Official Title of Study:

A Study of Nivolumab in Combination With Trametinib With Or Without Ipilimumab In Participants With Previously Treated Metastatic Colorectal Cancers

NCT Number: NCT03377361

Document Date (Date in which document was last revised): 03 May 2023

Protocol Number: CA2099N9
IND Number: 119,381
EUDRACT Number: 2017-001830-24
Date: 10-Aug-2017
Revised Date 03-May-2023

Clinical Protocol CA2099N9

A Study Of Nivolumab In Combination With Trametinib With Or Without Ipilimumab In Participants With Previously Treated Metastatic Colorectal Cancers

(CheckMate 9N9: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 9N9)

Protocol Amendment: 04

Incorporates Administrative Letter 06

[redacted]
Clinical Trial Physician
Bristol-Myers Squibb Company
3401 Princeton Pike
Lawrenceville, NJ 08648
Telephone (office): [redacted]
Email: [redacted]

[redacted]
Clinical Scientist
Bristol-Myers Squibb Company
86 Morris Avenue
Summit, NJ 07901
Telephone (office): [redacted]
Email: [redacted]

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

Bristol-Myers Squibb Research and Development
3401 Princeton Pike
Lawrenceville, NJ 08648
Avenue de Finlande 4
B-1420 Braine-l'Alleud, Belgium

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 04	03-May-2023	Based on the emerging data, Bristol-Myers Squibb Company (BMS) has made a strategic decision to expedite the CA2099N9 study closure. This decision is not related to any safety concerns. The protocol has been revised to reduce the assessments and data collection to minimize the burden on study participants and site staff. In addition, some of the [redacted] are removed, the key objectives are achievable with reduced data collection and shorter follow-up.
Administrative Letter 06	24-Feb-2022	Correction made to Synopsis: Ipilimumab sourcing 50 mg was added to the study treatment table. In Appendix 10 for BRAF, revised text to clarify that BRAF mutation status is required for participants for eligibility and stratification purposes.
Protocol Amendment 03	17-Dec-2021	The main reasons for Protocol Amendment 03 are to expand the eligibility criteria of Part 2 to include participants who have received at least 2 (no more than 4) prior lines of therapy, [redacted]. Additional updates include removal of the 40 mg (10 mg/mL) potency of nivolumab solution for use moving forward, [redacted], clarification of nivolumab intravenous administration procedure, and clarification of treatment discontinuation requirements. Administrative Letters 04 and 05 are also incorporated.
Administrative Letter 05	19-Jan-2021	Updated study personnel.
Administrative Letter 04	26-Oct-2020	Corrected a typo found in Table 2-3.
Revised Protocol 02	06-Oct-2020	CA2099N9 has been revised to enroll participants to the selected triplet regimen in the second line (2L) and third line (3L) setting. The sample size of the study expansion has been increased to a total of 200 patients to allow for further assessment of clinical safety, efficacy, [redacted] in microsatellite stable metastatic colorectal cancer (MSS mCRC). Part 1B [redacted] (2L) for the triplet regimen (80 participants) • Cohort 6: nivolumab 6 mg/kg Q4W plus ipilimumab 1 mg/kg Q8W plus trametinib 1.5 mg continuous QD Part 2 [redacted] (3L) for the triplet regimen (120 participants randomized 2:1): • Cohort 4: nivolumab 6 mg/kg Q4W plus ipilimumab 1 mg/kg Q8W plus trametinib 1.5 mg continuous QD • Cohort 5: A standard of care (SOC) arm with regorafenib All relevant sections of the protocol have been revised to support the revision of the study design. Major revisions are included in the following sections: • Sections 3.1 Study Rationale and 3.2 Background revised to include updated clinical data.

Document	Date of Issue	Summary of Change
		• Section 4 Objectives and Endpoints revised for Part 2 and Part 1B. • [redacted] • Section 10 Statistical Considerations updated to support new study design. Incorporates Administrative Letters 02 and 03.
Administrative Letter 03	23-Jul-2018	Correction to [redacted]
Administrative Letter 02	06-Apr-2018	Correction of two exclusion criteria bullets that were incorrectly renumbered.
Revised Protocol 01	01-Mar-2018	The protocol has been amended to include a randomized comparator arm (Cohort 7) for Part 2 consisting of standard-of-care regimens (regorafenib or TAS-102) per investigator's choice for ≥ 3rd line mCRC. Administrative Letter 01 has been incorporated. Of note, Revised Protocol 01 was not implemented.
Administrative Letter 01	09-Oct-2017	Correction of footnote in Table 2-4: On-Treatment Assessments (Part 1A mCRC 2nd line).Day 15 and Day 43 assessments are only required for the first cycle rather than the first 2 cycles, then may be performed as clinically indicated at investigators discretion.
Original Protocol	10-Aug-2017	Not applicable

OVERALL RATIONALE FOR THE PROTOCOL AMENDMENT 04

Based on the emerging data, Bristol-Myers Squibb Company (BMS) has made a strategic decision to expedite the CA2099N9 study closure. This decision is not related to any safety concerns. The protocol has been revised to reduce the assessments and data collection to minimize the burden on study participants and site staff. In addition, [redacted], the key objectives are achievable with reduced data collection and shorter follow-up.

SUMMARY OF KEY CHANGES OF PROTOCOL AMENDMENT 04

Section Number & Title	Description of Change	Brief Rationale
Title page	Updated Clinical Trial Physician and Clinical Scientist contact information.	Administrative update.
Section 1: Synopsis	Updated to match with relevant protocol revisions.	Updated to align with changes in the protocol body.
Section 2: Schedule of Activities	• In Table 2-1: ○ Under "Informed Consent", added that all cohorts are closed for enrollment. ○ Added to "Participant Registration and Treatment Assignment/Randomization" that all cohorts are closed for enrollment. • In Table 2-3: ○ Added "CLOSED FOR ENROLLMENT" to the title. ○ [redacted] ○ Added another specification to "Body Imaging" that imaging assessments will occur every 8 weeks until end of trial. • In Table 2-4: ○ Added "CLOSED FOR ENROLLMENT" to the title. ○ [redacted]. ○ Added another specification to "Body Imaging" that imaging assessments will occur every 8 weeks until end of trial.	Updated for consistency with the revised protocol.

SUMMARY OF KEY CHANGES OF PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	• In Table 2-5, added another specification to "Body Imaging" that imaging assessments will occur every 8 weeks until end of trial. • In Table 2-6: ○ Added "CLOSED FOR ENROLLMENT" to the title. ○ Added that [redacted] collection of Healthcare Resource data are discontinued. ○ Added another specification to "Body Imaging" that imaging assessments will occur every 8 weeks until end of trial. • In Table 2-7: ○ Added another specification to "Body Imaging" that imaging assessments will occur every 8 weeks until end of trial. ○ The collection of [redacted] Healthcare Resource Use and Survival Status is discontinued at Follow-up and/or Survival Follow-up. ○ Deleted "for up to 3 years" from the notes in "Survival Status" and changed visits during Survival Follow-up from 3 to 6 months. • Added new Tables 2-8, 2-9, 2-10, and 2-11.	Updated the duration of the imaging collection. Updated the duration and frequency of overall survival status collection. Added tables to the schedule of activities that have reduced assessments as a contingency in the event alternate means for providing study treatment are not available within approximately 9 months following last patient first treatment (LPFT) date.
Table 4-2: Objectives and Endpoints: Parts 1B and 2	Indicated in some of the [redacted] that they were not applicable per Protocol Amendment 04 or Part 1B Cohort 6 and Part 2 Cohort 4.	Updated for consistency with the revised protocol for Part 2 and Part 1B cohorts.
Section 5.1: Overall Design	Added text that defined what will be considered last patient last visit (LPLV) date and the maximum duration that a patient may receive experimental treatment.	Updated to provide clarification.

