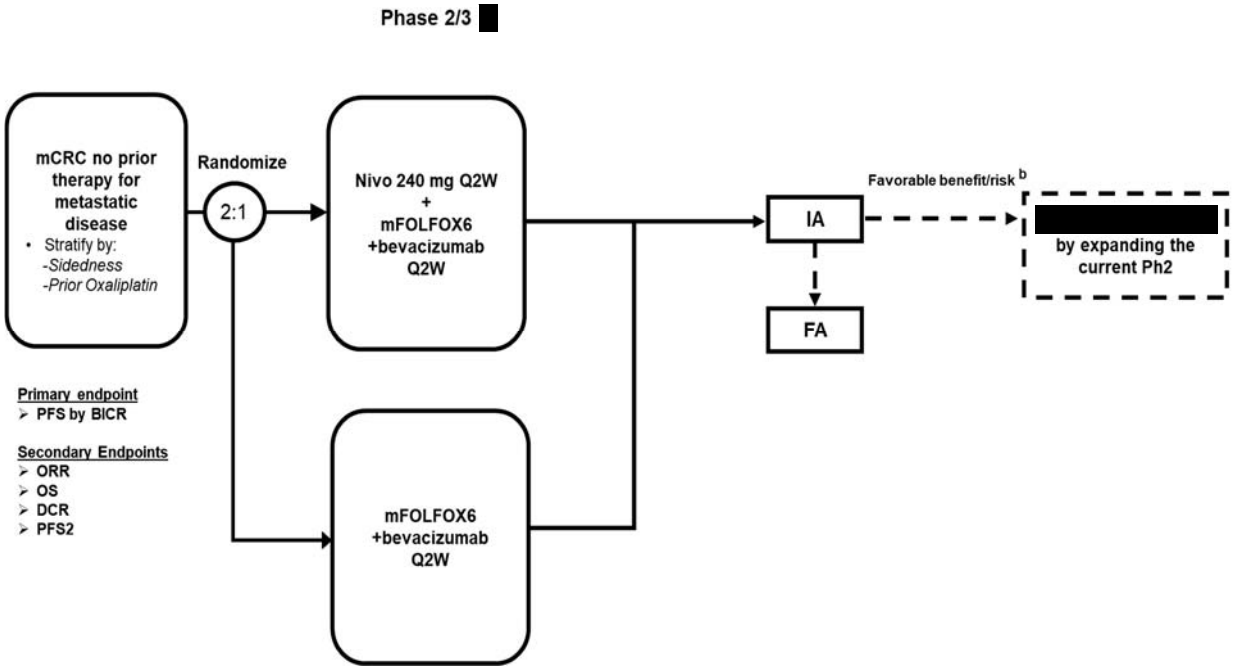
5.1 Overall Design

This is a Phase 2/3, randomized, open-label study of nivolumab plus SOC, or SOC alone, in the first-line treatment of participants with metastatic CRC.

[redacted]

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

Figure 5.1-1: Study Design Schematic



DCR, disease control rate; FA; final analysis; IA, interim analysis; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

[redacted]

[b] Depending on the results at the time of interim analysis (IA), different possible decisions may be made as indicated by dashed arrows. If there is not enough evidence of favorable benefit/risk at IA, the Phase 2 study will continue to complete with 180 participants unless unacceptable safety concerns arise.

One interim analysis (IA) is planned in the Phase 2 portion of the study [redacted].

[redacted] The interim results will guide the following decisions:

- When a strong efficacy signal is observed for all randomized participants, [redacted] is

observed and no substantial differential effects by subgroups, the study will expand [redacted].

- If the study does not expand at IA, enrollment continues as planned.

If there are not adequate data to support expanding the study at the time of IA, the study will continue to 180 randomized participants.

This study will consist of three phases: screening, treatment, and follow-up. For a complete list of study required procedures, please refer to Section 2.

Screening Phase

Screening begins by establishing the participant's initial eligibility and signing of the informed consent (ICF). Participant is enrolled using the Interactive Response Technology (IRT) system. Participant is assessed for study eligibility according to the inclusion (Section 6.1) and exclusion (Section 6.2) criteria. Completion of screening assessments must be completed in accordance with timelines as indicated in Table 2-1. The pathological reports confirming eligibility must be reviewed, dated, and signed by the investigator prior to randomization.

Participants must submit mandatory baseline tumor sample:

- Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections (minimum 20 slides from metastatic site or 25 from primary colon tumor), obtained within 180 days prior to enrollment and after the last dose of the most recent systemic anti-cancer therapy, with an associated pathology report, must be submitted to the core laboratory for inclusion. For participants with samples outside of the above criteria, a fresh biopsy will be required. Central lab must provide 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.
- In addition, at least 5 slides from the primary colon tumor must be submitted if the above specimen is from a metastatic site. The 5 slides from the primary tumor may be submitted after randomization.

The screening phase either ends with confirmation of full eligibility and randomization for the participants, or with the confirmation that the participant is a screen failure. This study permits the re-enrollment of a participant that has discontinued the study as a pre-treatment failure prior to randomization. If re-enrolled, the participant must be re-consented. A new participant identification number will be assigned by IRT at the time of re-enrollment.

Treatment Phase

Following confirmation of eligibility, treatment phase begins with the treatment assignment call to the IRT. Participants will be randomized 2:1 to one of the following treatment arms:

- Arm A: nivolumab plus SOC (Nivo +SOC)
- Arm B: SOC

Administration of study treatment is to begin within 3 calendar days of randomization. Participants will receive study treatment, until progression, unacceptable toxicity, or withdrawal of consent, or the study ends, whichever occurs first. Nivolumab will be given for a maximum of 24 months. Women of child bearing potential (WOCBP) must have a documented negative pregnancy test within 24 hours prior to the start of each dose of the investigational product. On-study vital sign assessments should be performed within 72 hours prior to the first dose and then prior to dosing. Please refer to Table 2-2. On-study laboratory assessments should be drawn within 72 hours prior to dosing and will be assessed at the local laboratory. Please refer to Table 2-2. Tumor assessments will occur in accordance with Table 2-2 until confirmed disease progression (by BICR). Each site should submit scans on a rolling basis and preferably within 7 days of image acquisition to a central vendor and report any pertinent cytology/pathology results for central review by the BICR. If progression (defined in Section 9.1.1) is assessed by the investigator, the site will inform the radiology vendor so that the BICR assessment/confirmation of progression can be performed.

Please refer to Section 9.1.1.2 for additional details.

- Participants whose progression is not confirmed by the BICR will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule or sooner if clinically indicated. Investigators are strongly encouraged to wait for BICR confirmation of progression prior to initiating any subsequent therapy.

[redacted] Treated participants will be evaluated for progression beginning at Week 12 (± 7 days), and then every 8 weeks (± 7 days) during treatment. Following initial progression, participants will continue to be followed during safety and survival follow up. [redacted] Treatment Phase ends when the participant is discontinued from study therapy. Please refer to Section 8.1 for a complete list of possible reasons for discontinuation.

Follow-up Phase

Follow-up Phase begins after the decision is made to discontinue a participant from study therapy (eg, due to toxicity, progression, etc.).

- Following initial progression, participants will continue to be followed during safety and survival follow up. [redacted]

Participants who enter the follow-up period without tumor progression will continue to have tumor imaging assessments per on-treatment schedule: at Week 12 (± 7 days) from randomization and then every 8 weeks (± 7 days). [redacted]

[redacted] Participants will have 2 follow-up visits (FU1 and FU2) for safety within approximately 100 days from the last dose of study treatment. Both follow-up visits should be conducted in person, according to Table 2-3. Beyond this time period, participants will be followed for survival and ongoing treatment-related AEs until these events have resolved, returned to baseline or are deemed irreversible. All toxicities will be documented for a minimum of 100 days after the last dose of study medication.

After the Follow-up 2 Visit, all participants will be followed for survival status every 3 months (± 14 days) until death, withdrawal of consent, lost to follow-up, or end of study.

- Survival status may be ascertained by telephone contact if the participant is unable to return to the site for a visit.
- If new anti-tumor therapy is initiated for either disease progression or a secondary malignancy at any time during this period, this and all other pertinent data obtained should be recorded on the appropriate Case Report Form (CRF).

[redacted]

5.1.2 Blinded Independent Central Review

A BICR will be utilized in this study for determination of BICR-assessed endpoints. Details of BICR procedures will be specified in the BICR Charter. Refer to Section 9.1.1 Imaging Assessment for the Study for further details.

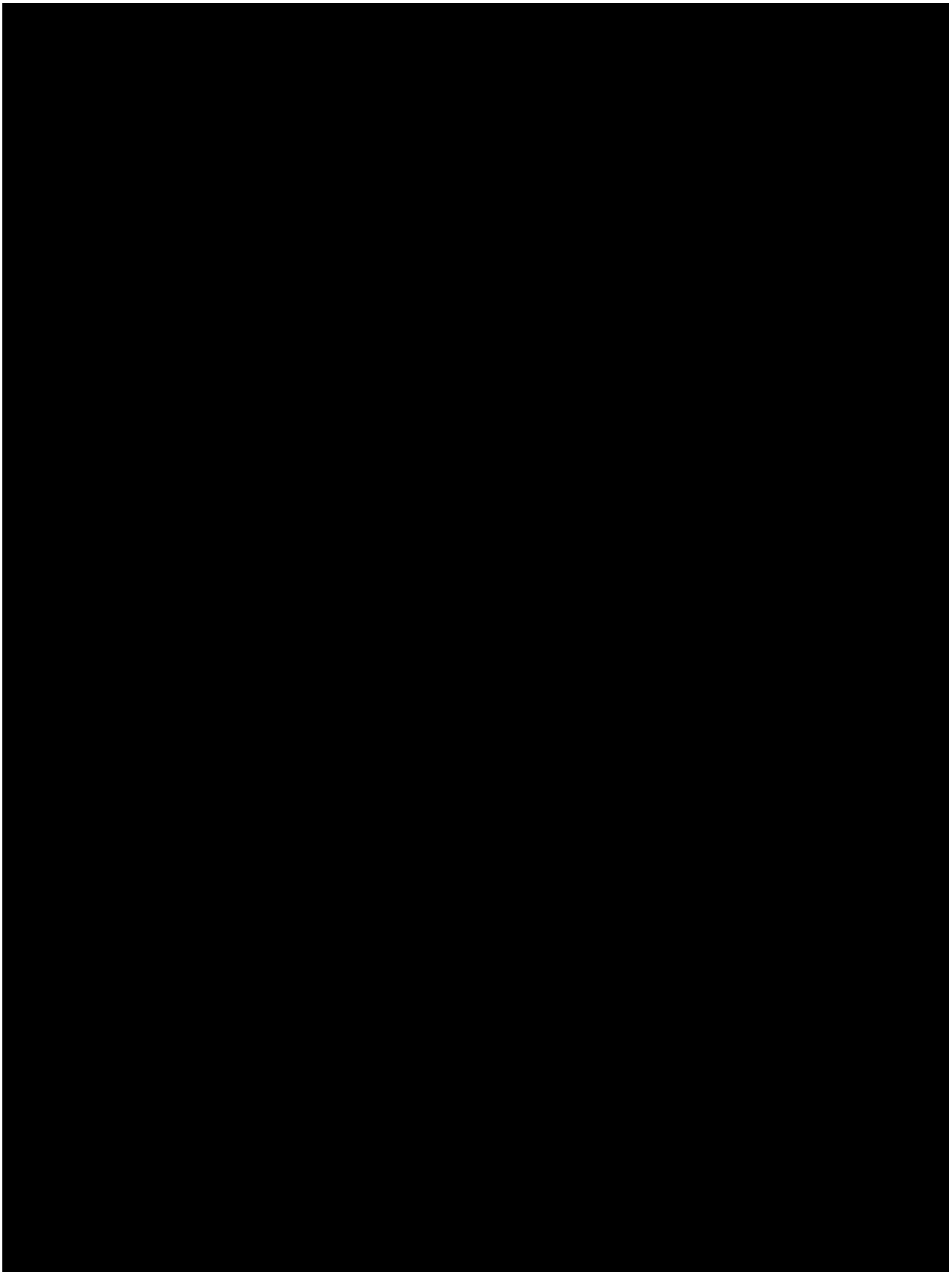
5.2 Number of Participants

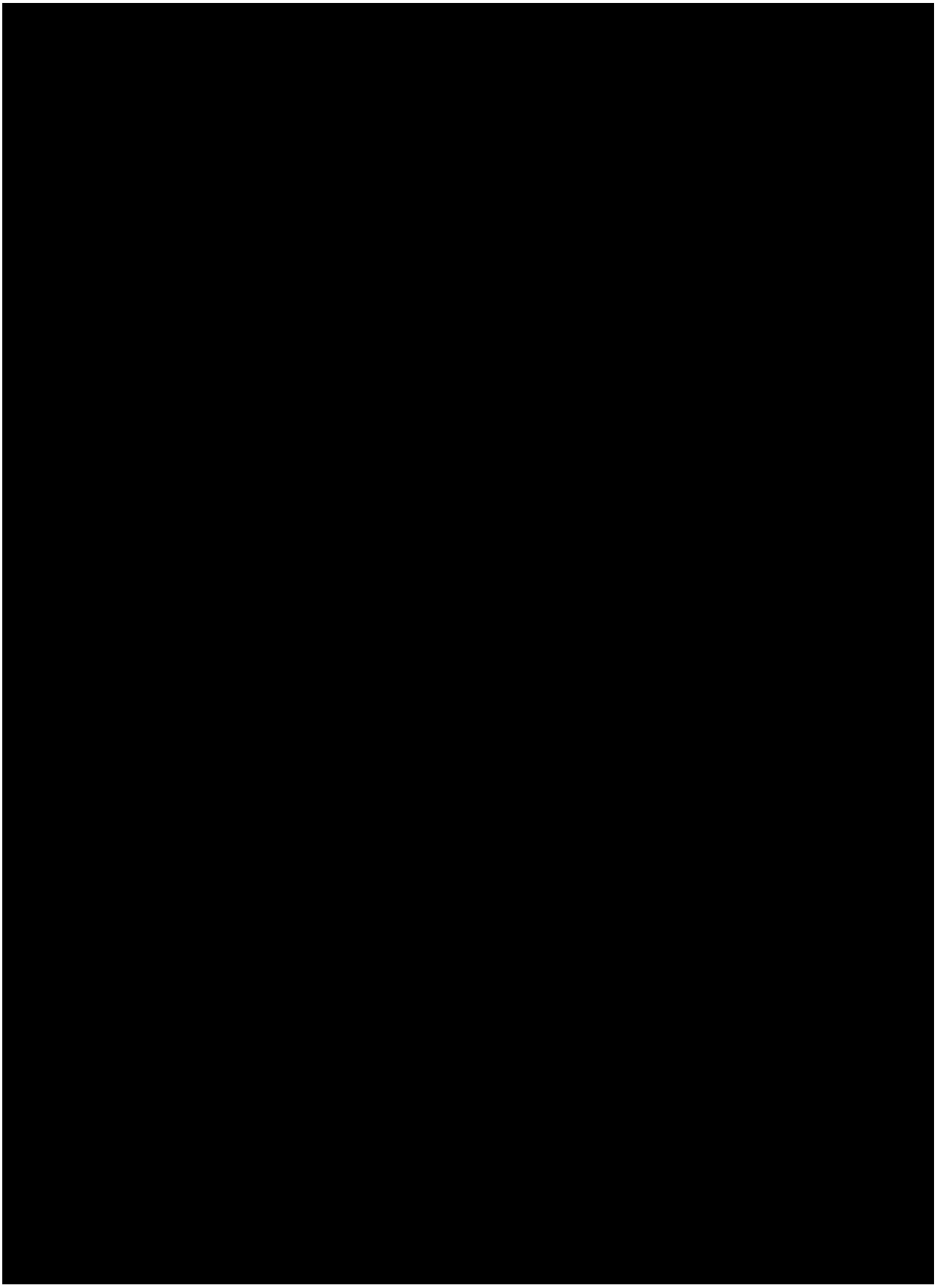
Approximately 180 (up to 450 depending on IA results) participants will be randomized in a 2:1 ratio. Approximately 120 participants in the nivolumab + SOC arm (Arm A) and approximately 60 in the SOC alone arm (Arm B).

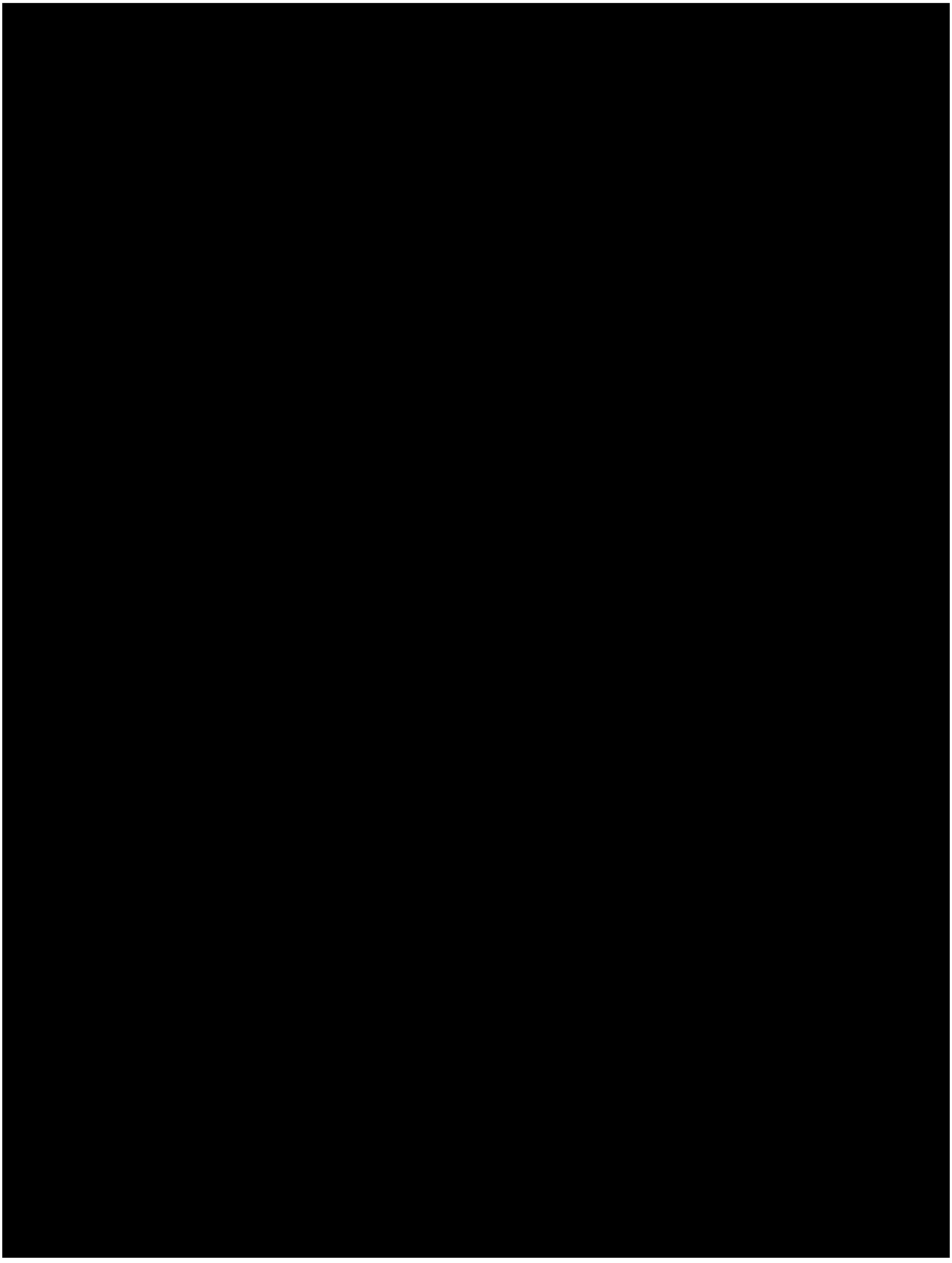
5.3 End of Study Definition

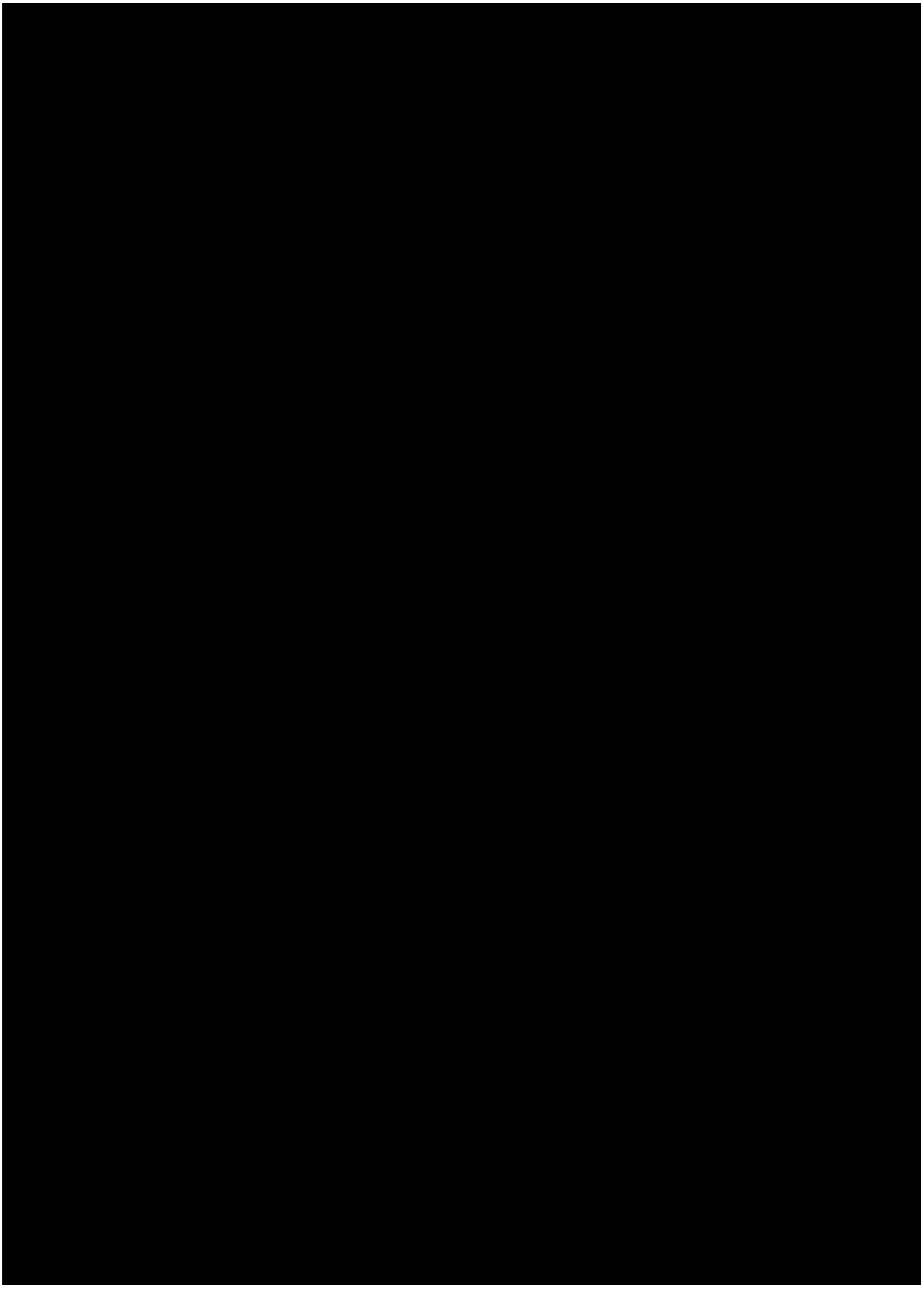
The start of the trial is defined as the first visit for first participant screened. End of trial is defined as the last visit or scheduled procedure shown in the schedule of activities (see Section 2). Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

[redacted]









[redacted]

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Participants must have signed and dated an 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, laboratory tests, tumor biopsies, and other requirements of the study.

2) Type of Participant and Target Disease Characteristics

a) Histologically confirmed metastatic colorectal cancer, not amenable to curative resection.

b) Available local test results for tumor BRAF, KRAS and NRAS (extended RAS) mutation status and Microsatellite/MMR testing in addition to available tumor sample as required per protocol (see 2(e))

c) No prior chemotherapy for metastatic colorectal cancer.

i) If participant has received adjuvant or neoadjuvant chemotherapy, there must be more than 6 months gap (> 6 months) between the completion of that therapy and diagnosis of recurrent or metastatic disease.

d) Presence of measurable disease by RECIST 1.1 criteria.

i) Previously irradiated lesions may not be the target lesion unless there has been documented progression in those lesions

e) Adequate tumor tissue available. Tumor tissue specimens:

i) Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections (minimum 20 slides from a metastatic site or 25 from a primary colon site), obtained within 180 days prior to enrollment and after the last dose of the most recent systemic anti-cancer therapy, with an associated pathology report, must be submitted to the core laboratory for inclusion. For participants with samples outside of the above criteria, a fresh biopsy will be required. Biopsy should be excisional, incisional or core needle. Fine needle aspiration is unacceptable for submission.

ii) If the above sample is not from the primary colon tumor, an additional archival sample of at least 5 slides must be submitted from the primary colon tumor. These additional 5 slides may be submitted after randomization.

iii) Central lab must confirm receipt of evaluable tumor tissue prior to randomization. Biopsies of bone lesions that do not have a soft tissue component are also unacceptable for submission.

f) ECOG Performance Status of 0-1. See Appendix 7 for ECOG Performance Status scale.

g) 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 treated). If re-enrolled, the participant must be re-consented and assigned a new participant number from IRT.

h) All participants will be required to undergo mandatory on-study biopsies. Participants will be required to undergo on-study biopsies at acceptable clinical risk as judged by the investigator in both arms.

i) The tumor tissue specimen must be a core needle biopsy, excisional or incisional biopsy. Fine needle biopsies, drainage of pleural effusions with cytospins, or punch biopsies are not considered adequate [redacted]. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable. Where possible, the biopsied lesion should be distinct from target lesions being evaluated for radiologic response, and when feasible the same lesion should be used for both the baseline and on-study sampling.

3) Age and Reproductive Status

a) Males and Females, ages ≥ 18 years of age

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 pregnant or breastfeeding

d) Women of childbearing potential (WOCBP) randomized to the nivolumab + SOC arm must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with study treatment(s) and 6 months after the last dose of study treatment.

e) Males randomized to the nivolumab + SOC arm who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with study treatment(s) 7 months after the last dose of nivolumab. In addition, male participants must be willing to refrain from sperm donation during this time.

f) Women of childbearing potential (WOCBP) randomized to the SOC arm must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with study treatment(s) and for at least 6 months after the last dose of investigational drug.

g) Males randomized to the SOC arm who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with study treatment(s) and for at least 7 months after the last dose of investigational drug. In addition, male participants must be willing to refrain from sperm donation during this time.

h) 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) Target Disease Exceptions

a) Active brain metastases or leptomeningeal metastases. Participants with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI except where contraindicated in which CT scan is acceptable) evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. Cases should be discussed with the medical monitor. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

b) Resectable oligometastastic only disease with multidisciplinary plan for complete resection of all disease.

c) Ascites that cannot be controlled with medical therapy alone.

2) Medical Conditions

a) 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.

b) 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.

c) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured (ie, basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast) and considered to be of low risk of recurrence

d) History of interstitial lung disease or pneumonitis.

e) Clinically significant cardiovascular disease. Pre-existing hypertension should be adequately controlled to < 140/90 mmHg.

f) Clinically significant bleeding diathesis or coagulopathy.

g) Deep venous thrombosis, pulmonary embolism, arterial thrombosis or cerebrovascular accident within 6 months prior to enrollment.

h) Non-healing wound, ulcer, or bone fracture.

i) Participants with > Grade 1 peripheral neuropathy.

j) Prior history of gastrointestinal perforation or abscess.

k) History of hemoptysis of ≥ half teaspoon (2.5 mL) of red blood within 3 months prior to enrollment.

l) Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the participant to receive protocol therapy, or interfere with the interpretation of study results.

m) Any other sound medical, psychiatric and/or social reason as determined by the investigator.

3) Prior/Concomitant Therapy

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

b) Received cancer-related investigational product(s) (IPs) and/or biologic therapy within 28 days or 5 half-lives, whichever is longer, prior to randomization.

c) Prior major surgery, open biopsy or significant traumatic injury within 28 days prior to randomization. Any wound-related AE(s) must have resolved at least 28 days prior to randomization.

d) Prior focal palliative radiotherapy must have been completed at least 14 days prior to randomization.

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

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

4) Physical and Laboratory Test Findings

a) WBC < 2000/μL

b) Neutrophils < 1500/μL

c) Platelets < 100×10^3/μL

d) Hemoglobin < 9.0 g/dL

e) PT/INR and PTT > 1.5 ×ULN

f) Serum creatinine > 1.5 ×ULN, unless creatinine clearance ≥ 40 mL/min (measured or calculated using the Cockroft-Gault formula)

g) AST/ALT: > 3.0 ×ULN, unless participant has documented liver metastases in which case AST/ALT > 5.0× ULN are exclusionary.

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

i) Albumin < 3.0 g/dL

j) For participants with proteinuria ≥2+ by urine dipstick or urinalysis at baseline, 24-hr urine must be collected. Proteinuria > 1g/24hrs is exclusionary. It is acceptable to estimate urine protein to creatinine ratio (UPCR) instead of 24hr urine collection. UPCR > 1000 mg/g is exclusionary.

k) Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, eg, Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).

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. See Appendix 10.

5) Allergies and Adverse Drug Reaction

a) Any contraindications to any of the study drugs of the chemotherapy regimen. Investigators should refer to local package insert of the SOC chemotherapy drugs and bevacizumab.

b) History of severe hypersensitivity reaction to any monoclonal antibody.

c) History of allergy or hypersensitivity to study drug components

6) Other Exclusion Criteria

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

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

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

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required. Please also refer to local SOC products labels for possible restrictions.

6.4 Screen Failures

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

6.4.1 Retesting During Screening

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 / has not been treated). If re-enrolled, the participant must be re-consented.

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

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

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

7 TREATMENT

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

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

- Nivolumab
- Oxaliplatin
- Leucovorin
- Fluorouracil
- Bevacizumab

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.

Table 7-1: Study treatments for CA2099X8

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Nivolumab (BMS-936558-01) Solution for Injection[a]	100 mg (10 mg/ml) and 40 mg (10 mg/mL)	IP	Open label	Vial and various packaging configurations	2° to 8°C. Protect from light and freezing.
Oxaliplatin[b]	various strengths	IP	Open label	Vial and various packaging configurations	Refer to the label on container and/or Pharmacy manual.
{Leucovorin Calcium Folinate}[b]	various strengths	IP	Open label	Vial and various packaging configurations	Refer to the label on container and/or Pharmacy manual.
Fluorouracil[b]	various strengths	IP	Open label	Vial and various packaging configurations	Refer to the label on container and/or Pharmacy manual.
Bevacizumab[b]	various strengths	IP	Open label	Vial and various packaging configurations	Refer to the label on container and/or Pharmacy manual.

Further instructions with regard to the preparation, handling, and storage for above product will be provided to sites separately as 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 products in certain countries if allowed by local regulations. In these cases, products may be in a different pack size/potency/pharmaceutical form than listed in the table. These products should be prepared/stored/administered in accordance with the package inserts or summaries of product characteristics (SmPCs).

7.1 Treatments Administered

The selection and timing of dose for each participant is as follows:

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
Oxaliplatin	85 mg/m^2	Q2W	IV
Leucovorin	400 mg/m^2 or 350 mg/m^2 as per local standards	Q2W	IV
Fluorouracil	Bolus 400 mg/m^2	Q2W	IV
Fluorouracil	1200 mg/m^2 continuous infusion on Day #1 (or Day #15) and 1200 mg/m^2 continuous infusion on Day #2 (or Day #16) OR 2400 mg/m^2 continuous infusion over 46 to 48 hours Day #1 (or Day #15) through Day #2 (or Day #16) as per local standards	Q2W	IV
Bevacizumab	5 mg/kg	Q2W	IV
Nivolumab	240 mg	Q2W	IV

IV, intravenous.

When study drugs (nivolumab and SOC therapy) are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting SOC therapy infusion(s). The second infusion will always be the standard of care and will start after the infusion line has been flushed, filters changed and the patient has been observed to ensure no infusion reaction has occurred. The time between infusions is expected to be approximately 30 minutes but may be more or less depending on the situation.

Participants will be treated until progression, unacceptable toxicity, withdrawal of consent, or the end of the study, whichever comes first. Nivolumab will be given for a maximum of 24 months.

Participants should receive nivolumab at a dose of 240 mg as a 30 minute infusion on Day 1 of each treatment cycle every 2 weeks (± 3 days) for a maximum of 24 months, or until confirmed progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. Participants should begin study treatment within 3 calendar days of randomization.

There will be no dose escalations or reductions of nivolumab allowed. Participants may be dosed no less than 12 days from the previous dose during Q2W cycles. Premedications are not recommended for the first dose of nivolumab.

Participants should be carefully monitored for infusion reactions during study drug administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed. Resumption of treatment should be at the next scheduled time point.

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 manual. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

Where applicable (ex. bevacizumab), dosing calculations should be based on the body weight assessed at baseline. It is not necessary to recalculate subsequent doses if the participant weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up to the nearest milligram per institutional standard.

Nivolumab plus SOC and bevacizumab arm

Participants assigned to nivolumab plus SOC will receive nivolumab 240 mg administered IV over 30 minutes first, then followed by bevacizumab administration and finally by the FOLFOX administration.

First administration (C1D1) of bevacizumab will be delivered over a 90-min infusion. If well tolerated the second administration (C1D15) will be delivered over 60 min; if the 60-min infusion is well tolerated, all subsequent infusions will be delivered over 30 min or as per local institutional standards.

Bevacizumab administration will then be followed by oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 400 mg/m^2 will be administered IV on Day 1 of each treatment cycle every 2 weeks, and fluorouracil 1200 mg/m^2 IV continuous infusion on Day 1 and on Day 2 or 2400 mg/m² over 46 to 48 hours of each treatment cycle every 2 weeks (see Table 7.1-1). Dosing windows for subsequent mFOLFOX doses should adhere to recommendations in the prescribing information or local standards, where indicated.

Premedication may be administrated per local standard, but are not recommended for the first dose of nivolumab.

SOC and bevacizumab arm

Participants assigned to SOC will receive bevacizumab first, followed by FOLFOX administration.

First administration (C1D1) of bevacizumab will be delivered over a 90-min infusion. If well tolerated the second administration (C1D15) will delivered over 60 min; if the 60-min infusion is well tolerated, all subsequent infusions will be delivered over 30 min or as per local institutional standards.

Bevacizumab administration will then be followed by oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 400 mg/m^2 administered IV on Day 1 of each treatment cycle, and

fluorouracil 1200 mg/m^2 IV continuous infusion on Day 1 and on Day 2 or 2400 mg/m² over 46 to 48 hours of each treatment cycle, every 2 weeks (see Table 7.1-1). Dosing windows for subsequent FOLFOX doses should adhere to recommendations in the prescribing information or local standards, where indicated.

Premedication may be administrated per local standard.

7.2 Method of Treatment Assignment

CA2099X8 is a randomized, open-label study. After the participant's initial eligibility is established and informed consent has been obtained, the participant must be enrolled into the study by using an Interactive Response Technology (IRT) to obtain the participant number. Every participant that signs the informed consent form must be assigned a participant number using IRT. Specific instructions for using IRT will be provided to the investigational site in a separate document.

All participants will be centrally randomized using an Interactive Response Technology (IRT). Before the study is initiated, each site user will receive log in information and directions on how to access the IRT. The investigator or designee will register the participant for enrollment by following the enrollment procedures established by BMS.

The following information is required for enrollment:

- Date that informed consent was obtained
- Date of birth, where applicable by local regulations
- Gender at birth

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

- Participant number
- Date of birth, where applicable per local regulations
- Tumor sidedness (left, right, transverse or unknown)
- Prior oxaliplatin-based adjuvant chemotherapy (yes or no)
- Confirmation that evaluable tumor tissue has been received at the central lab.

Participants meeting all eligibility criteria will be randomized in a 2:1 ratio to nivolumab + SOC or SOC arms stratified by tumor sidedness and prior oxaliplatin-based adjuvant chemotherapy. Study treatment will be dispensed at the study visits as listed in Schedule of Activities (Section 2). The exact procedures for using the IRT will be detailed in the IRT manual.

[redacted]

7.4 Dosage Modification

There are no dose modifications allowed for nivolumab, except treatment delay. If adverse events are considered to be related to study treatment, every attempt must be made to attribute individual study treatment to adverse event, if possible, or to the combination regimen.

- For adverse events that are deemed to be related to mFOLFOX6 + bevacizumab ONLY by the treating physician, dose modification criteria for SOC must be followed as described in Sections 7.4.2 and 7.4.3.
- For adverse events that are deemed to be related to nivolumab ONLY by the treating physician, dose modification criteria for nivolumab must be followed as described in Section 7.4.1 and Appendix 5.
- For adverse events that are possibly related to the combination regimen (nivolumab + mFOLFOX6 + bevacizumab), the most conservative toxicity management guidelines must be followed.
- If there is a delay in administration of study drug(s) due to toxicity, treatment with the other study agent(s) should continue as scheduled. Resumption of treatment should be at the next scheduled time point.

7.4.1 Nivolumab Dose Delay

Nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related AE
- 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)
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Participants who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met. If there is a delay or modification in administration of study drug(s) due to toxicity, treatment with the other study agent(s) should continue as scheduled. If clinically appropriate, the investigator can delay all treatment components up to a maximum of 7 days to allow synchronized administration of all agents.

7.4.2 Dose Modification Criteria for Oxaliplatin-Plus-Fluoropyrimidine Treatment

Dose modifications of oxaliplatin, leucovorin and fluorouracil are permitted according to local standards or local package inserts.

7.4.2.1 General Guidance for Dose Modification for Chemotherapy

- Treatment for the first cycle should only commence if all the inclusion criteria are met and the participant has been enrolled. For subsequent cycles, dose delay/modification is permitted per local standard.
- Doses of any study drug omitted for toxicity are not replaced or restored; instead, the patient should resume the planned treatment cycles. Supportive care (for example, colony-stimulating factors [CSFs], blood and blood products, etc. can be administered in accordance with the latest American Society of Clinical Oncology (ASCO) or other equivalent guidelines.
- Dose modification, for non-serious and non-life-threatening toxicities like alopecia, altered taste or nail changes may not be required and the final decision is left to the discretion of the treating investigator.
- In situations where concomitant toxicities of varying severity exist, dose modification will be tailored for the toxicity with highest CTCAE grading.
- If there is a delay or modification in administration of study drug(s) due to toxicity, treatment with the other study agent(s) should continue as scheduled. If clinically appropriate, the investigator can delay all treatment components up to a maximum of 7 days to allow synchronized administration of all agents.

If toxicity related to any component of chemotherapy does not resolve in the same treatment cycle, the administration of that component can be delayed up to 6 weeks. If the toxicity does not resolve within 6 weeks, that component will be discontinued unless it is determined by the treating investigator that the patient might benefit from continuation of the component.

7.4.3 Dose Modification Criteria for mFOLFOX6

Recommended dose modifications of FOLFOX are provided in Table 7.4.3-1 and Table 7.4.3-2. Modifications may be made as per local standards.

Table 7.4.3-1: Recommended Dose Modifications of FOLFOX

Drug	Starting Dose	Dose Modification	
		Dose Level - 1	Dose Level - 2
Oxaliplatin	85 mg/m^2	70 mg/m^2	50 mg/m^2
5-FU	Bolus 5-FU: 400 mg/m^2 Leucovorin: 400 mg/m^2 Infusion 5-FU: 2400 mg/m^2/ continuous infusion over 46-48 hours	Bolus 5-FU: 300 mg/m^2 Leucovorin: 300 mg/m^2 Infusion 5-FU: 2000 mg/m^2/ continuous infusion over 46-48 hours	Bolus 5-FU: 200 mg/m^2 Leucovorin: 200 mg/m^2 Infusion 5-FU: 1600 mg/m^2/ continuous infusion over 46-48 hours

5-FU: 5-fluorouracil.