SUMMARY OF KEY CHANGES OF PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1.4.1: Blinded Independent Central Review	Indicated that a blinded independent central review (BICR) "may" be utilized instead of "will" be utilized.	Updated to reflect the change in objectives as BICR may not be performed.
Section 5.4.1: Rationale for 2 year treatment duration for Immunotherapy (Nivolumab + Ipilimumab)	Added text to reference Section 7.8.	Added for clarification.
Section 6: Study Population	Added the date enrollment was closed.	Updated for consistency with the revised protocol for Part 2 and Part 1B cohorts.
Section 6.2 Exclusion Criteria	For exclusion criteria 3), changed the laboratory testing results to be obtained from within 14 days to 28 days prior to first dose.	Updated for consistency
Section 5.1.1: Part 1 and Part 1A: Dose Optimization Section 7.1.4: Part 2 (Triplet Regimen, Cohort 4 and Standard of Care (SOC) Arm, Cohort 5) Section 7.1.6: Part 1B (Triplet Regimen, Cohort 6) Section 7.2 Method of Treatment Assignment Section 7.3: Blinding	Added text stating that enrollment is closed for Part 2 and Part 1B.	Updated for consistency with the revised protocol for Part 2 and Part 1B cohorts.
Section 8.1.6: Post Study Treatment Study Follow-up	Deleted text stating that overall survival is the key endpoint. Replaced text for participants who discontinue study treatment, stating that they must be followed until LPLV.	Updated to provide the details on the follow-up based on change in the study timelines.
[redacted]		
Section 9.4.3: Ophthalmic Examination	Added that standard ophthalmic examination will occur prior to	Added for clarification.

SUMMARY OF KEY CHANGES OF PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	randomization and on Month 6 from the first dose date.	
[redacted]		
Section 10.3.7: Interim Analyses	Deleted text stating that interim analyses may be conducted for Part 2 and Part 1B.	Deleted to align with the reduced study timelines and early closure per revised protocol
Appendix 2: Study Governance Considerations	Added new sections: BMS Commitment to Diversity in Clinical Trials and Data Protection, Data Privacy, and Data Security, and Study and Site Closure as well as additional text to Clinical Study Report and Publications.	Added to align with BMS commitment to diversity in clinical trials and to comply with European Union Clinical Trials Regulation requirement.
Appendix 10: KRAS/NRAS and BRAF Mutational Testing	Updated BRAF mutation status requirement.	To incorporate Administrative Letter 06.

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: A Study Of Nivolumab In Combination With Trametinib With Or Without Ipilimumab In Participants With Previously Treated Metastatic Colorectal Cancers

(CheckMate 9N9: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 9N9)

Study Phase: 1/2

Rationale:

CA2099N9 (CHECKpoint pathway and nivoluMAb clinical Trial Evaluation [CHECKMATE] 9N9) is a Phase 1/2, open-label, multi-center trial of nivolumab in combination with trametinib, with or without ipilimumab for the treatment of proficient mismatch repair (pMMR)/microsatellite stable (MSS) metastatic colorectal cancer (mCRC). Parts 1A and 1B of this trial investigate nivolumab and ipilimumab plus trametinib as 2nd-line (2L) treatment for pMMR/MSS mCRC participants. Part 2 provides an opportunity to evaluate nivolumab and ipilimumab in combination with trametinib for the treatment of later-line (3rd line plus [3L+]) pMMR/MSS mCRC participants who failed at least 2 prior lines (no more than 4 prior lines) of therapy for metastatic disease. Part 2 will include 2 treatment arms, including the triplet regimen and standard of care treatment (SOC) option (regorafenib). The objective of Part 2 is to further develop and optimize a [redacted] patient selection strategy for combination therapy of immune checkpoint inhibitors with a mitogen-activated protein kinase enzymes (MEK) inhibitor.

Additionally, the study presents an opportunity to validate the tolerability and preliminary efficacy, and further optimize a [redacted] patient selection strategy for nivolumab and ipilimumab in combination with trametinib in earlier line (2nd line [2L]) pMMR/MSS mCRC participants who failed only 1 prior line of therapy for metastatic disease (Part 1B).

Study Population:

Participants with previously treated metastatic, pMMR/MSS colorectal cancer (CRC) in the 2L and 3L+ setting.

Participants must have progressed or been intolerant to 2 prior lines of chemotherapy in the metastatic disease setting (doublet regimen; Part 1), participants must have progressed or been intolerant to at least 2 prior lines (no more than 4 prior lines) in the metastatic disease setting (triplet regimen, Part 2), and participants must have progressed or been intolerant to 1 prior line of chemotherapy in the metastatic disease setting (triplet regimen, Parts 1A and 1B).

Objectives and Endpoints:

Objectives and Endpoints: Parts 1 and 1A

Objectives	Endpoints
Primary	
• To characterize the safety and tolerability of combination therapies	• DLTs in Part 1 and Part 1A, only, observed for 1 treatment cycle (4 weeks for the doublet regimen and 8 weeks for the triplet regimen)
• To establish recommended dosing regimen for the combination (nivolumab plus ipilimumab plus trametinib OR nivolumab plus trametinib)	• Safety (including but not limited to): AEs, SAEs, deaths, and clinical laboratory abnormalities per CTCAE (version 4.0)
Secondary	
• To evaluate preliminary efficacy	• ORR, DCR, DOR, TTR, and PFS by investigator per RECIST v1.1 • OS
[redacted]	

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; DLTs, dose limiting toxicities; ORR, objective response rate; DCR, disease control rate; DOR, duration of response; TTR, time to response; PFS, progression free survival; OS, overall survival.

Objectives and Endpoints: Parts 1B and 2

Objectives	Endpoints
Primary	
• To evaluate the ORR in all participants treated with nivolumab plus ipilimumab and trametinib in the 2L and 3L+[a] setting (Parts 1B and 2, respectively); and regorafenib in 3L+[a] (Part 2 Only).	• ORR by investigator[b]
Secondary	
• To evaluate efficacy in all participants treated with nivolumab plus ipilimumab and trametinib in the 2L and 3L+[a] setting (Parts 1B and 2, respectively) and regorafenib in 3L+[a] (Part 2 only). [redacted]	• BOR, DCR, DOR, TTR, and PFS by investigator [b] • OS
• To characterize the safety and tolerability of combination therapies.	• Safety (including but not limited to): AEs, SAEs, deaths, and clinical laboratory abnormalities per CTCAE (version 4.0)
[redacted]	

Objectives and Endpoints: Parts 1B and 2

[redacted]

AE, adverse event; [redacted], BOR, best overall response; [redacted]; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DOR, duration of response; [redacted]; [redacted]; [redacted]; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PFS2, time to second objective disease progression; [redacted]; [redacted]; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; TTR, time to response; [redacted]; 2l, second line; 3L+, third-line plus.

[a] No more than 4 prior lines of therapy.

[b] per RECIST v 1.1.