Table 7.4.3-2: Dose Modifications of FOLFOX

Toxicity	Definition	During a course of therapy	Dose adjustment for next treatments
Neutropenia	Grade 3 or greater	Interrupt until resolved to Grade 2	Dose level -1 *If treatment delayed for 4 consecutive weeks, discontinue all treatment
Thrombocytopenia	Grade 2	Interrupt until resolved to Grade 1	Dose level -1 *If Grade 2 persists > 7 days, oxaliplatin reduced by 2 dose levels when platelets improve to Grade 1
	Grade 3	Interrupt until resolved to Grade 1	Dose level -1 *If Grade 3 persists > 7 days, oxaliplatin reduced by 2 dose levels when platelets improve to Grade 1
	Grade 4	Interrupt until resolved to Grade 1	Dose level -2 *If Grade 4 persists > 7 days, oxaliplatin reduced by 2 dose levels when platelets improve to Grade 1
Neurologic toxicity	Grade 2 peripheral sensory neuropathy	Interrupt until resolved to Grade 1 or management as per institutional standard	Oxaliplatin dose -1 Continue 5-FU and leucovorin *If oxaliplatin delayed for neurologic toxicity for 4 consecutive weeks, discontinue oxaliplatin, continue 5-FU and leucovorin
	Grade 3 or greater peripheral sensory neuropathy	Discontinue oxaliplatin	Continue 5-FU and leucovorin
Gastrointestinal toxicities	Grade 2 or greater diarrhea	Interrupt until resolved to Grade 1	Dose level -1 If dose delayed for diarrhea for 4 consecutive weeks, discontinue all treatment

For toxicities not listed above, dose modifications are permitted per local standards.

Participants may also discontinue oxaliplatin following multiple cycles if, in the investigator's judgment, cumulative toxicity is likely to increase over time.

7.4.4 Dose Modification Criteria for bevacizumab

Dose modifications or delay for bevacizumab are allowed per institutional standards.

Table 7.4.4-1: Recommended Guidelines for Management of Proteinuria

Grade	Description	Management	
Grade 1	1+ protein on urinalysis, or 0.15 to 1g of protein in 24hrs urine collection, or 150 to 1000 mg/g if UPCR is used to assess the proteinuria	Continue Bevacizumab	
Grade 2	2+ or 3+, or 1 to 3.4g/24hrs, or 1000 to 3400 mg/g	Give Bevacizumab and collect 24 hour urine or test UPCR before the next cycle	Resume Bevacizumab only if <2g/24hours, or < 2000 mg/g If not <2g/24h, or < 2000 mg/g for 3 months, discontinue Bevacizumab
Grade 3	Urinary protein ≥3.5 g/24hrs, or ≥ 3500 mg/g	Discontinue Bevacizumab	

UPCR, urine protein to creatinine ratio

7.4.5 Treatment of Infusion-Related Reactions

If an infusion-related reaction should occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study Medical Monitor/designee and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI 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 required 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 study treatment infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further study treatment will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusion. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or 4 symptoms: (severe reaction, Grade 3: prolonged [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 study treatment. Begin an IV infusion of normal saline and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the investigator is comfortable that the symptoms will not recur. Study treatment will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.

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

7.5 Preparation/Handling/Storage/Accountability

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

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

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

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

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

[redacted]

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability. Drug accountability should be reviewed by the site study staff at each visit to confirm treatment compliance.

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 7.7.3)
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of CRC)
- Any botanical preparation (eg herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.
- Ongoing treatment with aspirin (>325 mg per day) or other medications known to predispose participants to gastrointestinal ulceration is prohibited for participants receiving bevacizumab.
- Also refer to local institutional guidelines and/or product labels of SOC components for possible prohibited and/or restricted treatments.
- Any live / attenuated vaccine (eg varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose.

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.

7.7.3 Permitted Therapy

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

7.7.3.1 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each participant. Imaging contraindications and contrast risks should be considered in this assessment. Participants with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast 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.

7.8 Post-Study Drug Access

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

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

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

Participants MUST discontinue 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, 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)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Documented radiographic disease progression per RECIST v1.1.
- Criteria listed Section 8.1.1 and 8.1.2

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

In the case of pregnancy, the investigator must immediately notify the Sponsor or designee of this event and study treatment must immediately be stopped. In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please contact the Sponsor or designee within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug (ie, allowing restart of study treatment if participant chose to terminate the pregnancy), a discussion between the investigator and the Sponsor or designee must occur so permission may be granted.

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 Dose Discontinuation

Nivolumab 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 AE lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, myocarditis, 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 drug-related AST, ALT or Total Bilirubin requires discontinuation*
    - Concurrent AST or ALT > 3 ×ULN and total bilirubin > 2 ×ULN

* In most cases of Grade 3 AST or ALT elevation, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the BMS 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.
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor (or designee).

Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks, the BMS Medical Monitor (or 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 SOC Dose Discontinuation

Except where specified below, the medications in the SOC chemotherapy regimen should be discontinued for any of the following:

- Any Grade ≥ 4 drug-related peripheral neuropathy requires discontinuation of oxaliplatin.
- In case of persistent Grade 3 drug-related paraesthesia, oxaliplatin should be discontinued.
- Any Grade ≥ 3 drug-related mucocutaneous reaction possibly attributable to leucovorin requires permanent discontinuation.
- Grade ≥ 3 drug-related thrombocytopenia associated with clinically significant bleeding, all treatment should be held until resolved to ≤ Grade 1. Subsequent dose reduction of any SOC medications or discontinuation of oxaliplatin will be at the discretion of the treating investigator.
- Any drug-related liver function test (LFT) abnormality that meets the following criteria requires discontinuation:
  - AST or ALT > 5-10 ×ULN for > 2 weeks
  - AST or ALT > 10 ×ULN
  - Total bilirubin > 5 ×ULN
  - Concurrent AST or ALT > 3 ×ULN and total bilirubin > 2 ×ULN
- Any oxaliplatin-related decrease in creatinine clearance to < 30 mL/min (using the Cockroft Gault formula) requires discontinuation of oxaliplatin.
- Any drug-related AE which recurs after 2 prior dose reductions for the same drug-related AE requires discontinuation of the drug(s) which was/were previously dose reduced.
- Any Grade ≥ 3 drug-related hypersensitivity reaction or infusion reaction requires discontinuation of the drug(s) felt to be causing the reaction. The drug not felt to be related to the hypersensitivity reaction or infusion reaction may be continued.
- Any Grade 4 drug-related AE which the investigator deems is inappropriate to be managed by dose reduction(s) requires discontinuation of the drug(s) felt to be causing the event. The drug not felt to be related to the event may be continued.
- If any drug-related toxicity does not resolve within 42 days, that component will be discontinued unless it is determined by the treating investigator that the participant might benefit from continuation of the component.
- In case of unexplained drug-related respiratory symptoms such as non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates, oxaliplatin should be discontinued until further pulmonary investigation excludes interstitial lung disease or pulmonary fibrosis.

Treatment with bevacizumab must be permanently discontinued according to the updated bevacizumab package insert including the following:

- Grade 4 drug-related hypertension including hypertensive encephalopathy
- Grade 3-4 drug-related hemorrhage
- Grade 4 drug-related non-pulmonary or non-CNS hemorrhage
- Grade ≥ 1 drug-related pulmonary or CNS hemorrhage
- Drug-related arterial thromboembolic event (any grade)
- Any grade of drug-related congestive heart failure
- Grade 3 drug-related proteinuria
- Participants who develop drug-related gastrointestinal perforation, tracheoesophageal fistula or any Grade 4 fistula. Discontinue in patients with fistula formation involving any internal organ
- Participants who develop a drug-related severe ATE
- Grade 4 drug-related VTE, including pulmonary embolism
- Drug-related wound dehiscence (any grade –requiring medical or surgical therapy)
- Drug-related reversible posterior leukoencephalopathy (any grade,- confirmed by MRI)
- Other unspecified bevacizumab related AE's (Grade 4)

For toxicities not listed above, the treating investigators can decide to discontinue any individual chemotherapy agent or all chemotherapy agents if it is not the best interest in the participant per the local standards.

Post-treatment study follow-up is critically important and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment will continue to be followed for collection of tumor surveillance assessments, safety, [redacted] as per protocol.

8.1.3 Criteria to Resume Treatment with Nivolumab

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

- Participants may resume treatment in the presence of Grade 2 fatigue
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- 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.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by BMS Medical Monitor (or designee).

- Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor (or designee). Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
- Resumption of treatment should be at the next scheduled time point.

8.1.4 Post Study Treatment Study Follow-up

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

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

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

Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or

assessments may be performed as clinically necessary or where required by institutional or local regulations.

9.1 Efficacy Assessments

9.1.1 Imaging Assessment for the Study

Images will be submitted to an imaging core lab. Sites should be trained prior to scanning the first study participant. Image acquisition guidelines and submission process will be outlined in the CA2099X8 Imaging Manual to be provided by the core lab.

Baseline imaging, including CT of the chest, CT/MRI of the abdomen, pelvis, and all known sites of disease should be performed within 28 days prior to first dose.

At Baseline, MRI of the brain without and with contrast is required for participants with known or suspected brain metastases. Participants with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated

First tumor assessment post-baseline should be performed at Week 12 (± 7 days) after randomization and then every 8 weeks (± 7 days) thereafter until confirmed progression, withdrawal of consent, or the study ends, whichever occurs first. If the investigator finds progression that is not confirmed by BICR, additional CT of the chest, CT/MRI of the abdomen, pelvis, and all known sites of disease should be performed 4 weeks later, prior to subsequent therapy.

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

Any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled timepoints and/or at an outside institution) should be collected for RECIST v1.1 tumor assessment and submitted to the BICR.

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 42 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.

9.1.1.1 Methods of Measurement

Tumor assessment with contrast-enhanced computed tomography (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 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 time points.

Use of CT component of a PET-CT scanner: Combined modality scanning such as with FDG PET-CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined FDG PET-CT are of limited use in anatomically-based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically-based RECIST measurements. However, if a site can document that the CT performed as part of a FDG PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the FDG PET-CT can be used for RECIST 1.1 measurements. Note, however, that the FDG PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Participants with a history of bone metastasis may have a bone scan, if clinically indicated.

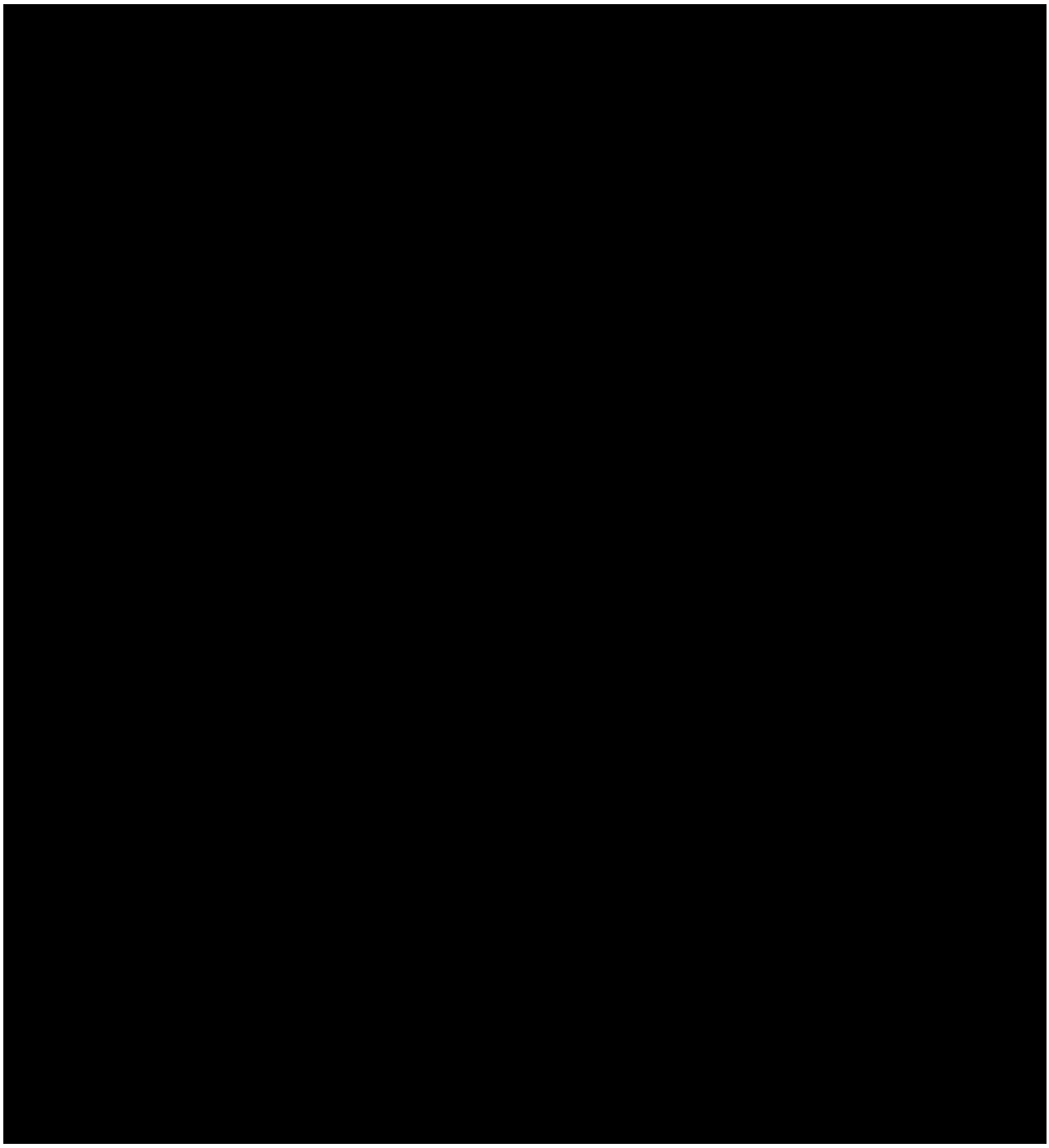
9.1.1.2 BICR Assessment of Progression

Sites should submit all scans to a BICR, preferably within 7 days of scan acquisition, throughout the duration of the study. BICR will review scans, and remain blinded to treatment arm and investigator assessment of submitted scans. When progression per RECIST 1.1 criteria is assessed by the investigator, the site will inform the imaging core lab, so that the BICR assessment of progression can be expedited in a manner that does not unnecessarily alert the BICR team to the investigator's assessment. The BICR review will be completed and limited results provided to the site.

Participants whose progression is not confirmed by the BICR should perform an additional CT of the chest, CT/MRI of the abdomen, pelvis, and all known sites of disease 4 weeks after initial progression, prior to subsequent therapy. Also, if participants discontinue treatment without radiographic progression, tumor assessments will continue according to the protocol-specified schedule, as noted in until progression has been confirmed by BICR.

All study treatment decisions will be based on the investigator’s assessment of tumor images and not on the BICR assessment. The BICR assessment of progression is only relevant for determining

when tumor assessments for a given participant are no longer required to be submitted to the imaging vendor.



9.2 Adverse Events

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

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.

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

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

Contacts for SAE reporting specified in Appendix 3

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment until the time points 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 Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. 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 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 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 module.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of this updated information being available.

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

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

9.2.2 Method of Detecting AEs and SAEs

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

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 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 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 BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form

to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, or re-initiation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur. If, for whatever reason, the pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended), following approvals of participant /sponsor /IRB/EC, as applicable.

In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the BMS Medical Monitor 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 Sponsor or designee. In order for Sponsor 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 Appendix 3 for reporting details).

Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 ×ULN

AND

2) Total bilirubin > 2 ×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.

For participants with elevated AST or ALT or Total bilirubin at baseline, potential DILI is defined as:

1) AT (ALT or AST) elevation > 2× baseline AND 3× ULN; OR

AT elevation 8 times ULN

AND

2) Total bilirubin > 2× baseline AND >2× 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. Overdoses that meet the regulatory definition of SAE will be reported as an SAE (see Appendix 3).

9.4 Safety

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

9.4.1 Physical Examinations

Refer to Schedule of Activities (see Section 2).

9.4.2 Vital signs

Refer to Schedule of Activities (see Section 2).

9.4.3 Clinical Safety Laboratory Assessments

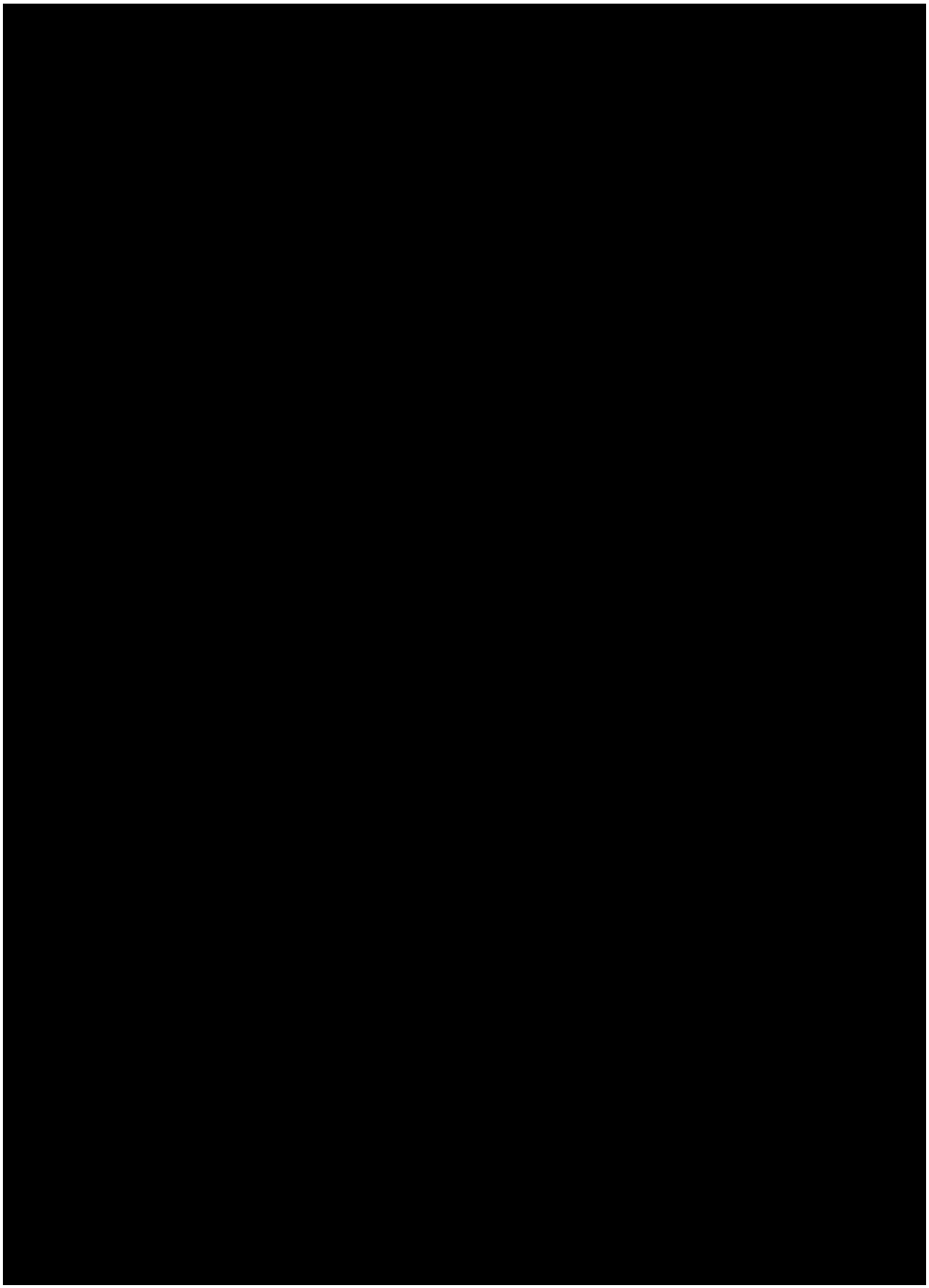
Investigators must document their review of each laboratory safety report.

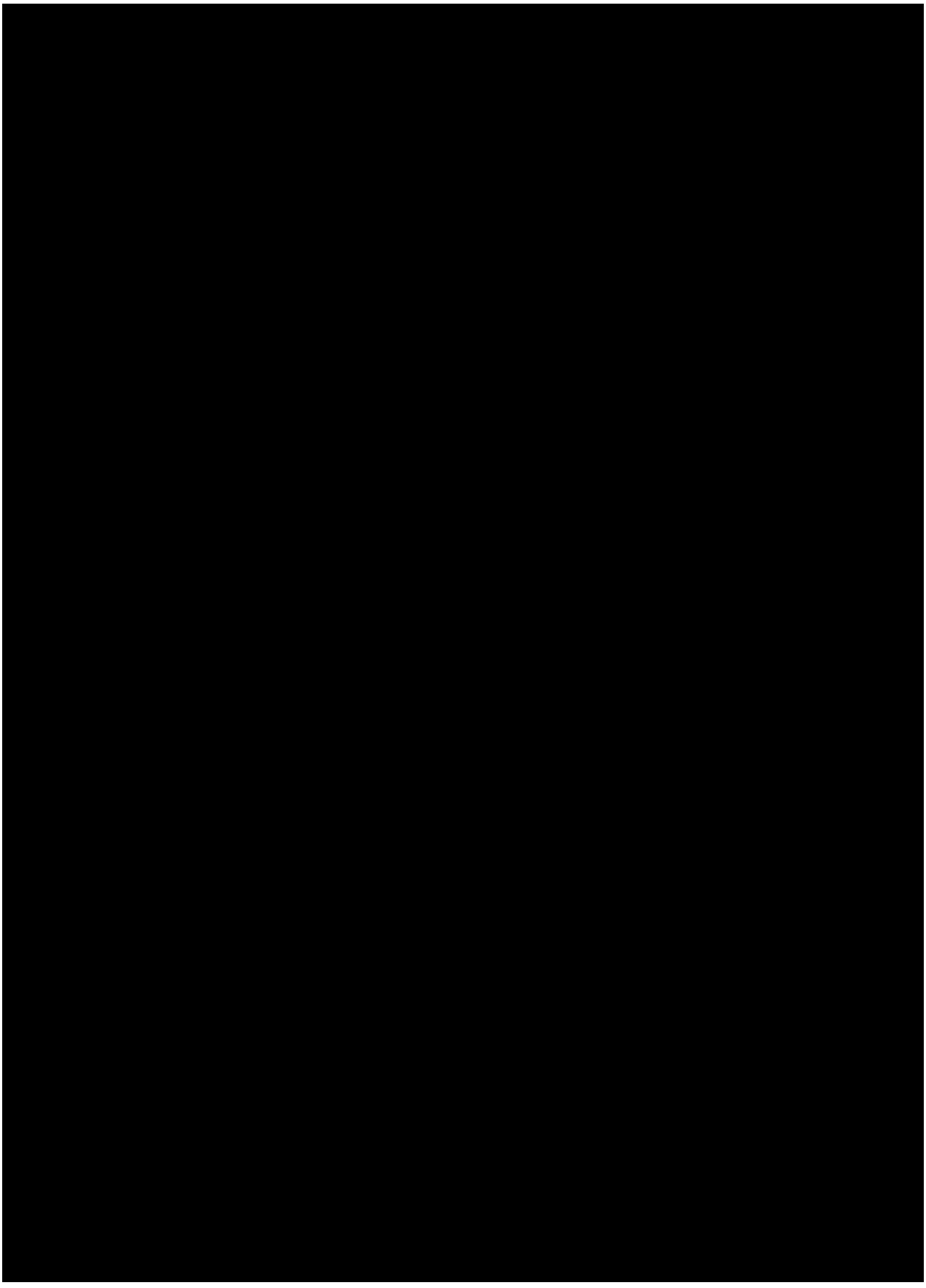
Hematology - CBC	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Alkaline phosphatase (ALP) Lactate dehydrogenase (LDH) Creatinine Blood Urea Nitrogen (BUN) or serum UREA Glucose (fasting or not) PT/INR – screening and as clinically indicated during bevacizumab treatment PTT - screening	Albumin - screening only Sodium Potassium Chloride Calcium Phosphorus TSH, free T3 and free T4 - screening TSH, with reflexive fT3 and fT4 if TSH is abnormal - on treatment
Urinalysis	
Urinalysis or urine dipstick including protein, glucose, blood, leukocyte esterase, specific gravity, pH. 24hr urine collection or UPCR required if a protein urine dipstick reading is ≥2+.	
Serology	
Hepatitis B/C, (HBV sAG, HCV antibody or HCV RNA), - screening only. If anti-HCV test is positive, then HCV RNA is mandatory.	
Other Analyses	
CEA (and CA19-9) Assessment	
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)	

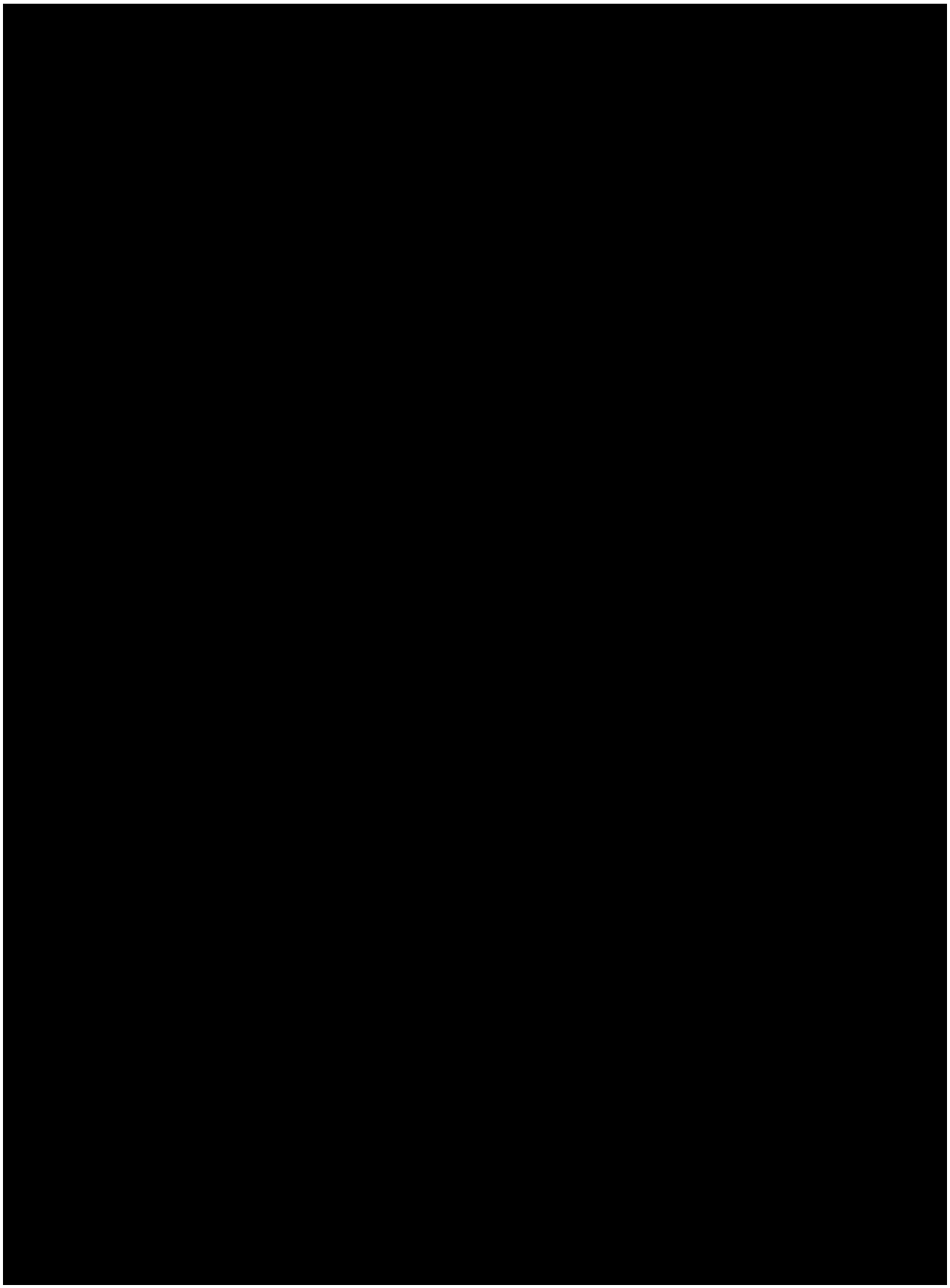
9.4.4 Imaging Safety Assessment

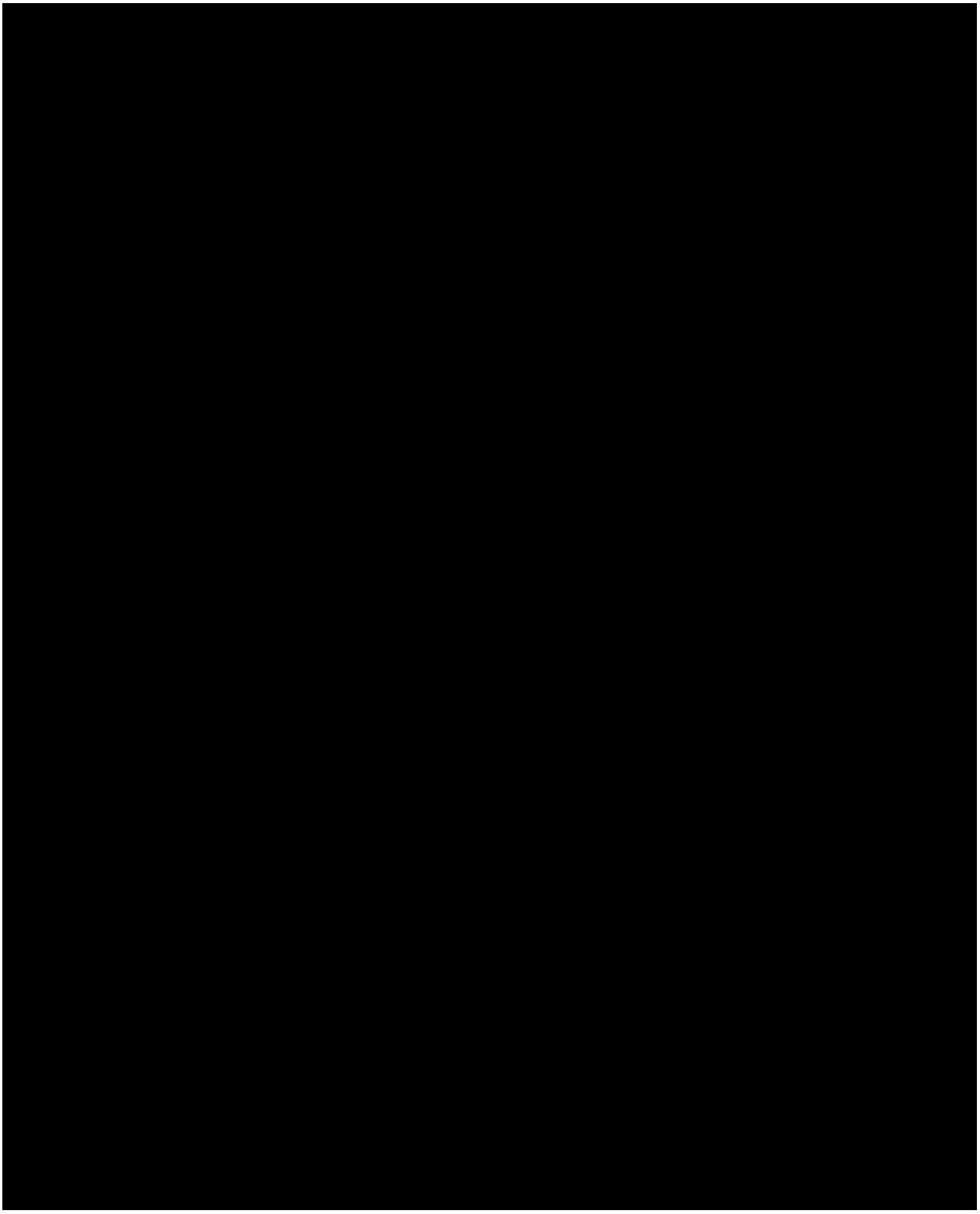
Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

[redacted]









10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who signed an informed consent form and were registered into the IRT system
Randomized	All participants who were randomized to any treatment arm in the study. This is the primary population for analyses of efficacy.
Treated (Safety)	All participants who received at least one dose of study treatment (nivolumab or SOC).

[redacted]

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Below is a summary of planned statistical analyses of the primary and secondary endpoints. A description of the participant population will be included in the statistical output reported, including subgroup of age, gender, and race.

10.3.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Progression-free survival (PFS) is defined as the time from randomization date to the date of the first documented tumor progression, as determined by BICR (per RECIST v1.1), or death due to any cause, whichever occurs first. • Participants who die without a reported prior progression and without initiation of subsequent anti-cancer therapy will be considered to have progressed on the date of their death. • Participants who did not progress or die will be censored on the date of their last evaluable tumor assessment. • Participants who did not have any on study tumor assessments and did not die will be censored on the randomization date.

Endpoint	Statistical Analysis Methods
	• Participants who started any subsequent anti-cancer therapy without a prior reported progression or prior to death will be censored at the last tumor assessment prior to initiation of the subsequent anti-cancer therapy. Further explanation for various censoring scenarios for PFS will be specified in SAP. The distribution of PFS will be compared in the two randomized arms via a two-sided, log-rank test stratified by randomization stratification factors of tumor sidedness and prior oxaliplatin-based adjuvant chemotherapy at the overall significance level of .20 (two-sided). The hazard ratio (HR) and the corresponding 95% confidence interval (CI) will be estimated in a stratified Cox proportional hazards model using the randomized arm as a single covariate, stratified by tumor sidedness and prior oxaliplatin-based adjuvant chemotherapy. The PFS curves for each randomized arm will be estimated using the Kaplan-Meier (KM) product limit method. Median PFS and the corresponding two-sided 95% CIs using the log-log transformation will be computed. In addition, PFS rates at a specified time point (e.g., 12, 24 months), and the corresponding two-sided 95% CIs using the log-log transformation, will be computed.
Secondary	Objective Response Rate (ORR) is defined as the number and percentage of participants with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR). Best overall response (BOR) is defined as the best response designation, recorded between the date of randomization and the date of the initial objectively documented tumor progression per RECIST v1.1 or the date of subsequent therapy, whichever occurs first. For participants without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination. Disease Control Rate (DCR) is defined as the proportion of participants whose BOR is CR or PR or SD among all randomized participants. Time to Response (TTR) is defined as the time from the date of randomization to the date of first confirmed CR or PR. TTR will be evaluated for responders only. Duration of objective response (DoR) is defined as the time between the date of first confirmed response to the date of the first documented tumor progression (per RECIST 1.1), or death due to any cause, whichever occurs first. The rules of censoring are the same as PFS. DoR will be evaluated for responders (ie, participants with confirmed CR or PR) only.

Endpoint	Statistical Analysis Methods
	The endpoints above will be assessed by both BICR and investigator where applicable. OS is defined as the time from the date of randomization to the date of death. A participant who has not died will be censored at last known date alive. The ORR will be summarized by binomial response rates and their corresponding two-sided 95% exact CIs are calculated using the Clopper-Pearson method. OS curves will be estimated using KM product-limit methodology. Median OS with two-sided 95% CIs using the log-log transformation will be computed. In addition, OS rates at a specific time point (e.g., 12, 24 months) with two-sided 95% CIs using the log-log transformation, will be computed. Other secondary variables including TTR, DoR, and DCR will be summarized in the following ways. Time to event variables will be analyzed in a similar way as OS. Binary variables will be summarized in a similar way as ORR. Quantitative variables will be summarized using the mean, median, minimum and maximum values, and standard deviation. Categorical variables will be summarized using tables presenting counts and percentages for each category.
[redacted]	

10.3.2 Safety Analyses

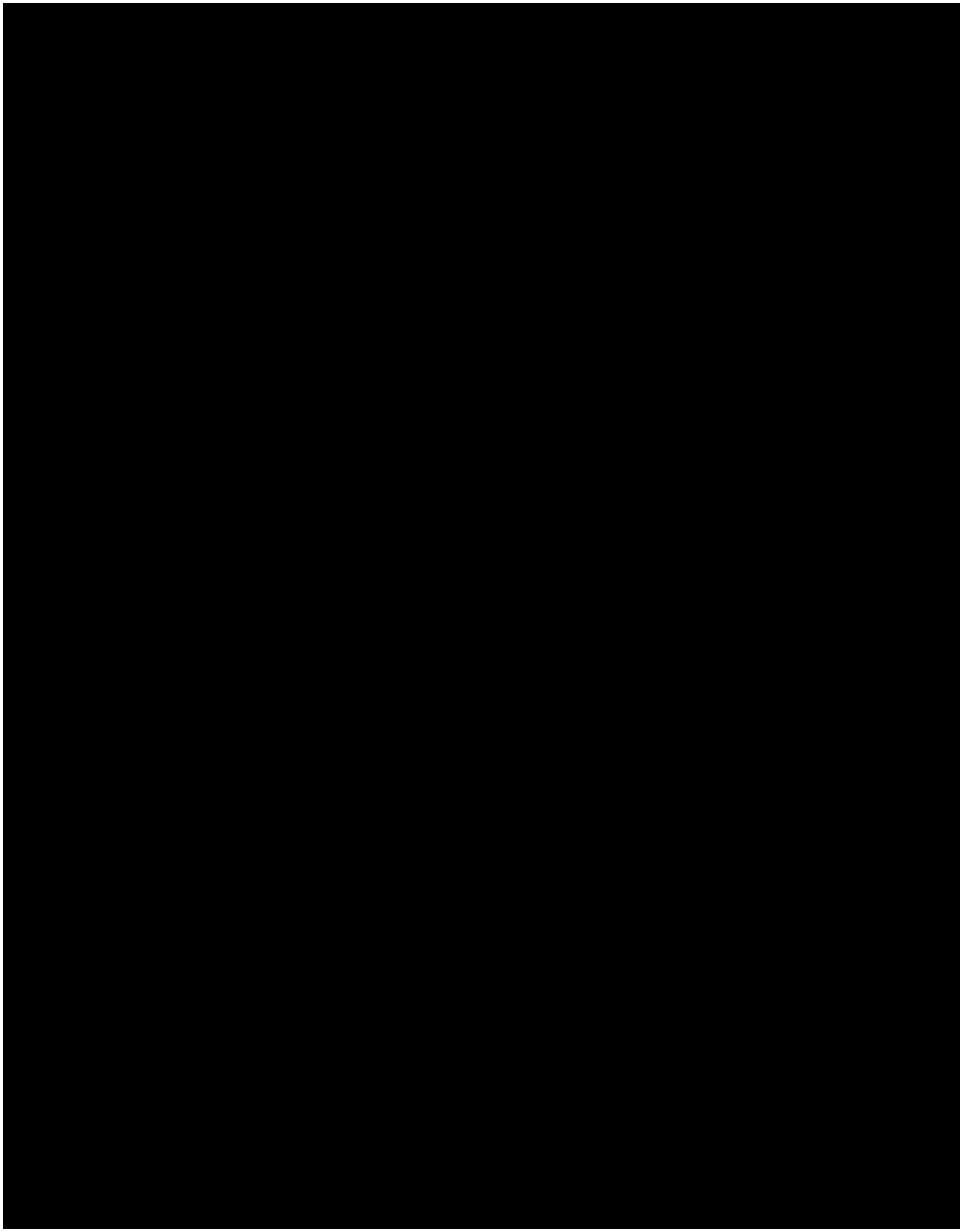
Endpoint	Statistical Analysis Methods
Secondary	The safety analysis will be performed in all participants who have received at least 1 dose of study treatment. Descriptive statistics of safety will be presented using CTCAE (Version 4) by treatment arm. Adverse events, treatment-related AEs, SAEs and treatment-related SAEs will be tabulated using worst grade per CTCAE (Version 4) by system organ class and preferred term. On-study clinical laboratory abnormalities will be summarized using worst grade per CTCAE (Version 4).
[redacted]	