Overall Design:

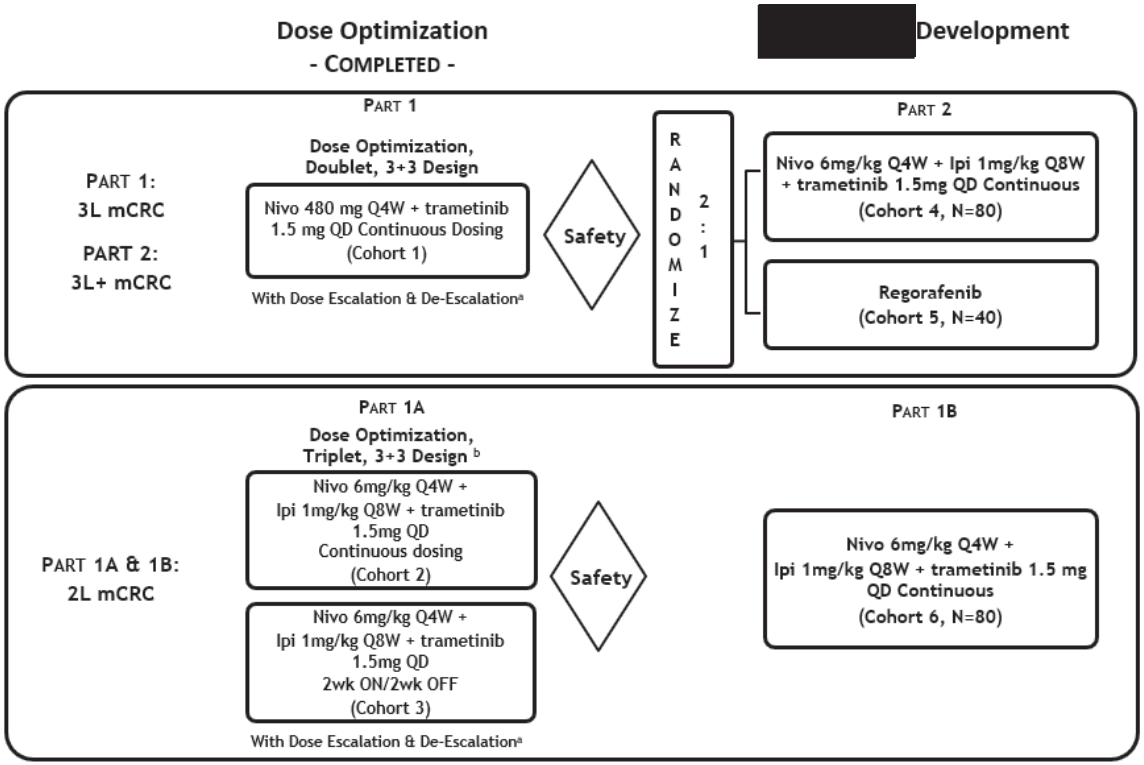
This is a Phase 1/2 open-label, multi-center trial of nivolumab in combination with trametinib, with or without ipilimumab, to evaluate the safety profile and clinical activity of these regimens in participants with metastatic colorectal cancer (mCRC).

Participants were dosed in the dose optimization phases of the study (Parts 1 and 1A) with either the doublet (nivolumab + trametinib) in third line participants or triplet (nivolumab + ipilimumab + trametinib) regimen in second line participants. The dose optimization phase of the study is now completed. Decisions regarding dosages of trametinib to be used in Parts 1B and 2 are based on observed safety and efficacy signals in Parts 1A and 1. The recommended Phase 2 dose for Part 2 and 1B was determined to be the triplet regimen (nivolumab 6 mg/kg Q4W + ipilimumab 1 mg/kg Q8W + trametinib 1.5 mg continuous QD). Assessment of the preliminary benefit/risk based on the safety and efficacy profile for the doublet and triplet regimens used in the non-randomized parts of the study was reviewed along with additional emerging safety and efficacy data from other relevant trials to determine the optimal dose of trametinib to be used in Part 2 and Part 1B in combination with nivolumab and ipilimumab as presented in Figure 1-1. Participants in each part of the study will be treated until progression, unacceptable toxicity, withdrawal of consent, or a maximum of 2 years. Maximum treatment duration is not applicable to participants receiving

standard of care (SOC) therapy in Part 2, Cohort 5, which may be continued until progression of disease, unacceptable toxicity, or withdrawal of consent.

Per Protocol Amendment 04, due to early study closure the last participant last treatment (LPLT) date on CA209-9N9 study will occur approximately 9 months after last participant first treatment (LPFT); and last participant last visit (LPLV) date will occur approximately 12 months after LPFT. When this LPLV date is reached, participants follow-up will be ceased and all participants will complete the study. Any participant still on treatment after LPLT date who continue to demonstrate clinical benefit will be eligible to receive treatment outside of this study in accordance with protocol Section 7.8. For Cohort 4 and Cohort 6 participants the total maximum duration of treatment will be 2 years, including the treatment duration on CA209-9N9. For participants in Cohort 5, the treatment will be administered as per the local standard of care. In the event alternative means of supplying study treatment as described in Section 7.8 is not accessible by approximately 9 months after LPFT, the study may remain open until such means become available or last participant ends treatment and completes follow-up visits 1 and 2, under these circumstances the study procedures will be in accordance with Table 2-8, Table 2-9, Table 2-10, and Table 2-11.

Figure 1-1: Study Schematic



mCRC, metastatic colorectal cancer; Ipi, ipilimumab; MSS, microsatellite stable; Nivo, nivolumab; pMMR, proficient mismatch repair; QD, quaque die, once daily; Q4W, every 4 weeks; Q8W, every 8 weeks; wk, week; 2L, second line; 3L, third line; 3L+, third line plus.

[a] See Table 7.2-1 for unique cohort numbers for dose escalation and de-escalation.

[b] Participants in Part 1A were assigned to each treatment cohort on an alternating basis in IRT (interactive response technology). NOTE: Enrollment is closed.

NOTE: Participants in each part of the study will be treated until progression, unacceptable toxicity, withdrawal of consent, or a maximum of 2 years. Maximum treatment duration is not applicable to standard of care therapy (regorafenib).

Number of Participants:

Part 1 and Part 1A follow a 3 + 3 design with potential dose escalation and de-escalation based on DLT observations, will treat up to approximately 18 and 24 participants, respectively. **NOTE: Part 1 and Part 1A have completed**.

Part 1B will treat approximately 80 participants. Part 2 will randomize approximately 120 participants into 2 arms, nivolumab + ipilimumab +trametinib and regorafenib, in a 2:1 ratio. See Section 10.1 for sample size determination.

Treatment Arms and Duration: Dose optimization phase of the study (Part 1 and Part 1A) has been completed. Enrollment is closed in Part 1 and Part 1A cohorts.

For **dose optimization (Parts 1 and 1A) phase**, participants will be allocated to treatment as follows:

- Part 1: Participants with 3rd line mCRC will be assigned to receive doublet therapy as nivolumab 480 mg Q4W plus trametinib 1.5 mg QD (continuous dosing, Cohort 1)
- Part 1A: Participants with 2nd line mCRC will be assigned to receive triplet therapy of either:
  - 6 mg/kg nivolumab (Q4W) plus ipilimumab 1 mg/kg (Q8W) plus trametinib 1.5 mg QD (continuous dosing, Cohort 2), OR
  - 6 mg/kg nivolumab (Q4W) plus ipilimumab 1 mg/kg (Q8W) plus trametinib 1.5 mg QD (2 week ON/2 week OFF, Cohort 3)

Only pMMR/MSS participants can be enrolled in Part 1 and Part 1A.

For [redacted] **(Part 1B) phase**: Participants with 2nd line pMMR/MSS mCRC will be assigned to receive 6 mg/kg nivolumab (Q4W) plus ipilimumab 1 mg/kg (Q8W) plus trametinib 1.5 mg continuous QD (Cohort 6).

For [redacted] **(Part 2) phase**: Participants with 3L+ (no more than 4 prior lines of therapy) pMMR/MSS mCRC will be randomized at 2:1 ratio to receive nivolumab 6 mg/kg Q4W plus ipilimumab 1 mg/kg Q8W plus trametinib 1.5 mg continuous QD (Cohort 4), OR regorafenib in the SOC arm (Cohort 5).

For Part 1B (Cohort 6) and Part 2 (Cohorts 4 and 5), the proportion of participants with RAS mutations will be monitored on an ongoing basis. The IRT system will be set up to notify the Sponsor once the pre-defined number of RAS mutant participants have been enrolled. The target will be approximately 65% mutant, 35% wild type. If accrual diverges significantly from this goal, accrual in a cohort may be paused after discussion between the Sponsor and the investigators. Patients with BRAF V600 mutations are not eligible for the study.

An interim analysis (IA) of Part 2 and Part 1B cohorts will be conducted after an overall total of approximately 100 treated participants (including approximately 60 treated participants from Part 2) have a minimum of 4 months of follow-up after the first treatment (corresponding to at least 2 tumor assessments).

Study treatment:

Study Drug for CA2099N9		
Medication	**Potency**	**IP/Non-IP**
Nivolumab Solution for Injection	100 mg (10 mg/mL)	IP
Ipilimumab Solution for Injection	200 mg 50 mg (5 mg/mL)	IP
Trametinib tablet	0.5 mg and various strengths	IP
Regorafenib tablet	40 mg and various strengths	IP

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA2099N9)

Procedure	Screening Procedures[a]	Notes
Eligibility Assessments		
Informed Consent	X	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 Interactive Response system IRT. All cohorts on the study are now closed for enrollment. Contact Sponsor to ensure that the appropriate Part is open to enrollment prior to consenting a participant.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening (re-enrollment if applicable) and must be confirmed prior to first dose.
Medical History	X	Includes prior conditions and any toxicities or allergy related to previous treatments. For Part 2, participant's primary tumor location (sidedness), detailed in Appendix 13, is required for randomization/stratification.
Prior anti-cancer therapy	X	
Prior Radiotherapy	X	
ECOG Status Assessment	X	Within 28 days prior to first dose
Safety Assessments		
Assessment of Signs and Symptoms	X	Within 28 days prior to first dose
Physical Examination (PE)	X	If the screening PE is performed within 24 hours prior to first dose, then a single exam may count as both the screening and pre-dose evaluation.
Physical Measurements	X	Includes height and weight
Vital Signs	X	BP, HR, temperature
Serious Adverse Event Assessment	X	All SAEs must be collected from the date of participant's written consent. See Section 9.2, and Appendix 3.

Table 2-1: Screening Procedural Outline (CA2099N9)

Procedure	Screening Procedures[a]	Notes
Concomitant Medication Use	X	Includes medications taken within 14 days prior to first dose. Vaccine use must be collected within 30 days prior to first dose. For Part 2 and Part 1B participants, includes antibiotics taken within 2 months prior to first dose.
Echocardiogram or MUGA	X	Within 28 days prior to first dose. Refer to eligibility criteria.
ECG	X	Within 28 days prior to first dose. Refer to eligibility criteria.
Ophthalmic Evaluation	X	Participants will be evaluated for baseline visual disturbances; Refer to eligibility criteria.
Laboratory Tests	X	Local testing must be performed within 28 days prior to first dose. • CBC w/differential and platelet count • Chemistry panel including: AST, ALT, ALP, total bilirubin, blood urea nitrogen (BUN) or serum urea level, creatinine (if abnormal creatinine clearance should be reported), phosphate, Ca, Na, K, Mg, Cl, LDH, glucose, albumin • Urinalysis including protein, glucose, blood, leukocyte esterase, specific gravity, pH[b] • Coagulation including PT/INR and PTT • Thyroid panel including TSH, Free T4, Free T3 • Hepatitis B/C (HBsAg, HCV antibody or HCV RNA) Testing for HIV must be performed at sites where mandated locally. (see Appendix 12) • Carcinoembryonic antigen (CEA) for participants with unknown results or history of abnormal results per local testing. For Part 2 and Part 1B, CEA for all participants and for participants with history of normal CEA, collect CA19-9.
Pregnancy Test (WOCBP only)	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. See Appendix 4 For females under the age of 55, FSH > 40mIU/mL is required to confirm menopause.
pMMR/MSS Assessment	X	Verify pMMR/Microsatellite stable (MSS) based on available local testing results as part of medical history prior to study entry. Confirm availability of pathology report for MMR or MSS testing results. Report must contain MMR or MSS results and should also contain specific results per markers tested for MMR or MSS.

Table 2-1: Screening Procedural Outline (CA2099N9)

Procedure	Screening Procedures[a]	Notes
		Please see inclusion criteria (Section 6.1) and Appendix 9 for details.
RAS mutation status	X	Verify RAS mutation status, including KRAS and NRAS, based on available local testing results as part of medical history prior to study entry. Refer to Appendix 10 for local testing methodology permitted by the study.
BRAF Mutation status	X	Verify BRAF mutation status based on available local testing results as part of medical history prior to study entry (Appendix 10). BRAF V600 mutant participants are NOT eligible. (Exclusion Criteria Section 6.2).
Body Imaging	X	See Section 9.1.1. Existing scans performed within 28 days prior to first dose could be used as baseline scan for the study provided all requirements are met.
Brain Imaging	X	See Section 9.1.1. Performed at screening for participants with a history or clinical symptoms of brain metastasis. Existing scans performed within 28 days prior to first dose could be used as baseline scan for the study provided all requirements are met.
Other Imaging Bone Scan	X	As clinically indicated. See Section 9.1.1.2.

[redacted]

Table 2-1: Screening Procedural Outline (CA2099N9)

Procedure	Screening Procedures[a]	Notes
Clinical Drug Supply		
IRT		
Participant Registration and Treatment Assignment/Randomization	X	Register in IRT to obtain participant number. All cohorts on the study are now closed for enrollment. Treatment assignment/randomization will occur after eligibility is confirmed. Refer to Section 7.2 for stratification factors. Refer to IRT instruction manual for details.

[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.

Table 2-2: On-Treatment Assessments (Part 1 mCRC 3rd line, DOUBLET, DOSE OPTIMIZATION CA2099N9 [Cohort 1 Group]) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 4 weeks)		Notes
	C1D1 and subsequent cycles D1 (C2D1, C3D1 etc.)	C1D15 and C2D15 [b] C1D8 and C1D22 [c]	
Safety Assessments			
Targeted Physical Examination	X	X	Targeted examination must include at a minimum the following body systems: Cardiovascular Gastrointestinal Pulmonary Neurological exam for participants with brain metastases
Ophthalmic Evaluation	Participants are required to have a standard ophthalmic examination conducted by an ophthalmologist at C2D1, Month 6, and then annually thereafter unless clinically indicated sooner. (See Section 9.4.3) For C2D1: Results must be evaluated within 7 days prior to study treatment.		
Vital Signs	X	X	Including BP, HR, and temperature. Obtain vital signs within 72 hours prior to dosing.
Physical Measurements (including performance status)	X	X	Weight and ECOG performance status within 72 hours prior to dosing. ECOG must be assessed prior to first dose on Cycle 1 Day 1 to re-confirm eligibility. See Appendix 7 for ECOG Performance Status scale.
Echocardiogram or MUGA	Evaluate LVEF within 7 days prior to C2D1, C4D1, and then every 12 weeks thereafter until discontinuation of treatment. Results must be evaluated within 7 days prior to study treatment.		
ECG	Participants will be evaluated within 7 days prior to C2D1 of treatment, and then as clinically indicated until discontinuation of treatment.		
Adverse Events Assessment	Continuously		Adverse events will be graded according to the NCI-CTCAE (version 4.0)
Serious Adverse Event Assessment	Continuously		Adverse events will be graded according to the NCI-CTCAE (version 4.0).