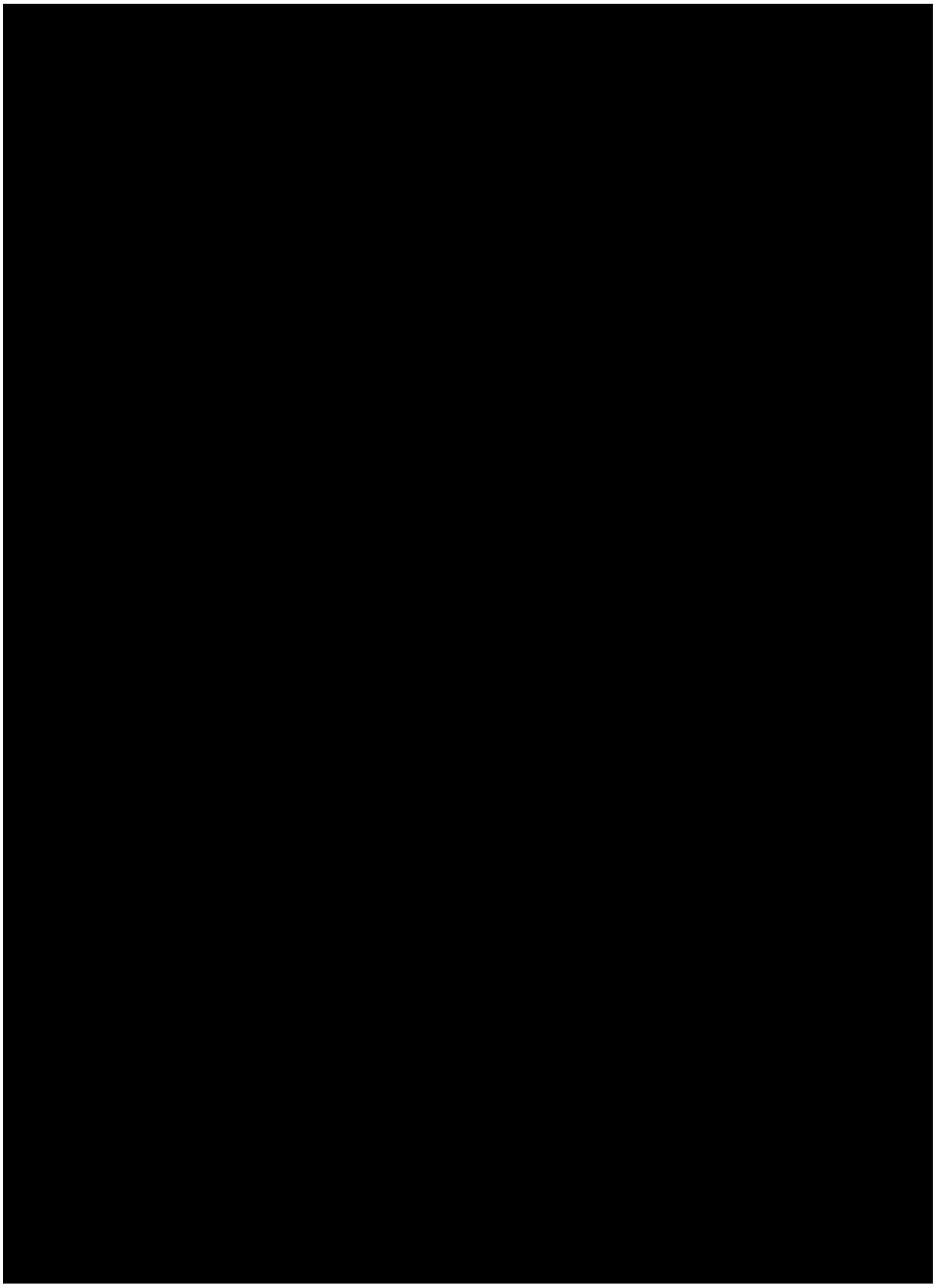
[redacted]

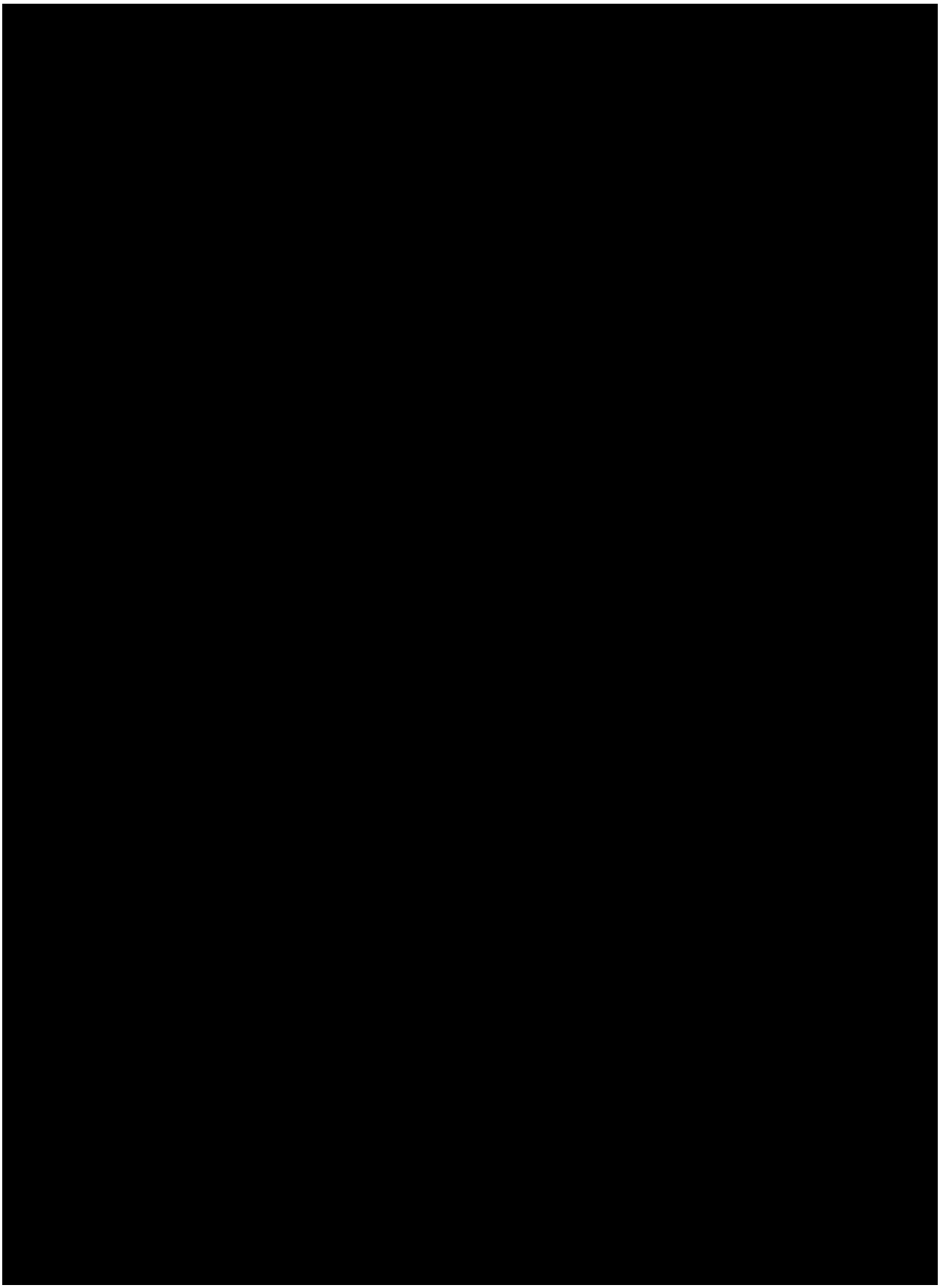
10.3.4 Interim Analyses

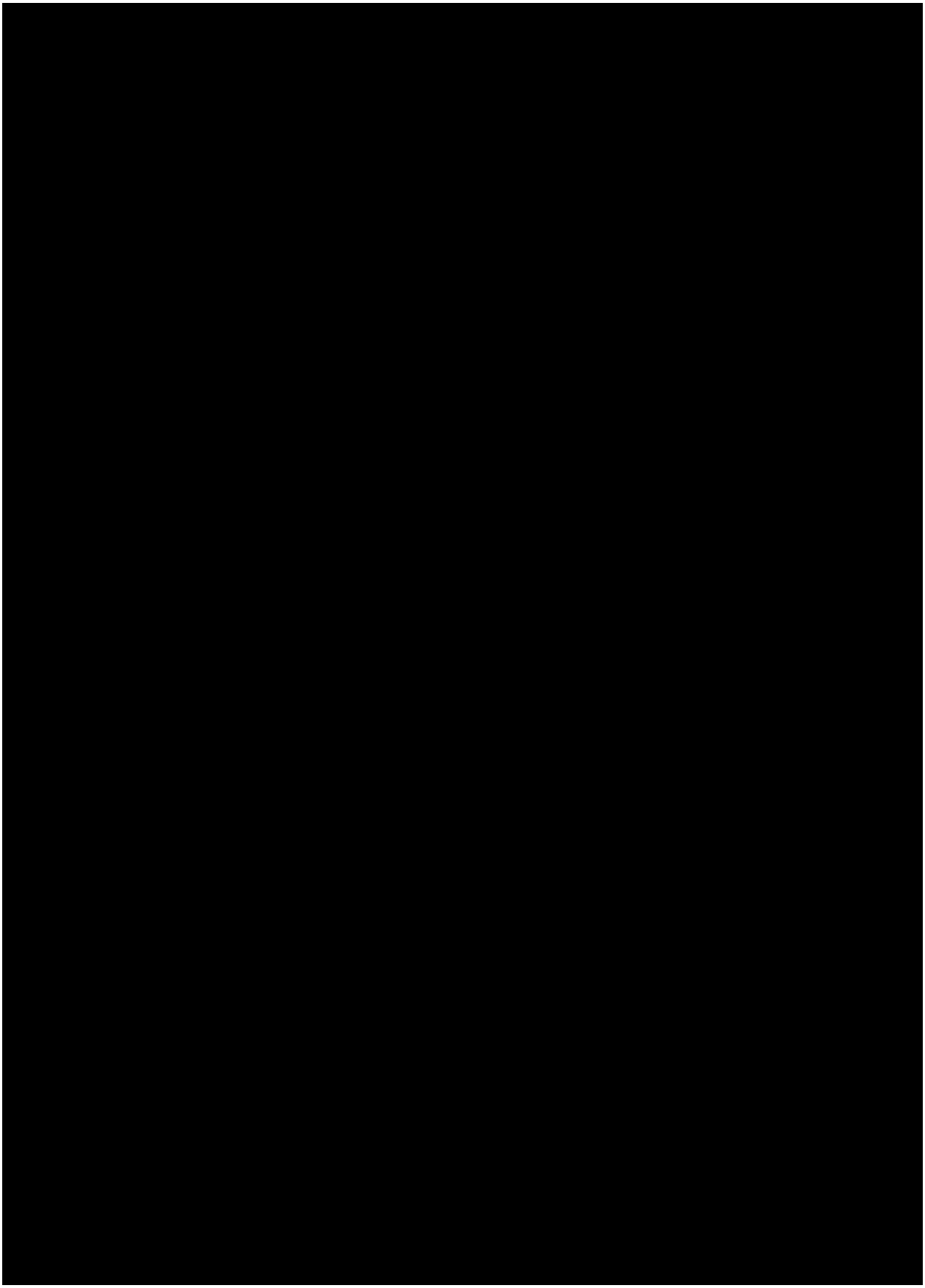
One interim analysis (IA) is planned in the Phase 2 portion of the study [redacted]. The decision flow is described in Section 5.1.

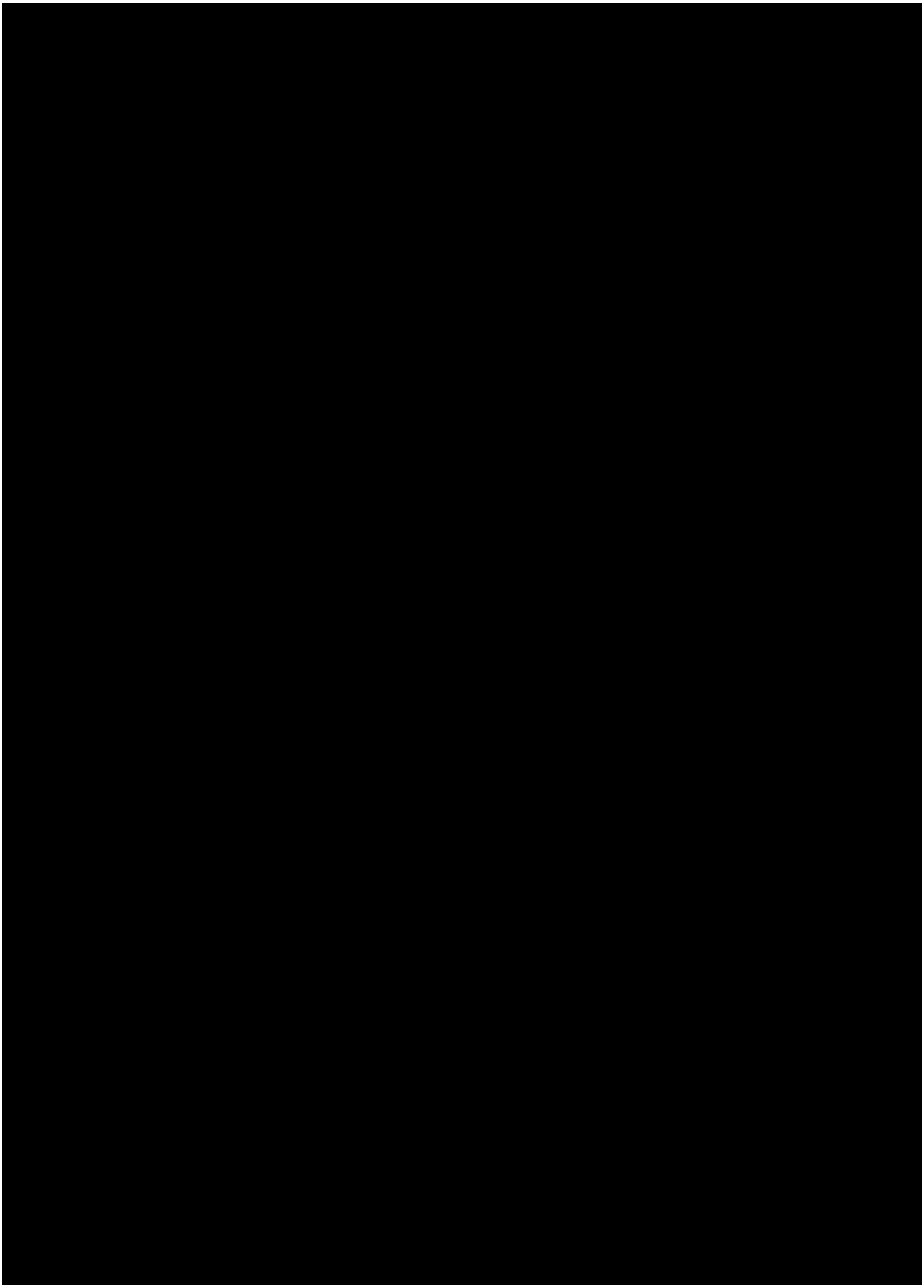
The Statistical Analysis Plan will further describe the planned interim analysis.