Table 2-2: On-Treatment Assessments (Part 1 mCRC 3rd line, DOUBLET, DOSE OPTIMIZATION CA2099N9 [Cohort 1 Group]) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 4 weeks)		Notes
	C1D1 and subsequent cycles D1 (C2D1, C3D1 etc.)	C1D15 and C2D15 [b] C1D8 and C1D22 [c]	
Review of Concomitant Medications	X	X	
Laboratory Tests	X	X	Local CBC, chemistry assessments, and thyroid panel should be performed within 72 hours prior to Day 1 of each cycle through Cycle 13 and may be collected every alternate cycle thereafter if deemed medically appropriate. Laboratory tests do not need to be repeated on C1D1 if screening lab results are deemed still clinically valid by the treating investigator. Lab assessments will include: • CBC w/differential and platelet count • Chemistry panel including: AST, ALT, ALP, T.Bili, BUN, or serum urea level, creatinine (if abnormal creatinine clearance should be reported), phosphate, Ca, Na, Mg, K, Cl, LDH, glucose, and albumin • Urinalysis including protein, glucose, blood, leukocyte esterase, specific gravity, pH[d,e] • Coagulation including PT/INR and PTT (as clinically indicated) • TSH with reflexive Free T4, and Free T3 if TSH is abnormal (not required at D15 of each cycle if not clinically indicated) • CEA every 8 weeks for participants with history of abnormal results per local testing
Pregnancy Test (WOCBP Only)	X		Serum or urine pregnancy test to be done within 24 hours prior to first dose, and then every 4 weeks (± 1 week) regardless of dosing schedule. See Appendix 4.

Table 2-2: On-Treatment Assessments (Part 1 mCRC 3rd line, DOUBLET, DOSE OPTIMIZATION CA2099N9 [Cohort 1 Group]) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 4 weeks)		Notes
	C1D1 and subsequent cycles D1 (C2D1, C3D1 etc.)	C1D15 and C2D15 [b] C1D8 and C1D22 [c]	
[redacted]			
Efficacy Assessments			
Body Imaging	See notes		See Section 9.1.1. Imaging assessments will occur every 8 weeks (± 7 days) from the date of first dose until disease progression, or withdrawal of consent, whichever occurs first.
Brain Imaging	See notes		See Section 9.1.1. Participants with a history or clinical symptoms of brain metastasis should have surveillance MRI per local standard of care (SOC) (approximately every 12 weeks) or sooner if clinically indicated.
Other Imaging Bone Scan	See notes		As clinically indicated. See Section 9.1.1.
Clinical Drug Supply			
IRT contact	X		First dose should be administered within 3 calendar days of treatment assignment.
Administer Nivolumab (480 mg)	X		Nivolumab flat dosing every 4 weeks.
Administer Trametinib	See note		Trametinib dosing described in Section 7.1.3.

Note: All scheduled clinic visits are to occur within ± 3 days of scheduled day. Part 1 enrolls participants assigned to Cohort 1 Group (Refer to Table 7.2-1).

[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 regulation. If a dose is delayed, the procedures are to be delayed if deemed appropriate by treating physicians, except for tumor assessments that continue per schedule.

[b] Day 15 assessments are mandatory for the first 2 cycles, and then as clinically indicated by treating physicians.

[c] Telephone contact with participants on C1D8 and C1D22 are mandatory to assess adverse events and provide toxicity management. If clinically indicated, participants should be evaluated in the clinic.

[d] Urinalysis should be assessed every 4 weeks for the first year of study treatment, and then every 8 weeks unless more frequent testing is clinically indicated.

[e] Urinalysis or urine dipstick. If blood, protein or leukocytes esterase are positive on the dipstick, microscopic examination of the sediment is required.

Table 2-3: On-Treatment Assessments (Part 2 mCRC 3rd line, TRIPLET, [redacted] [redacted] CA2099N9 Cohort 4) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 8 weeks)			Notes
	Day 1	C1D15 (required); C1D43 (optional) [b]	Day 29	
Safety Assessments				
Targeted Physical Examination	X	X	X	Targeted examination must include at a minimum the following body systems: Cardiovascular Gastrointestinal Pulmonary Neurological exam for participants with brain metastases
Ophthalmic Evaluation	Participants are required to have a standard ophthalmic examination conducted by an ophthalmologist at Month 1, Month 6, and then annually thereafter unless clinically indicated sooner. (See Section 9.4.3) For Month 1: Results must be evaluated within 7 days prior to study treatment.			
Vital Signs	X	X	X	Including BP, HR, and temperature. Obtain vital signs within 72 hours prior to first dose.
Physical Measurements (including performance status)	X	X	X	Weight and ECOG performance status within 72 hours prior to dosing. ECOG must be assessed prior to first dose on Cycle 1 Day 1 to re-confirm eligibility See Appendix 7 for ECOG Performance Status scale.
ECG	Participants will be evaluated within 7 days prior to C1D29 of treatment, and then as clinically indicated until discontinuation of treatment.			
Echocardiogram or MUGA	Evaluate LVEF within 7 days prior to C1D29 and C2D29, and then every 12 weeks thereafter until discontinuation of treatment.			
Adverse Events Assessment	Continuously			Adverse events will be graded according to the NCI-CTCAE (version 4.0).
Serious Adverse Event Assessment	Continuously			Serious adverse events will be graded according to the NCI-CTCAE (version 4.0).

Table 2-3: On-Treatment Assessments (Part 2 mCRC 3rd line, TRIPLET, [redacted] [redacted] CA2099N9 Cohort 4) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 8 weeks)			Notes
	Day 1	C1D15 (required); C1D43 (optional) [b]	Day 29	
Review of Concomitant Medications	X	X	X	
Laboratory Tests	X	X	X	Local CBC, chemistry assessments, and thyroid panel should be done within 72 hours prior to D1 and D29 of each cycle through Cycle 6 (in addition to C1D15 and C1D43), and may be collected only prior to D1 of each cycle thereafter if deemed medically appropriate. Laboratory tests do not need to be repeated on C1D1 if screening labs results are deemed still clinically valid by the treating investigator. Lab assessments will include: • CBC w/differential and platelet count, • Chemistry panel including: AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine (if abnormal creatinine clearance should be reported), phosphate, Ca, Na, K, Mg, Cl, LDH, glucose, albumin • Urinalysis including protein, glucose, blood, leukocyte esterase, specific gravity, pHc,[c] • Coagulation including PT/INR and PTT (as clinically indicated) • If TSH is abnormal, refer to Appendix 5 for instructions on Free T4 and Free T3. (TSH is not required at C1D15 and C1D43 if not clinically indicated)

Table 2-3: On-Treatment Assessments (Part 2 mCRC 3rd line, TRIPLET, [redacted] [redacted] CA2099N9 Cohort 4) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 8 weeks)			Notes
	Day 1	C1D15 (required); C1D43 (optional) [b]	Day 29	
				• CEA every 4 weeks CEA for all participants. For participants with elevated CA19-9 at screening, monitor CA19-9 AND CEA.
Pregnancy Test (WOCBP Only)	X		X	Serum or urine pregnancy test to be done within 24 hours prior to first dose, and then every 4 weeks (± 1 week) regardless of dosing schedule. See Appendix 4.
[redacted]				

Table 2-3: On-Treatment Assessments (Part 2 mCRC 3rd line, TRIPLET, [redacted] [redacted] CA2099N9 Cohort 4) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 8 weeks)			Notes
	Day 1	C1D15 (required); C1D43 (optional) [b]	Day 29	
Efficacy Assessments				
Body Imaging	See notes			See Section 9.1.1. Imaging assessments will occur every 8 weeks (± 7 days) from the date of first dose until disease progression, end of trial, or withdrawal of consent, whichever occurs first. For participants who continue treatment beyond initial progression see Section 8.1.5. Tumor assessment scans should be submitted to the imaging vendor within 14 days of acquisition.
Brain Imaging	See notes			See Section 9.1.1. Participants with a history or clinical symptoms of brain metastasis should have surveillance MRI per local SOC (approximately every 12 weeks) or sooner if clinically indicated.
Other Imaging Bone Scan	See notes			As clinically indicated. See Section 9.1.1.2

[redacted]

Table 2-3: On-Treatment Assessments (Part 2 mCRC 3rd line, TRIPLET, [redacted] [redacted] CA2099N9 Cohort 4) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 8 weeks)			Notes
	Day 1	C1D15 (required); C1D43 (optional) [b]	Day 29	
[redacted]				
Healthcare Resource Use	X		X	See Section 9.9.
Clinical Drug Supply				
Contact IRT	X		X	First dose should be administered within 3 calendar days of randomization.
Administer Nivolumab (6 mg/kg)	X		X	Nivolumab dosing will occur every 4 weeks.
Administer Ipilimumab (1 mg/kg)	X			Ipilimumab dosing will occur every 8 weeks.

Table 2-3: On-Treatment Assessments (Part 2 mCRC 3rd line, TRIPLET, [redacted] [redacted] CA2099N9 Cohort 4) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 8 weeks)			Notes
	Day 1	C1D15 (required); C1D43 (optional) [b]	Day 29	
Administer Trametinib (1.5mg QD)	See notes			Trametinib dosing will occur once daily. Trametinib bottles will be dispensed at D1 and D29 of each cycle

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 regulation. If a dose is delayed, the procedures are to be delayed if deemed appropriate by treating physicians, except for tumor assessments that continue per schedule.

[b] Cycle 1 Day 15 assessments are required for the first cycle. C1 D43 and subsequent D15 and D43 assessments are optional and may be performed as clinically indicated at the investigator's discretion.

[c] Urinalysis should be assessed every 4 weeks for the first year of study treatment, and then every 8 weeks unless more frequent testing is clinically indicated. Urinalysis or urine dipstick. If blood, protein, or leukocytes esterase are positive on the dipstick, microscopic examination of the sediment is required.

Table 2-4: On-Treatment Assessments (Part 2 mCRC 3rd line, Regorafenib, [redacted] [redacted] CA2099N9 [Cohort 5]) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 4 weeks)		Notes
	Day 1	C1 D15 (required); subsequent cycle D15 (if clinically indicated)[b]	
Safety Assessments			
Targeted Physical Examination	X	X	Targeted examination must include at a minimum the following body systems: Cardiovascular Gastrointestinal Pulmonary Neurological exam for participants with brain metastases
Vital Signs	X	See Note	Including BP[c], HR, and temperature. Obtain vital signs within 72 hours prior to dosing
Physical Measurements (including performance status)	X	See Note	Weight and ECOG performance status within 72 hours prior to dosing. ECOG must be assessed prior to first dose on Cycle 1 Day 1 to re-confirm eligibility. See Appendix 7 for ECOG Performance Status scale.
ECG	Participants will be evaluated within 7 days prior to C2D1 of treatment, and then as clinically indicated until discontinuation of treatment.		
Adverse Events Assessment	Continuously		Adverse events will be graded according to the NCI-CTCAE (version 4.0).
Serious Adverse Event Assessment	Continuously		Serious adverse events will be graded according to the NCI-CTCAE (version 4.0).
Review of Concomitant Medications	X	X	
Laboratory Tests	X	See Notes	Local CBC and chemistry assessments should be done within 72 hours prior to D1 of each cycle, and D15 of each cycle if clinically indicated (C1D15 is

Table 2-4: On-Treatment Assessments (Part 2 mCRC 3rd line, Regorafenib, [redacted] [redacted] CA2099N9 [Cohort 5]) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 4 weeks)		Notes
	Day 1	C1 D15 (required); subsequent cycle D15 (if clinically indicated)[b]	
			required). Laboratory tests do not need to be repeated on C1D1 if screening laboratory results are deemed still clinically valid by the treating investigator. Lab assessments will include: • CBC w/differential and platelet count,[d] • Chemistry panel including: AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine (if abnormal creatinine clearance should be reported), phosphate, Ca, Na, K, Cl, Mg, LDH, glucose, albumin • Coagulation including PT/INR and PTT (as clinically indicated) • TSH every 4 weeks.[e] If TSH is abnormal, see Appendix 5 for instructions on Free T4 and Free T3. (TSH is not required at C1D15 if not clinically indicated). • CEA for all participants. For participants with elevated CA19-9 at screening, monitor CA19-9 AND CEA.[f] • Urine dipstick or urinalysis[g]
Pregnancy Test (WOCBP Only)	X		Serum or urine pregnancy test to be done within 24 hours prior to first dose, and then every 4 weeks (± 1 week) regardless of dosing schedule. See Appendix 4.
[redacted]			

Table 2-4: On-Treatment Assessments (Part 2 mCRC 3rd line, Regorafenib, [redacted] CA2099N9 [Cohort 5]) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 4 weeks)		Notes
	Day 1	C1 D15 (required); subsequent cycle D15 (if clinically indicated)[b]	
Efficacy Assessments			
Body Imaging	See notes		See Section 9.1.1. Imaging assessments will occur every 8 weeks (±7 days) from the date of first dose until disease progression, end of trial, or withdrawal of consent, whichever occurs first. Tumor assessment scans should be submitted to the imaging vendor within 14 days of acquisition.
Brain Imaging	See notes		See Section 9.1.1. Participants with a history or clinical symptoms of brain metastasis should have surveillance MRI per local SOC (approximately every 12 weeks) or sooner if clinically indicated.
Other Imaging Bone Scan	See notes		As clinically indicated. See Section 9.1.1.2
[redacted]			

Table 2-4: On-Treatment Assessments (Part 2 mCRC 3rd line, Regorafenib, [redacted] [redacted] CA2099N9 [Cohort 5]) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 4 weeks)		Notes
	Day 1	C1 D15 (required); subsequent cycle D15 (if clinically indicated)[b]	
[redacted]			
Healthcare Resource Use	See notes	See notes	To be collected at C1D1, and at D1 of each subsequent cycle. See Section 9.9.
Clinical Drug Supply			
IRT contact	X		First dose should be administered within 3 calendar days of randomization
Administer Regorafenib (160 mg)	See notes		Orally, once daily for the first 21 days (D1 to D21) of each cycle. See Section 7.1.4

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 regulation. If a dose is delayed, the procedures are to be delayed if deemed appropriate by treating physicians, except for tumor assessments that continue per schedule.

[b] Cycle 1, D15 clinic visit is required. Day 15 visits in the subsequent cycles are optional and should be performed as clinically indicated or per local institutional guidelines.

[c] Monitor BP more frequently as clinically indicated or per local institutional guidelines.

[d] Monitor coagulation more frequently for increased risk of bleeding per local institutional guidelines.

[e] Monitor TSH per local product label and/or institutional guideline.

[f] CEA at C1D1, C1D15, C2D1, C3D1, C4D1, C5D1, and then every 8 weeks thereafter or more frequent if clinically indicated. If CA19-9 is also monitored, follow same collection frequency as CEA.

[g] Urine dipstick or urinalysis to monitor urine protein per local product label and/or institutional guideline. Protocol recommended frequency is every 4 weeks.

Table 2-5: On-Treatment Assessments (Part 1A mCRC 2nd line, TRIPLET, DOSE OPTIMIZATION CA2099N9 [Cohorts 2 and 3 Groups]) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 8 weeks)			Notes
	C1D1 (and D1 each subsequent cycle, C2D1, C3D1, etc.)	C1D15 and C1D43;[b] C1D8, C1D22, C1D36, C1D50[c]	C1D29 (and D29 each subsequent cycle, C2D29, C3D29, etc.)	
Safety Assessments				
Targeted Physical Examination	X	X	X	Targeted examination must include at a minimum the following body systems: Cardiovascular Gastrointestinal Pulmonary Neurological exam for participants with brain metastases
Ophthalmic Evaluation	Participants are required to have a standard ophthalmic examination conducted by an ophthalmologist at C1D29, Month 6, and then annually thereafter unless clinically indicated sooner. (See Section 9.4.3) For C1D29: Results must be evaluated within 7 days prior to study treatment.			
Vital Signs	X	X	X	Including BP, HR, and temperature. Obtain vital signs within 72 hours prior to first dose.
Physical Measurements (including performance status)	X	X	X	Weight and ECOG performance status within 72 hours prior to dosing. ECOG must be assessed prior to first dose on Cycle 1 Day 1 to re-confirm eligibility. See Appendix 7 for ECOG Performance Status scale.
ECG on treatment	Participants will be evaluated within 7 days prior to C1D29 of treatment, and then as clinically indicated until discontinuation of treatment.			
Echocardiogram or MUGA	Evaluate LVEF within 7 days prior to C1D29 and C2D29, and then every 12 weeks thereafter until discontinuation of treatment. Results must be evaluated within 7 days prior to study treatment.			