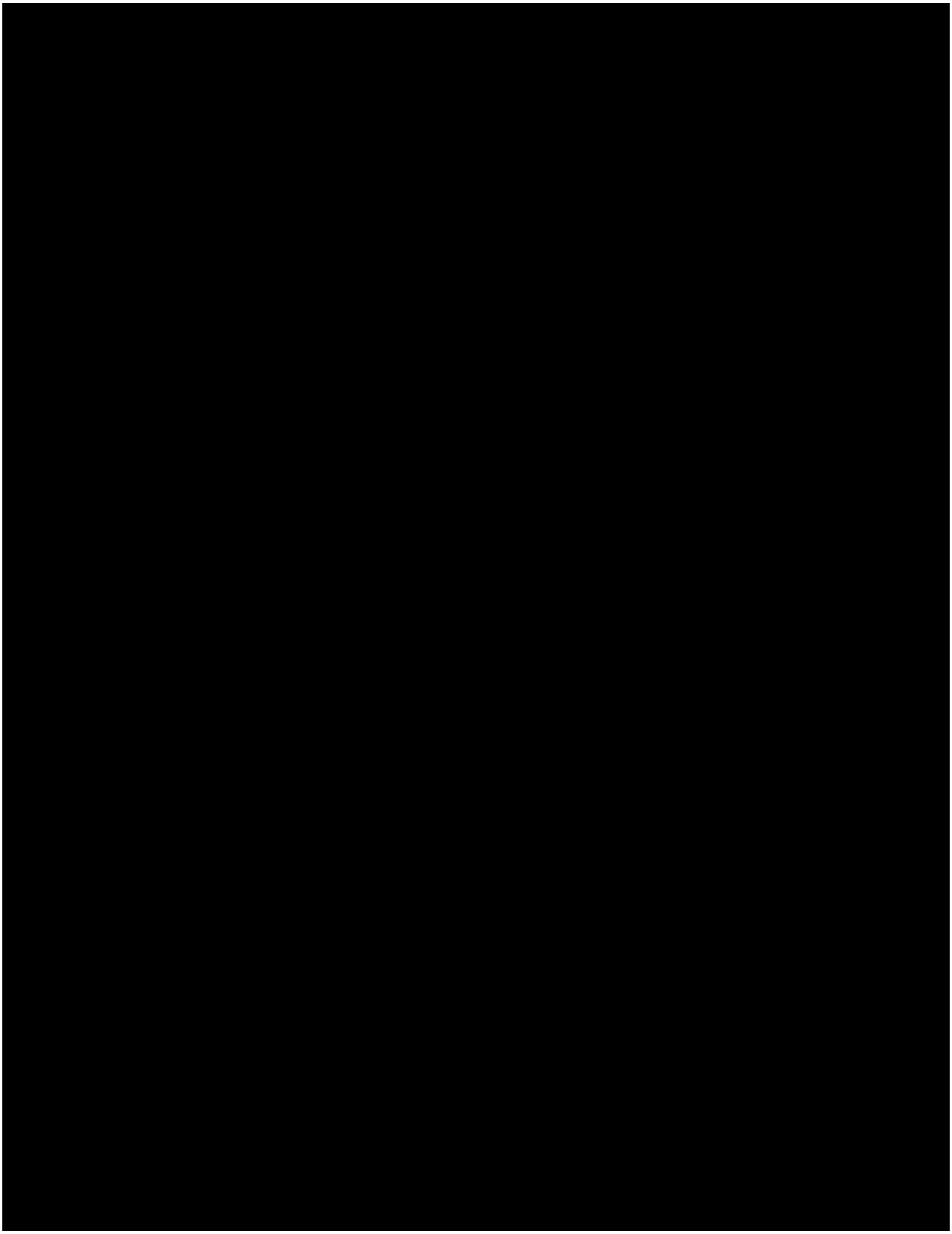












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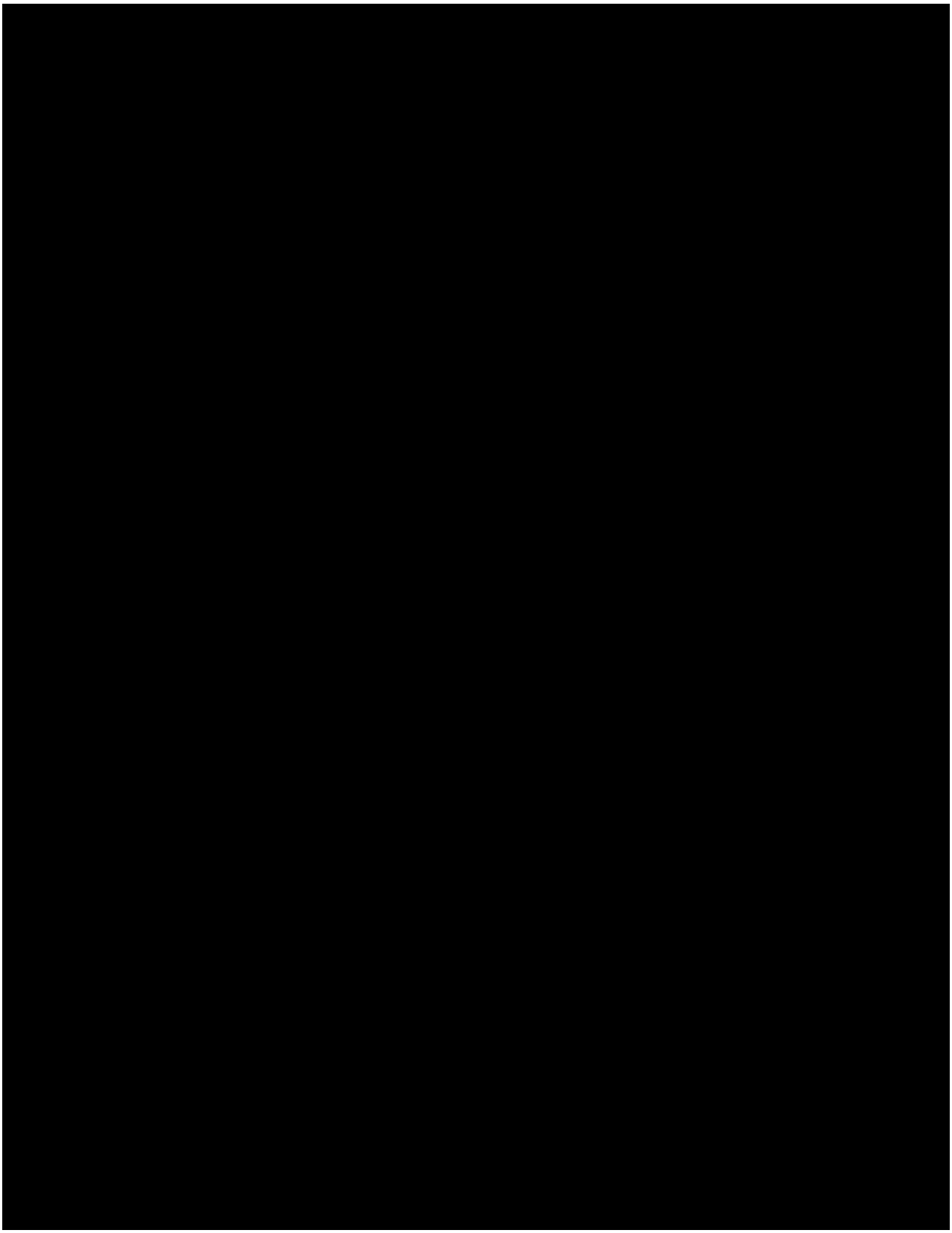


12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
5-FU	5-Fluorouracil
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BICR	blinded independent central review
BMS	Bristol-Myers Squibb
BOR	best overall response
BP	blood pressure
[redacted]	
BUN	blood urea nitrogen
CBC	complete blood count
CEA	Carcinoembryonic Antigen
CFR	Code of Federal Regulations
[redacted]	
CI	confidence interval
[redacted]	
CNS	Central nervous system
CR	complete response
CRC	colorectal cancer
CRF	Case Report Form, paper or electronic
CTAg	Clinical Trial Agreement
DCR	disease control rate
dL	deciliter
[redacted]	
DOR	Duration of response
ECG	electrocardiogram
ECOG	eastern cooperative oncology group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eg	exempli gratia (for example)

Term	Definition
[redacted]	
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin embeded
FSH	follicle stimulating hormone
g	Gram
GCP	Good Clinical Practice
[redacted]	
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	human chorionic gonadotrophin
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	heart rate
[redacted]	
ICH	International Conference on Harmonisation
[redacted]	
ie	id est (that is)
IEC	Independent Ethics Committee
IHC	immunohistochemistry
[redacted]	
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
I-O	Immuno-oncology
IP/IMP	investigational product/investigational medicinal product
IRB	Institutional Review Board
IRT	interactive response technology
IU	International Unit
IV	intravenous
kg	kilogram
L	Liter
LDH	lactate dehydrogenase
LFT	Liver function tests

Term	Definition
mCRC	metastatic colorectal cancer
[redacted]	
mg	milligram
mg	microgram
min	minute
mL	milliliter
mmHg	millimeters of mercury
MMR	mismatch repair (of DNA)
mOS	median overall survival
MRI	magnetic resonance imagining
MSI	microsatellite instability
MSI-H	microsatellite instability high
MSS	microsatellite stability
[redacted]	
N/A	not applicable
NCCN	national comprehensive cancer network
[redacted]	
ORR	objective response rate
OS	overall survival
[redacted]	
PD-L1	program cell death ligand 1
[redacted]	
PFS	progression-free survival
[redacted]	

Term	Definition
PR	partial response
[redacted]	
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOP	Standard Operating Procedures
[redacted]	
TSH	Thyroid stimulating hormone
[redacted]	
TTR	time to response
[redacted]	
ULN	Upper limit of normal
US	united states
[redacted]	
WBC	white blood cell
[redacted]	
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Good Clinical Practice (GCP),
- consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines Good Clinical Practice (GCP)
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

Sponsor or designee will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable

regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

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

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

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

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

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

Participants unable to give their written consent (e.g., stroke or participants 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 participants are the most important considerations and should prevail over interests of science and society.

SOURCE DOCUMENTS

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

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

STUDY TREATMENT RECORDS

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

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

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

CASE REPORT FORMS

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

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

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

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

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

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

MONITORING

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

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

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

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

RECORDS RETENTION

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

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

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

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

RETURN OF STUDY TREATMENT

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

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

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

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

method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.

- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

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

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

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:

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

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

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

ADVERSE EVENTS

Adverse Event Definition:
An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term
Events <u>NOT</u> Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) • medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases • admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

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

EVALUATING AES AND SAES

Assessment of Causality

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

Follow-up of AEs and SAEs

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

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

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 6 months after the end of study treatment.*

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

• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • 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)

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

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

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

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

COLLECTION OF PREGNANCY INFORMATION

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

APPENDIX 5 NIVOLUMAB 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.

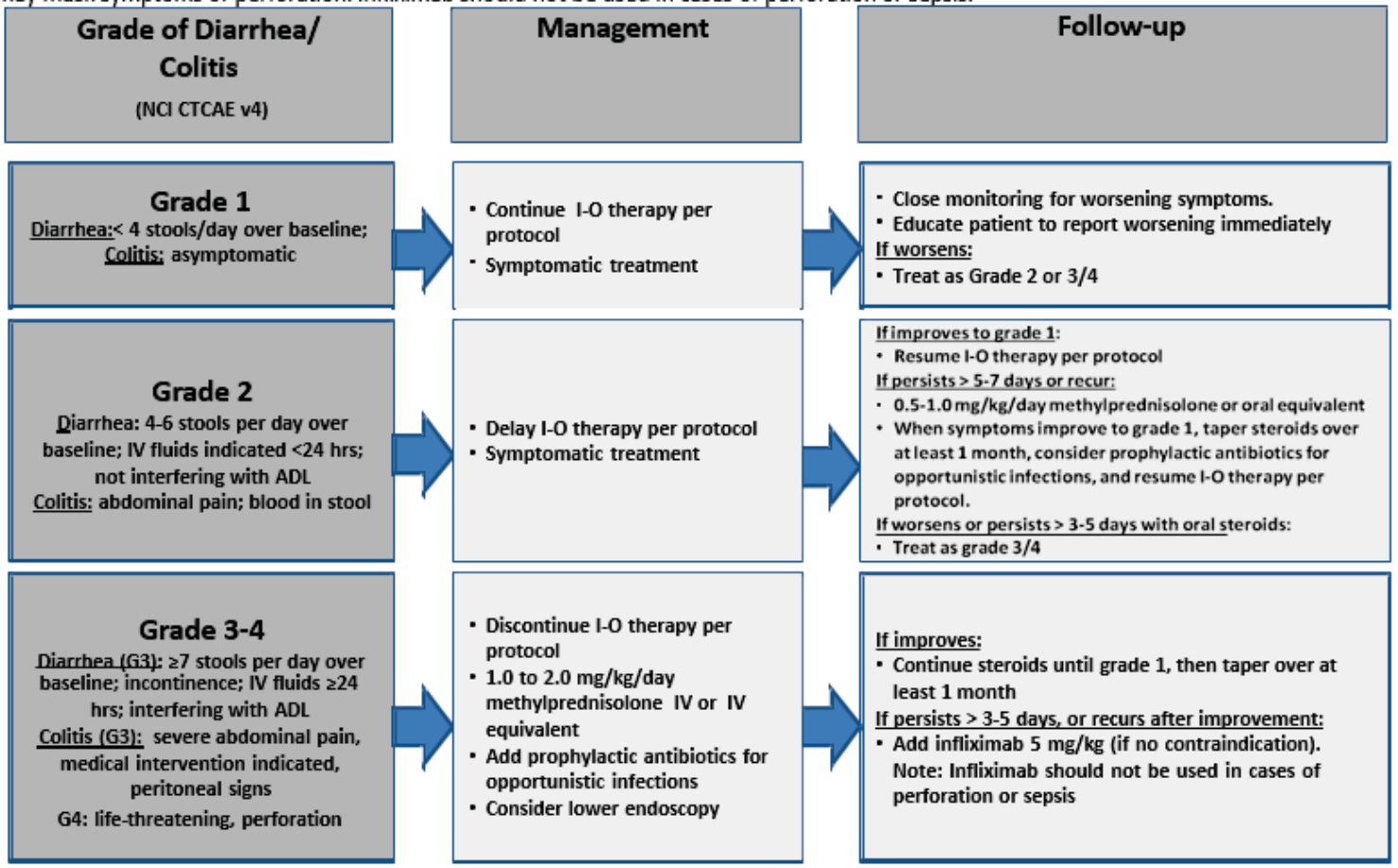
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