Table 2-5: On-Treatment Assessments (Part 1A mCRC 2nd line, TRIPLET, DOSE OPTIMIZATION CA2099N9 [Cohorts 2 and 3 Groups]) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 8 weeks)			Notes
	C1D1 (and D1 each subsequent cycle, C2D1, C3D1, etc.)	C1D15 and C1D43;[b] C1D8, C1D22, C1D36, C1D50[c]	C1D29 (and D29 each subsequent cycle, C2D29, C3D29, etc.)	
Adverse Events Assessment	Continuously			Adverse events will be graded according to the NCI-CTCAE (version 4.0).
Serious Adverse Event Assessment	Continuously			Serious adverse events will be graded according to the NCI-CTCAE (version 4.0).
Review of Concomitant Medications	X	X	X	
Laboratory Tests	X	X	X	Local CBC, chemistry assessments, and thyroid panel should be done within 72 hours prior to D1 and D29 of each cycle through Cycle 6 (in addition to C1D15 and C1D43), and may be collected only prior to D1 of each cycle thereafter if deemed medically appropriate. Laboratory tests do not need to be repeated on C1D1 if screening labs were performed within 72 hours prior to first dose. Lab assessments will include: • CBC w/differential and platelet count, • Chemistry panel including: AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine (if abnormal creatinine clearance should be reported), phosphate, Ca, Na, K, Mg, Cl, LDH, glucose, albumin • Urinalysis including protein, glucose, blood, leukocyte esterase, specific gravity, pH[d,e] • Coagulation including PT/INR and PTT (as clinically indicated)

Table 2-5: On-Treatment Assessments (Part 1A mCRC 2nd line, TRIPLET, DOSE OPTIMIZATION CA2099N9 [Cohorts 2 and 3 Groups]) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 8 weeks)			Notes
	C1D1 (and D1 each subsequent cycle, C2D1, C3D1, etc.)	C1D15 and C1D43;[b] C1D8, C1D22, C1D36, C1D50[c]	C1D29 (and D29 each subsequent cycle, C2D29, C3D29, etc.)	
				• TSH with reflexive Free T4, and Free T3 if TSH is abnormal (not required at C1D15 and C1D43 if not clinically indicated) • CEA every 8 weeks for participants with history of abnormal results per local testing
Pregnancy Test (WOCBP Only)	X		X	Serum or urine pregnancy test to be done within 24 hours prior to first dose, and then every 4 weeks (± 1 week) regardless of dosing schedule. See Appendix 4.
[redacted]				
Efficacy Assessments				
Body Imaging	See notes			See Section 9.1.1. Imaging assessments will occur every 8 weeks (±7 days) from the date of first dose until disease progression, end of trial, or withdrawal of consent, whichever occurs first.

Table 2-5: On-Treatment Assessments (Part 1A mCRC 2nd line, TRIPLET, DOSE OPTIMIZATION CA2099N9 [Cohorts 2 and 3 Groups]) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 8 weeks)			Notes
	C1D1 (and D1 each subsequent cycle, C2D1, C3D1, etc.)	C1D15 and C1D43;[b] C1D8, C1D22, C1D36, C1D50[c]	C1D29 (and D29 each subsequent cycle, C2D29, C3D29, etc.)	
Brain Imaging	See notes			See Section 9.1.1. Participants with a history or clinical symptoms of brain metastasis should have surveillance MRI per local SOC (approximately every 12 weeks) or sooner if clinically indicated.
Other Imaging Bone Scan	See notes			As clinically indicated. See Section 9.1.1.
Clinical Drug Supply				
IRT contact	X		X	First dose should be administered within 3 calendar days of treatment assignment.
Administer Nivolumab (6 mg/kg)	X		X	Nivolumab weight-based dosing every 4 weeks.
Administer Ipilimumab (1 mg/kg)	X			Ipilimumab weight-based dosing every 8 weeks.
Administer Trametinib (see note)	See notes			Participants will receive Trametinib as described in Section 7.1.5. Obtain confirmation on dosing from sponsor study team prior to first dose.

Note: All scheduled clinic visits are to occur within ±3 days of scheduled day. Part 1A enrolls participants assigned to Cohort 2 and Cohort 3 Group (Refer to Table 7.2-1).

[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 regulation. If a dose is delayed, the procedures are to be delayed if deemed appropriate by treating physicians, except for tumor assessments that continue per schedule.

[b] Day 15 and Day 43 assessments are required for the first cycle; then may be performed as clinically indicated at investigators discretion.

[c] Telephone contact with participants on C1D8, C1D22, C1D36 and C1D50 are mandatory to assess adverse events and provide toxicity management. If clinically indicated, participants should be evaluated in the clinic.

[d] Urinalysis should be assessed every 4 weeks for the first year of study treatment, and then every 8 weeks unless more frequent testing is clinically indicated.

[e] Urinalysis or urine dipstick. If blood, protein, or leukocytes esterase are positive on the dipstick, microscopic examination of the sediment is required.

Table 2-6: On-Treatment Assessments (Part 1B mCRC 2nd line, TRIPLET, [redacted], CA2099N9 [Cohort 6]) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 8 weeks)			Notes
	Day 1	C1D15 (required), C1D43 (optional)[b]	Day 29	
Safety Assessments				
Targeted Physical Examination	X	X	X	Targeted examination must include at a minimum the following body systems: Cardiovascular Gastrointestinal Pulmonary Neurological exam for participants with brain metastases
Ophthalmic Evaluation	Participants are required to have a standard ophthalmic examination conducted by an ophthalmologist at Month 1, Month 6, and then annually thereafter unless clinically indicated sooner. (See Section 9.4.3) For Month 1: Results must be evaluated within 7 days prior to study treatment.			
Vital Signs	X	X	X	Including BP, HR, and temperature. Obtain vital signs within 72 hours prior to first dose.
Physical Measurements (including performance status)	X	X	X	Weight and ECOG performance status within 72 hours prior to dosing. ECOG must be assessed prior to first dose on Cycle 1 Day 1 to re-confirm eligibility See Appendix 7 for ECOG Performance Status scale.
ECG	Participants will be evaluated within 7 days prior to C1D29 of treatment, and then as clinically indicated until discontinuation of treatment.			
Echocardiogram or MUGA	Evaluate LVEF within 7 days prior to C1D29 and C2D29, and then every 12 weeks thereafter until discontinuation of treatment.			
Adverse Events Assessment	Continuously			Adverse events will be graded according to the NCI-CTCAE (version 4.0).
Serious Adverse Event Assessment	Continuously			Serious adverse events will be graded according to the NCI-CTCAE (version 4.0).