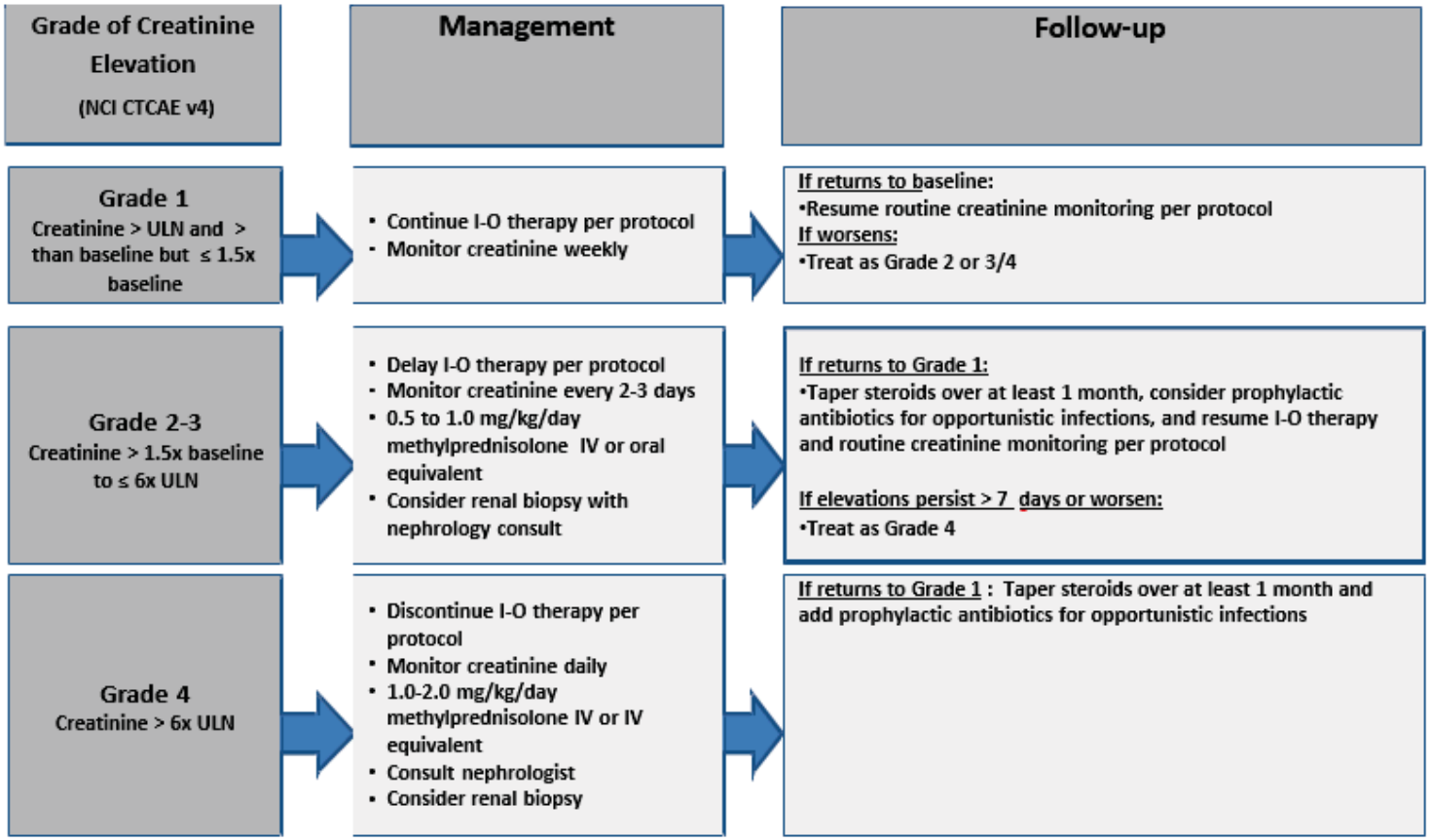


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

Renal Adverse Event Management Algorithm

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

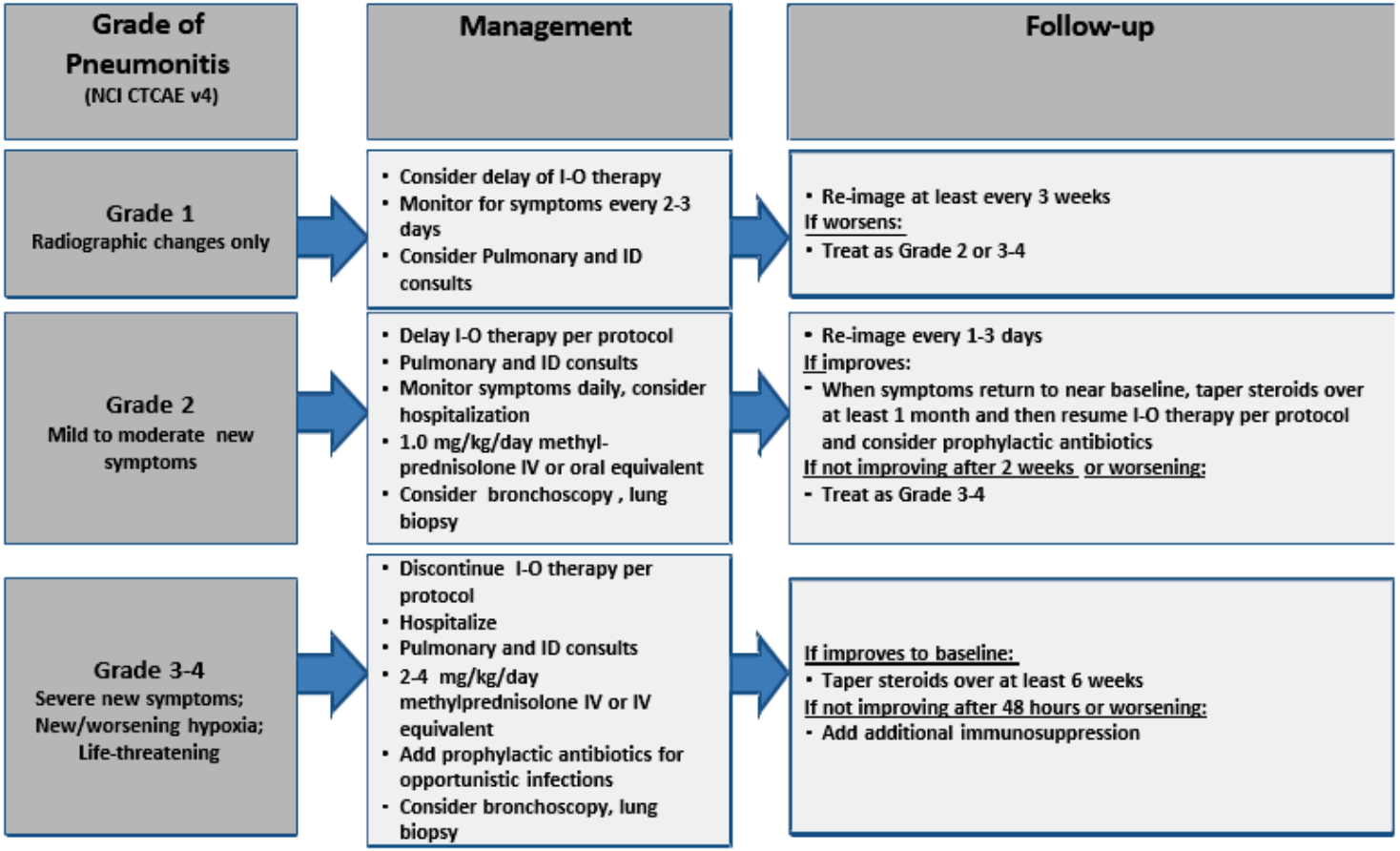


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

Pulmonary Adverse Event Management Algorithm

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

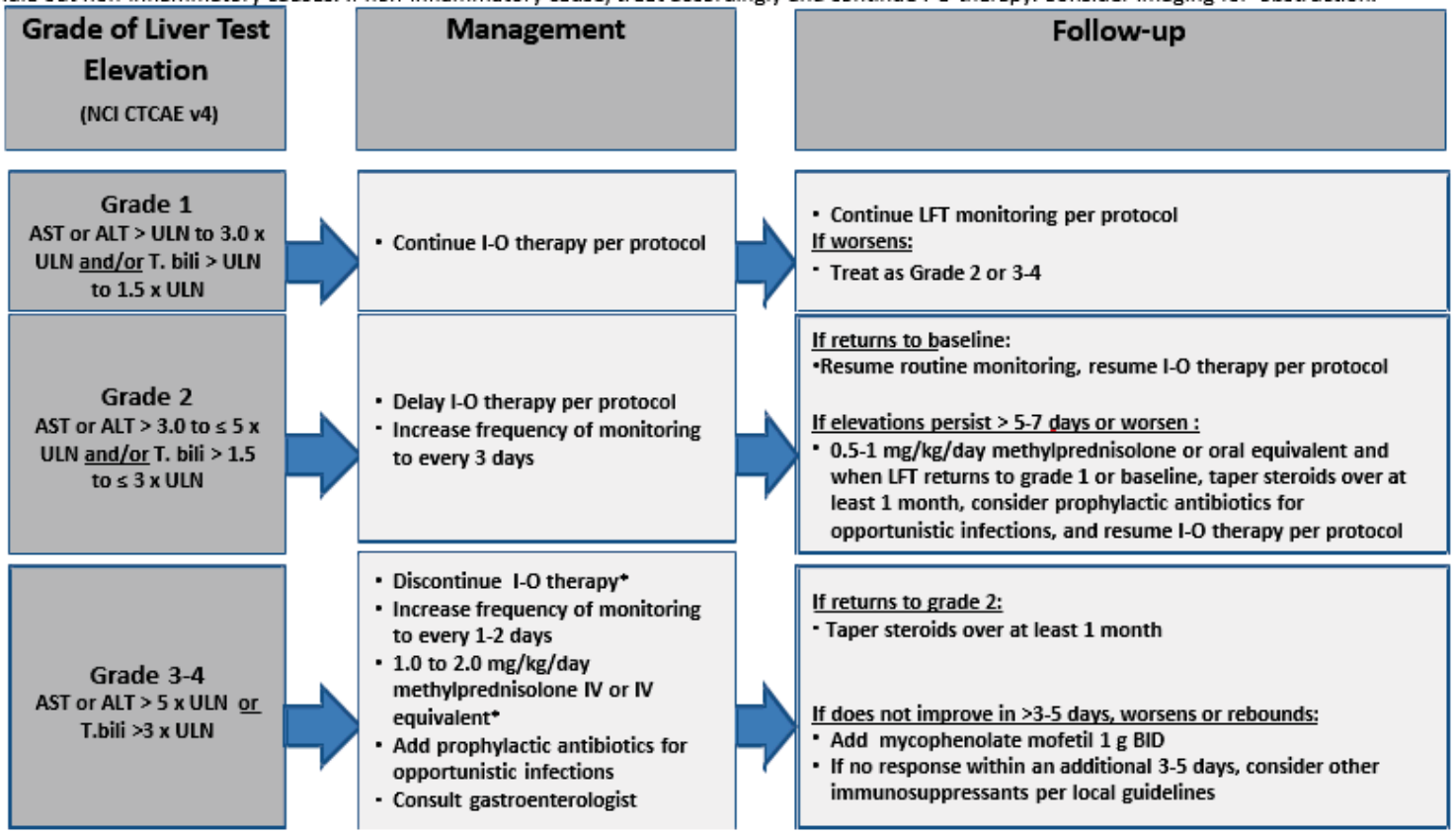


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

Hepatic Adverse Event Management Algorithm

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



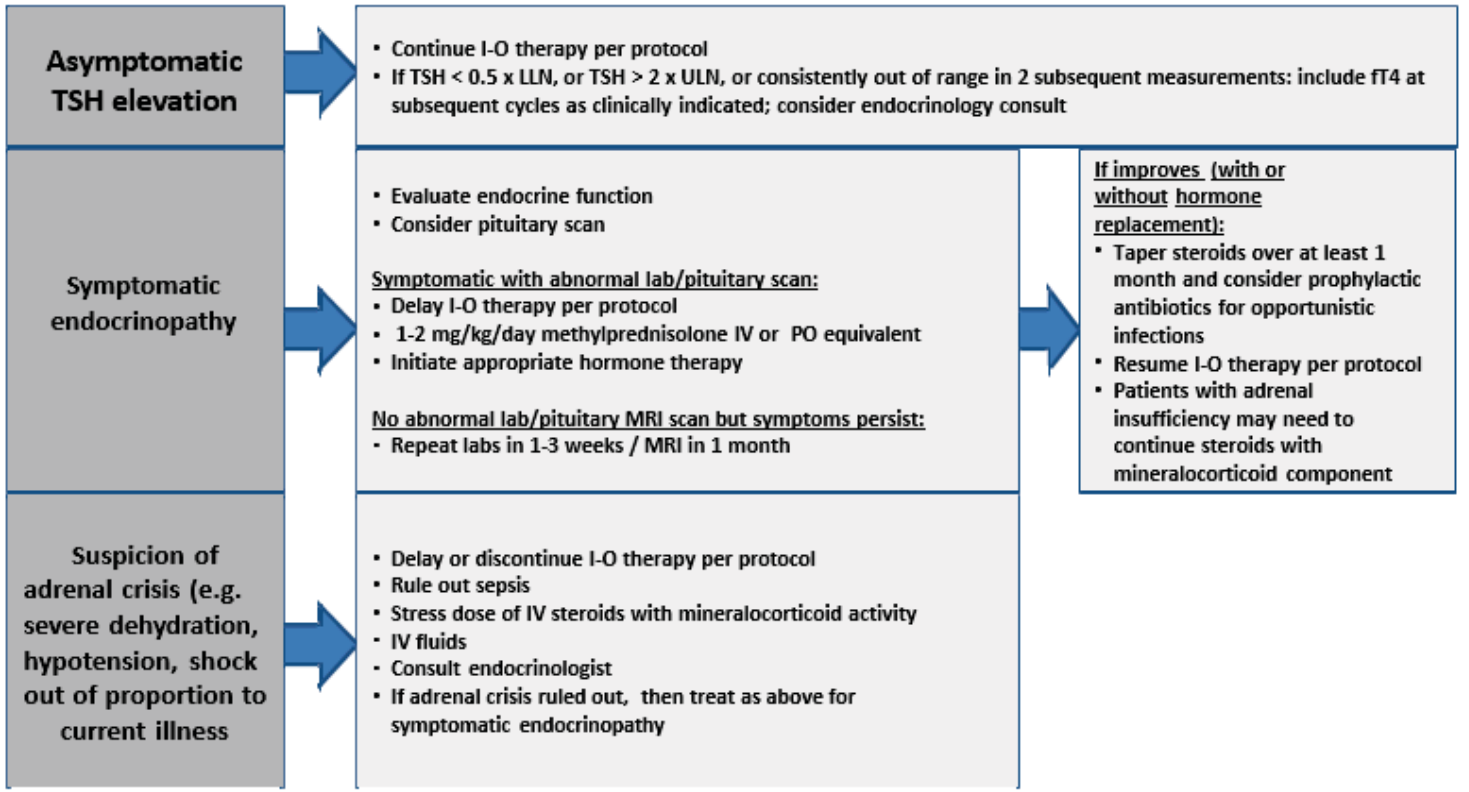
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

27-Jun-2019

Endocrinopathy Adverse Event Management Algorithm

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

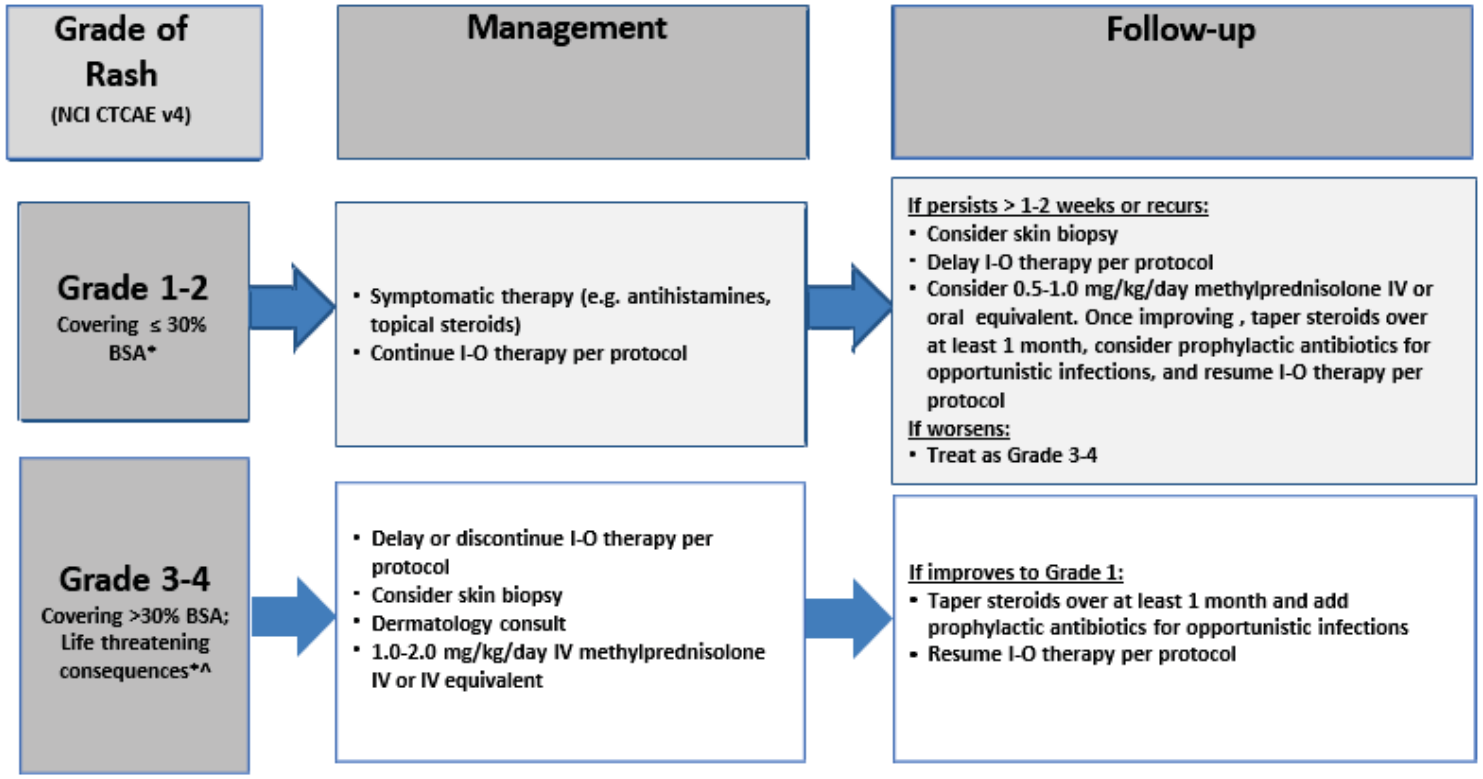


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

Skin Adverse Event Management Algorithm

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



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

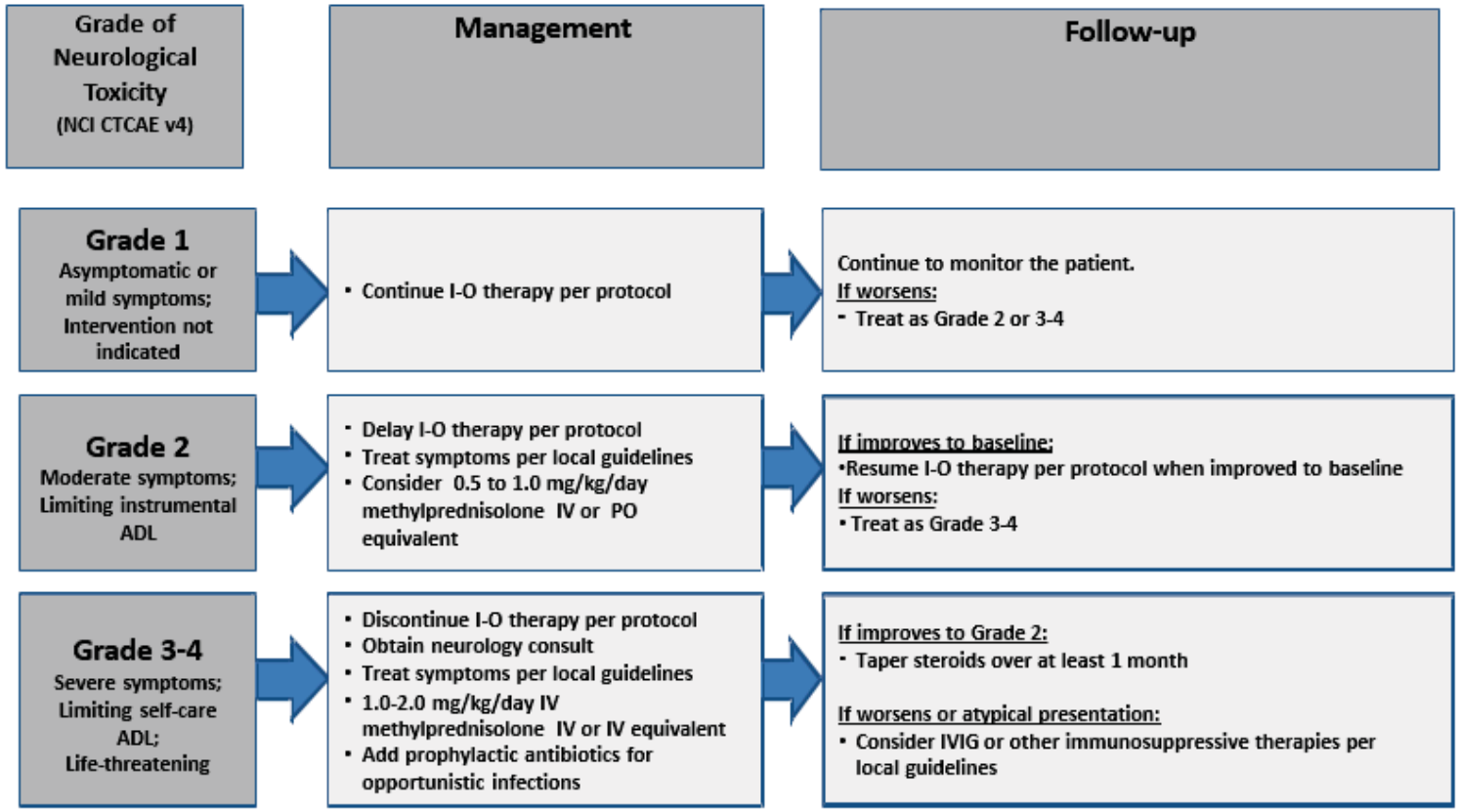
*Refer to NCI CTCAE v4 for term-specific grading criteria.

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

27-Jun-2019

Neurological Adverse Event Management Algorithm

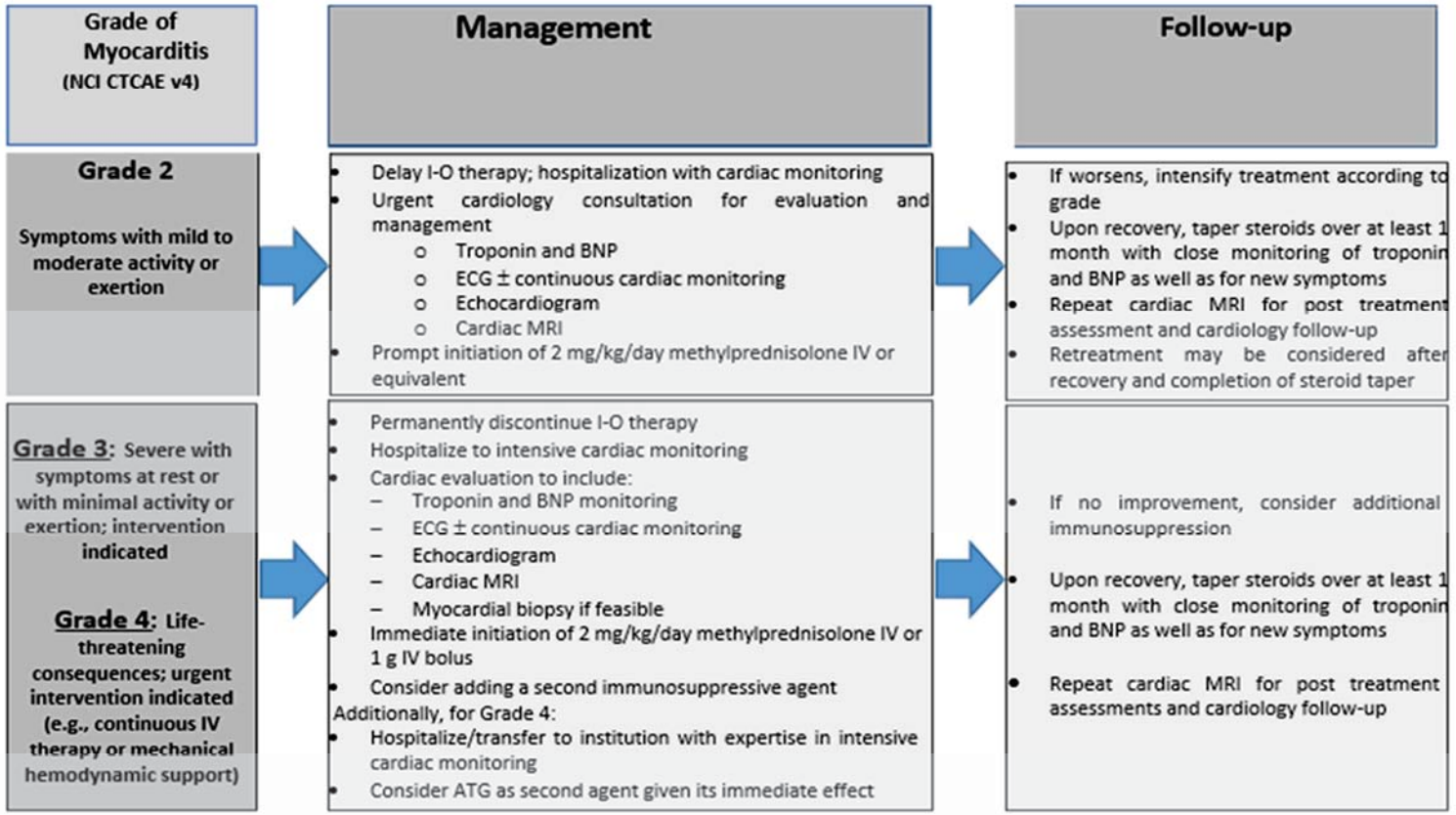
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

27-Jun-2019

Myocarditis Adverse Event Management Algorithm



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

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

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

27-Jun-2019

APPENDIX 6 ECOG PERFORMANCE STATUS

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
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, e.g., 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**

[redacted]

APPENDIX 7 RECIST 1.1 GUIDELINES [redacted]

1 EVALUATION OF LESIONS

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

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

1.1 Measurable

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

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

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

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

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

1.2 Non-Measurable

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

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

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

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

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

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

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

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

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

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

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

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

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

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

2.1.1.2 Target lesions that become 'too small to measure'

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

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

2.1.1.3 Lesions that split or coalesce on treatment

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

2.2 Evaluation of Non-Target Lesions

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

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

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

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

2.2.1.1 When the patient also has measurable disease

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

2.2.1.2 When the patient has only non-measurable disease

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

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

2.2.2 New Lesions

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

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

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

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

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

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

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

2.3.2 Time Point Response

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

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

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

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

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease and NE = inevaluable		

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

2.3.3 Best Overall Response

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

For example, if the first scheduled follow-up imaging visit is Week 6 (± 7 days) for a particular protocol, a Best Response of SD can only be made after the participant 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 participant 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		

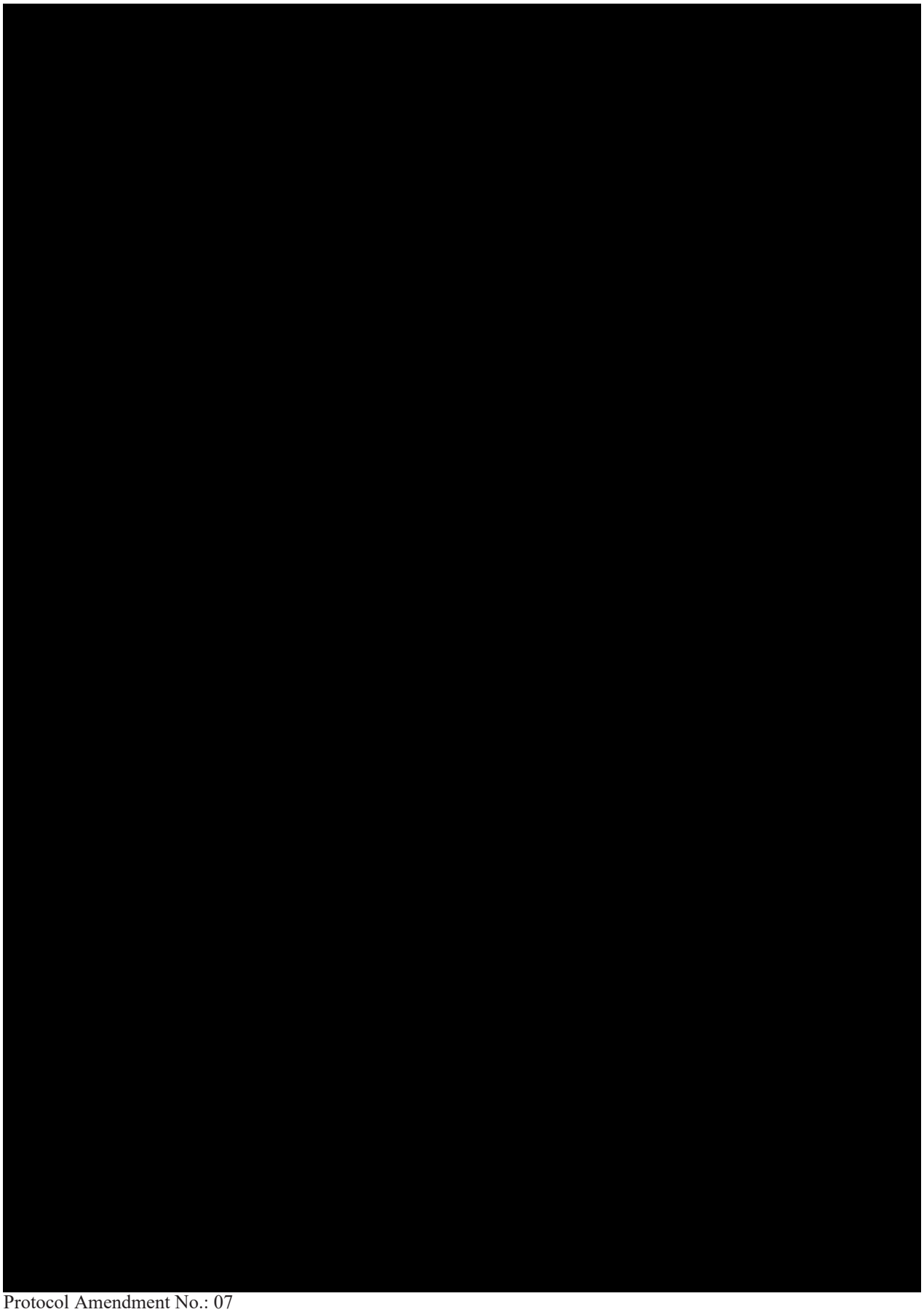
[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. 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.

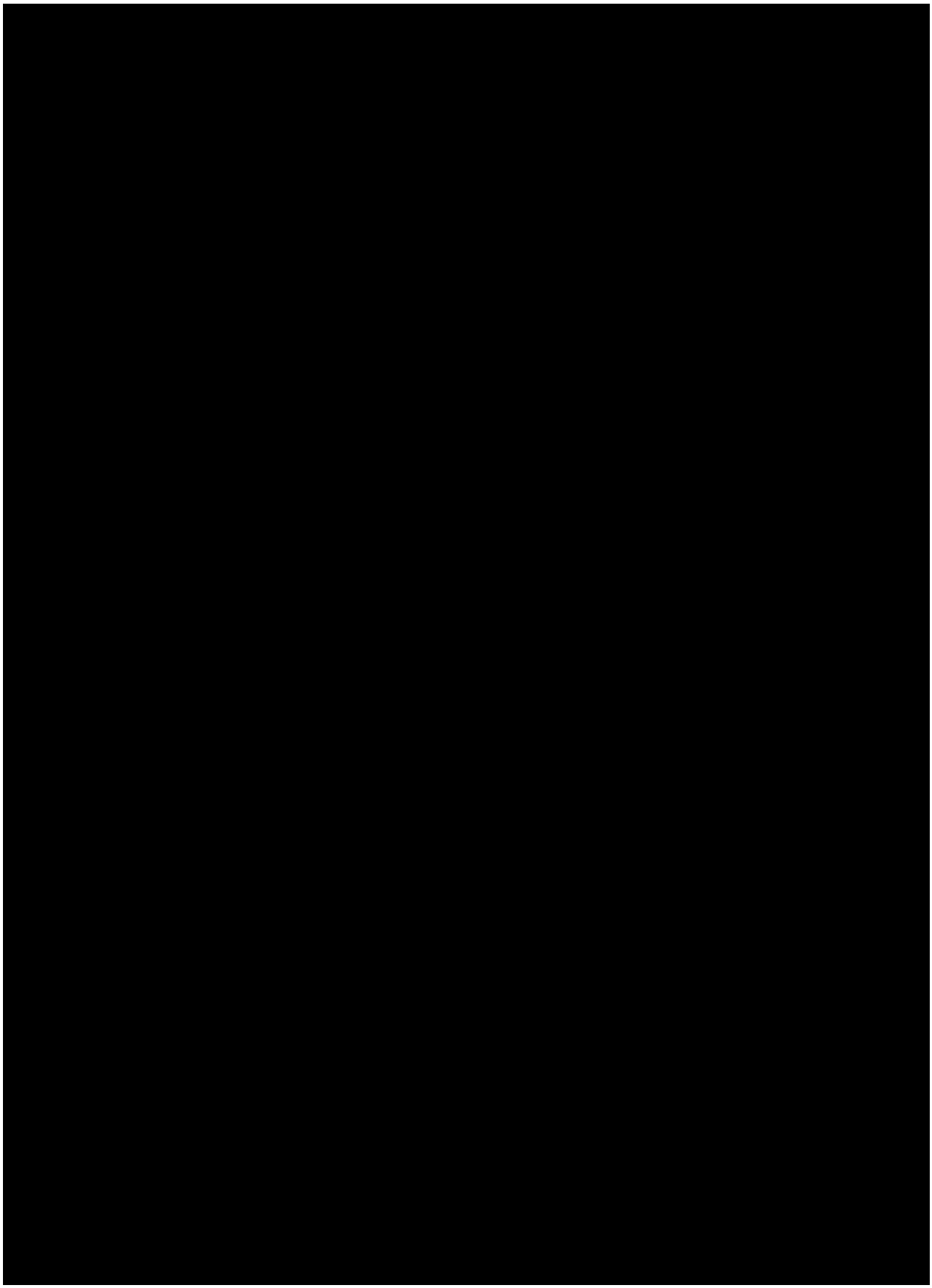
2.3.4 Confirmation Scans

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 participant is considered to not have progressive disease.

[redacted]





APPENDIX 10 COUNTRY SPECIFIC APPENDIX

Table 1: Criteria for exclusion of HIV-positive participants in Germany and other countries as applicable

Section 6.2 Exclusion Criteria, Exclusion criterion 4) Physical and Laboratory Test Findings, l)	"Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)"to be replaced with "Positive test for HIV".
Section 2 Flow Chart/Time and Events Schedule, Table 2- 1: Screening Assessments- Laboratory Tests	Add "HIV" to the list of laboratory tests

APPENDIX 11 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

[redacted] **Revised Protocol 06, 02-Jun-2020**

[redacted]

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
• Synopsis: Overall Design • Section 5.1 Overall Design • Section 5.1 Overall Design, Treatment Phase • Section 7.1 Treatments Administered	Text has been added to clarify that treatment with SOC may continue, after the maximum treatment duration of 24 months for nivolumab, until progression, unacceptable toxicity, withdrawal of consent, or the end of the study, whichever comes first.	Clarification for study sites that treatment with SOC may continue, after the maximum treatment duration of 24 months for nivolumab, until progression, unacceptable toxicity, withdrawal of consent, or the end of the study, whichever comes first, which is consistent with NCCN guidelines for 1L treatment for mCRC.
Throughout	Minor editorial or format changes that do not change content.	Clarify text.

[redacted] **Revised Protocol 05, 19-Dec-2019**

[redacted]

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis; Section 5, Overall Study Design	Updated Figure and footnotes, and description of analyses to remove reference of IA2.	As described in the overall rationale.
Section 2, Schedule of Activities, Table 2-2, On-Treatment Procedural Outline, CEA (and CA19-9) Assessment	Collection window (± 7 day) added.	This collection is intended to align with tumor assessments, therefore the 7 day window as added as clarification.
Section 10.3.4, Interim Analyses	Updated to remove reference to IA2.	As described in the overall rationale

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 5	Management Algorithms Updated. Myocarditis Algorithm added.	Algorithms have been updated to contain the most recent version from the 27-Jun-2019 IB. The only update to the algorithms in the latest IB is addition of the myocarditis algorithm.

[redacted] **Revised Protocol 04, 07-Dec-2018**

[redacted]

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2, Schedule of Activities, Table 2-2, On-Treatment Procedural Outline (CA2099X8), IRT Vial Assignment, Fluorouracil 1200 mg and 2400 mg infusions	Revised Notes regarding schedule of fluorouracil infusion.	To clarify the fluorouracil infusion days.
Section 7.1, Treatments Administered, Table 7.1-1, Section and Timing of Dose, Fluorouracil 1200 mg and 2400 mg infusions; paragraph e, under Nivolumab plus SOC and bevacizumab arm; and paragraph 2 under SOC and bevacizumab arm.	Revised text regarding schedule of fluorouracil infusion.	To clarify the fluorouracil infusion days.
Section 7.1, Treatments Administered	Paragraph 8 was revised and paragraph 9 was removed.	Detailed text regarding treatment administration of nivolumab is addressed in the Pharmacy Manual.
Appendix 3	Revised text in the following sections: Events Meeting the AE Definition, Events Not Meeting the	Updated to reflect the most recent language for BMS studies.

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	AE Definition, Definition of SAE, and Follow-up of AEs and SAEs.	
Appendix 4	Removed text regarding women treated with hormone replacement therapy. Revised text regarding highly effective methods of contraception that are user independent and unacceptable methods of contraception.	Update to Appendix 4 in the previous version was incorrect. The current version has been updated to align with contraceptive guidance for participants being treated with nivolumab and other components of study treatment.

[redacted] **Revised Protocol 03, 13-Sep-2018**

[redacted]

Summary of key changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.2, Exclusion Criteria, 2), j)	Exclusion criteria removed in Revised Protocol 02, has been returned to the document.	Feedback from [redacted] requested we reinstate exclusion criteria 2j, due to concerns of GI perforation highlighted in the Avastin black box warning.

[redacted] **Revised Protocol 02, 06-Aug-2018**

[redacted]

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2, Schedule of Activities, Table 2-1; Section 5.1, Overall Design, Screening Phase, Participants must submit mandatory baseline tumor sample, bullet	Regarding baseline tumor submission, text was deleted regarding tissue submission from a resected primary tumor, archival tissue from an endoscopic biopsy, or baseline tumor	Language removed to clarify that tissue from the primary tumor will be required in order to enroll in this study, without exception.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
2;Section 6.1, Inclusion Criteria 2) Type of Participant and Target Disease Characteristics e) ii)	submission that occurred 6 or more years prior to randomization.	
Section 2, Schedule of Activities, Table 2-1	Regarding laboratory tests, a note was added stating that laboratory tests do not need to be repeated on C1D1 if screening laboratory results are deemed still clinically valid by the treating investigator.	In alignment with other protocols, to provide reasonable flexibility to sites and subjects in terms of timing of lab test blood draws
Section 2, Schedule of Activities, Table 2-1, Footnote b; Table 2-2, Footnote d, and Table 2-3, Footnote d.	Footnote was revised to allow for urine protein to creatinine ratio (UPCR) in place of the 24-hour urine collection.	Urine protein to creatinine ratio is an acceptable method to assess and manage proteinuria and less cumbersome as a 24-hr urine collection.
[redacted]		
Section 2, Schedule of Activities, Table 2-2	Regarding IRT vial assignment, timing of fluorouracil was revised.	To clarify the schedule of 5-FU infusion.
Section 2, Schedule of Activities, Table 2-2	Table footnote b includes revised dose delay information.	[redacted] Added text to clarify that CEA and CA19-9 should be collected on schedule regardless of dose delays.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 6.1, Inclusion Criteria, 2) c) i	Revised language for time gap between the completion of adjuvant or neoadjuvant chemotherapy and diagnosis of recurrent or metastatic disease.	Clarification of eligibility criteria.
Section 6.1, Inclusion Criteria, 2) h	Criterion was added to require that all participants will be required to undergo on-treatment biopsies.	Added with the addition of mandatory on-treatment biopsies.
Section 6.1, Inclusion Criteria, 3) d) and f	Revised the time from last dose of investigation drug	Updated to reflect the most recent language for BMS studies.
Section 6.2, Exclusion Criteria, 2) Medical Conditions	Criterion g was revised to within 6 months of enrollment. Criterion j is no longer applicable.	Modified to align with clinical practice.
Section 6.2, Exclusion Criteria, 3) Prior/Concomitant Therapy	Revised criterion c.	To align with current bevacizumab label. The current label states that bevacizumab should be discontinued at least 28 days prior to surgery, and should be held for at least 28 days after surgery.
Section 6.2, Exclusion Criteria, 3) Prior/Concomitant Therapy	Added criterion 3f to exclude participants who have received a live / attenuated vaccine within 30 days of first treatment.	Alignment with current BMS standards for studies using nivolumab.
Section 6.2, Exclusion Criteria, Physical and laboratory test findings; and Section 9.4.3, Clinical Safety Laboratory Assessments	Criterion 4j revised to include a statement to allow for urine protein to creatinine ratio in place of the 24-hour urine collection	Urine protein to creatinine ratio is an acceptable method to assess and manage proteinuria and less cumbersome as a 24-hr urine collection
Section 7, Treatment; Table 7.1-1; section on Nivolumab plus SOC and bevacizumab arm	Added text regarding dosing calculations to Table 7.1-1; paragraph 3 under the section titled, Nivolumab plus SOC and	To clarify the dose and the schedule of 5-FU infusion.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	bevacizumab arm; and paragraph 3 under the section titled, SOC and bevacizumab arm.	
Section 7, Treatment	Below paragraph 8, a paragraph was added regarding dosing calculations for bevacizumab administration.	To clarify that weight based dosing does not need to be recalculated if the patient's weight is within 10% of the weight used to calculate the previous dose.
Section 7.4.4, Table 7.4.4-1	Revisions were made to the recommended guidelines for management of proteinuria.	To include information on urine protein to creatinine ratio
Section 7.7.1, Prohibited and/or Restricted Treatments	Added a new bullet to prohibit administration of any live / attenuated vaccine (eg varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose.	Alignment with current BMS standards for studies using nivolumab.
Section 8.1.1, Nivolumab Dose Discontinuation	Myocarditis added to the list of drug-related events requiring discontinuation.	Update to be consistent with SmPC and the label for nivolumab.
Section 8.1.2, SOC Dose Discontinuation	Revised bullet items for bevacizumab discontinuations.	To align with current bevacizumab label.
Section 9.2.5, Pregnancy	Added paragraph regarding possible pregnancy.	Updated to reflect the most recent language for BMS studies.
Section 9.3, Overdose	Revised reporting text.	Updated to reflect the most recent language for BMS studies.
Section 9.4.3, Clinical Safety Laboratory Assessments, Other Analyses	Added CEA and CA19-9 testing	To be consistent with section 2, schedule of activity.
[redacted]		

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Appendix 2, Study Governance Considerations	Minor revisions to language Good Clinical Practice potential serious breach reporting. Deleted return of study treatment language that specified study treatments supplied by BMS or its vendors.	Updated to reflect the most recent language for BMS studies.
Appendix 3, Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up and Reporting	Added sections: Events Meeting the AE Definitions and Events NOT Meeting the AE Definition; and Definition of SAE Revised text regarding pregnancy and potential drug induced liver injury. Revised text for the following: Evaluating AEs and SAEs, Assessment of Causality, Follow-up of AE and SAEs; Reporting of SAEs to Sponsor or Designee.	Updated to reflect the most recent language for BMS studies.
Appendix 4, Women of Childbearing Potential Definitions and Methods of Contraception	Added note regarding women treated with hormone replacement therapy. Revised the definition relevant systemic exposure. Revised text regarding highly effective methods of contraception that are user independent. Revised section on unacceptable methods of contraception to include section on less than highly effective contraceptive methods that are user dependent.	Updated to reflect the most recent language for BMS studies.
Appendix 5, Hepatic Adverse Event Management Algorithm	Footnote *, regarding delay of I-O therapy was deleted.	Hepatic algorithm updated to align with most recent guidance in the IB.
Appendix 10, Country Specific Appendix	Added additional countries as applicable.	Updated to reflect the most recent language for BMS studies.
All	Minor formatting and typographical corrections.	Minor, therefore have not been summarized

[redacted] **Revised Protocol 01, 02-Feb-2018**

[redacted]

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
2, Schedule of Activities, Tables 2-1, 2-2, 2-3	Addition of urinalysis requirements	To ensure assessment of proteinuria at screening and management of proteinuria during and after treatment
[redacted]		
6.1 Inclusion Criteria, 2) Type of Participant and Target Disease Charact.eristics	Inclusion criteria 2.b rephrased	Inclusion criteria reworded for better clarity
6.1 Inclusion Criteria, 2) Type of	Inclusion criteria 2.c.i updated	Inclusion criteria updated to allow participants who had neoadjuvant

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Participant and Target Disease Charact.eristics		chemotherapy to be eligible, if > 6 months have elapsed since completion of that therapy and diagnosis of recurrent or metastatic disease
6.1 Inclusion Criteria, 2) Type of Participant and Target Disease Charact.eristics	Inclusion criteria 2.e rephrased	Sentence added to specify that adequate tumor tissue must be available for eligibility
6.2 Exclusion Criteria, 2) Medical Conditions	Exclusion criteria 2 k updated	Clarifies half-teaspoon volume
6.2 Exclusion Criteria, 2) Physical and Laboratory Test Findings	Exclusion criteria 4.g and 4.j updated	Clarifies AST/ALT exclusion criteria for participants with liver metastases and eligibility requirements for proteinuria
6.3 Lifestyle Restrictions	Lifestyle restrictions updated	Specifies that there may be restrictions associated to the SOC components
7.4 Dosage Modification	4th bullet added	Bullet added to specify that if there is a delay in administration of study drug(s) due to toxicity, treatment with the other study agent(s) should continue as scheduled and resumption of treatment should be at the next scheduled time point
7.4.1 Nivolumab Dose Delay	Last paragraph updated with guidelines on what to do with other study agents in case of nivolumab dose delay	Clarifies what to do with other study agents in case of nivolumab delay.
7.4.4 Dose Modification Criteria for bevazicumab	Dose modification criteria updated with recommended guidelines for the management of proteinuria	Bevacizumab may be discontinued without other study drugs needing to be discontinued.
7.7.1 Prohibited and/or Restricted Treatment	Restrictions on botanical preparation updated with conditions of use of marijuana and its derivatives	Under certain conditions use of marijuana and its derivatives will be permitted in this protocol as per latest BMS standards
7.7.1 Prohibited and/or Restricted Treatment	Ongoing treatment with aspirin (>325 mg/day) or other medications known to predispose participants to gastrointestinal ulceration and reference to local institutional standards and product labels of SOC components added to the list of prohibited/restricted treatments	Restriction on aspirin treatment or medications known to predispose participants to gastrointestinal ulceration added specifically for bevacizumab treatment. Reference to institutional standards or product labels added for clarity.

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
8.1 Discontinuation from Study Treatment	Third paragraph related to discontinuation guidelines in case of pregnancy revised	Updated as per latest BMS standard language. In case of pregnancy, study treatment must be discontinued. Conditions to restart study treatment have been clarified.
8.1.2 SOC Dose Discontinuation	Discontinuation criteria list for SOC drugs updated	Clarifies that certain criteria for discontinuation must be drug related and list of bevacizumab discontinuation criteria updated to better align with bevacizumab label
8.1.3	Last bullet added to specify when to resume treatment	Last bullet specifies that resumption of treatment should be at the next scheduled time point
9.2.7 Potential Drug Induced Liver Injury (DILI)	Section updated with definition of DILI for participants with elevated AST, ALT or Total Bilirubin at baseline	Definition of DILI updated in order to take into account potential participants enrolled with elevated liver function tests
9.4.3 Clinical Safety Laboratory Assessments	Glucose fasting status updated, coagulation testing (PT/INR) updated to be performed if clinically indicated, urinalysis testing updated as per updated schedule of activities (section 2)	Fasting status for glucose clarified as not mandatory, coagulation testing may be performed during bevacizumab treatment if clinically indicated, urinalysis testing requirements updated for proteinuria assessment and management
[redacted]		
Throughout protocol	Typographical, formatting and wording updates	Typographical, formatting and wording updates