Table 2-6: On-Treatment Assessments (Part 1B mCRC 2nd line, TRIPLET, [redacted], CA2099N9 [Cohort 6]) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 8 weeks)			Notes
	Day 1	C1D15 (required), C1D43 (optional)[b]	Day 29	
Review of Concomitant Medications	X	X	X	
Laboratory Tests	X	X	X	Local CBC, chemistry assessments, and thyroid panel should be done within 72 hours prior to D1 and D29 of each cycle through Cycle 6 (in addition to C1D15 and C1D43) and may be collected only prior to D1 of each cycle thereafter if deemed medically appropriate. Laboratory tests do not need to be repeated on C1D1 if screening labs results are deemed still clinically valid by the treating investigator. Lab assessments will include: • CBC w/differential and platelet count, • Chemistry panel including: AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine (if abnormal creatinine clearance should be reported), phosphate, Ca, Na, K, Mg, Cl, LDH, glucose, albumin • Urinalysis including protein, glucose, blood, leukocyte esterase, specific gravity, pH[c,d] • Coagulation including PT/INR and PTT (as clinically indicated) • TSH. If TSH is abnormal, see Appendix 5 for instructions on Free T4 and Free T3. (TSH is not required at C1D15 and C1D43 if not clinically indicated). • CEA every 4 weeks for all participants. For participants with elevated CA19-9 at screening, monitor CA19-9 AND CEA.

Table 2-6: On-Treatment Assessments (Part 1B mCRC 2nd line, TRIPLET, [redacted], CA2099N9 [Cohort 6]) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 8 weeks)			Notes
	Day 1	C1D15 (required), C1D43 (optional)[b]	Day 29	
Pregnancy Test (WOCBP Only)	X		X	Serum or urine pregnancy test to be done within 24 hours prior to first dose, and then every 4 weeks (± 1 week) regardless of dosing schedule. See Appendix 4.
[redacted]				
Efficacy Assessments				
Body Imaging	See notes			See Section 9.1.1. Imaging assessments will occur every 8 weeks (± 7 days) from the date of first dose until disease progression, end of trial, or withdrawal of consent, whichever occurs first. For participants who continue treatment beyond initial progression see Section 8.1.5. Tumor assessment scans should be submitted to the imaging vendor within 14 days of acquisition.

Table 2-6: On-Treatment Assessments (Part 1B mCRC 2nd line, TRIPLET, [redacted], CA2099N9 [Cohort 6]) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 8 weeks)			Notes
	Day 1	C1D15 (required), C1D43 (optional)[b]	Day 29	
Brain Imaging	See notes			See Section 9.1.1. Participants with a history or clinical symptoms of brain metastasis should have surveillance MRI per local SOC (approximately every 12 weeks) or sooner if clinically indicated.
Other Imaging Bone Scan	See notes			As clinically indicated. See Section 9.1.1.2
[redacted]				

Table 2-6: On-Treatment Assessments (Part 1B mCRC 2nd line, TRIPLET, [redacted], CA2099N9 [Cohort 6]) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 8 weeks)			Notes
	Day 1	C1D15 (required), C1D43 (optional)[b]	Day 29	
[redacted]				
Healthcare Resource Use	See notes			See Section 9.9. Per Protocol Amendment 04, the collection of Healthcare Resource Use data for Cohort 6 must be discontinued.
Clinical Drug Supply				
Contact IRT	X		X	First dose should be administered within 3 calendar days of treatment assignment.
Administer Nivolumab (6 mg/kg)	X		X	Nivolumab dosing will occur every 4 weeks.
Administer Ipilimumab (1 mg/kg)	X			Ipilimumab dosing will occur every 8 weeks.
Administer Trametinib (1.5mg QD)	See notes			Trametinib dosing will occur once daily. Trametinib bottles will be dispensed at D1 and D29 of each cycle.

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 regulation. If a dose is delayed, the procedures are to be delayed if deemed appropriate by treating physicians, except for tumor assessments that continue per schedule.

[b] Cycle 1, Day 15 assessments are required. C1, D43 and subsequent D15 and D43 assessments are optional and may be performed as clinically indicated at the investigator's discretion.

[c] Urinalysis should be assessed every 4 weeks for the first year of study treatment, and then every 8 weeks unless more frequent testing is clinically indicated.

[d] Urinalysis or urine dipstick. If blood, protein, or leukocytes esterase are positive on the dipstick, microscopic examination of the sediment is required.

Table 2-7: Follow-Up Period (All treatment cohorts, CA2099N9)

Procedure[a]	Follow-Up, Visits 1 and 2[b]	Survival Follow-Up Visits[c]	Notes
Safety Assessments			
Targeted Physical Examination	X		To assess for potential late emergent study drug related issues, Targeted examination must include at a minimum the following body systems: • Cardiovascular • Gastrointestinal • Pulmonary • Neurological exam for participants with brain metastases
Ophthalmic Evaluation	X		To be performed at Follow Up Visit 1 only, and at any time a participant reports new or worsening visual disturbances (See Section 9.4.3). Not required for Cohort 5 unless clinically indicated.
Echocardiogram or MUGA	X*		*At Follow-up Visit 1 only, not required for Cohort 5 unless clinically indicated.
Adverse Events Assessment	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)
ECG	X		At Follow-up Visit 1 only
Review of Concomitant Medication	X		
Review of Subsequent Cancer Therapies	X	X	Additional subsequent cancer therapy details such as regimen, line of therapy, start date and end date of each regimen, best response to the regimen, and date of progression after additional line of therapy will be collected.

Table 2-7: Follow-Up Period (All treatment cohorts, CA2099N9)

Procedure[a]	Follow-Up, Visits 1 and 2[b]	Survival Follow-Up Visits[c]	Notes
Laboratory Tests	X		• Local testing: • CBC w/differential and platelet count, • Chemistry panel including: AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine (if abnormal creatinine clearance should be reported), phosphate, Ca, Na, K, Mg, Cl, LDH, glucose, albumin • Urinalysis including protein, glucose, blood, leukocyte esterase, specific gravity, pH[d] • Coagulation including PT/INR and PTT (as clinically indicated) • TSH. If TSH is abnormal, see Appendix 5 for instructions on Free T4 and Free T3. To be done at FU1. To be repeated at FU2 if study related toxicity persists.
Pregnancy Test (WOCBP only)	X		Serum or urine
Efficacy Assessments			
Body Imaging	See note		Only for participants without progression on study therapy. See Section 9.1.1. Imaging assessments will occur every 8 weeks (± 7 days) from the date of first dose until disease progression, end of study, or withdrawal of consent, whichever occurs first. For Part 1B and Part 2: Tumor assessment scans should be submitted to the imaging vendor within 14 days of acquisition.
Brain Imaging	See note		See Section 9.1.1. Participants with a history or clinical symptoms of brain metastasis should have surveillance MRI per local SOC (approximately every 12 weeks) or sooner if clinically indicated.
Other Imaging: Bone Scan	See note		As clinically indicated. See Section 9.1.1.2.

Table 2-7: Follow-Up Period (All treatment cohorts, CA2099N9)

Procedure[a]	Follow-Up, Visits 1 and 2[b]	Survival Follow-Up Visits[c]	Notes
[redacted]			
Healthcare Resource Use			Per Protocol Amendment 04, the collection of data for Healthcare Resource use must be discontinued.
Participant Status			
Survival Status	X	X	Per Protocol Amendment 04, survival status collection will end at the LPLV date, which is defined in Section 5.1. Every 6 months after FU 2; may be accomplished by visit, phone contact or email, to assess subsequent anti-cancer therapy.

[a] Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulation.

[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 may be conducted in clinic or via telephone contact: Every 6 Months (± 14 days) from FU2. BMS may request that survival data be collected on all treated participants outside of the 6-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.

Table 2-8: On-Treatment REDUCED ASSESSMENTS (Part 2 mCRC 3rd line, TRIPLET, [redacted] CA2099N9 Cohort 4) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 8 weeks)			Notes
	Day 1	C1D15 (required); C1D43 (optional)[b]	Day 29	
Safety Assessments				
Targeted Physical Examination	X	X	X	Targeted examination must include at a minimum the following body systems: Cardiovascular Gastrointestinal Pulmonary Neurological exam for participants with brain metastases
Ophthalmic Evaluation	Participants are required to have a standard ophthalmic examination conducted by an ophthalmologist at Month 1, Month 6, and then annually thereafter unless clinically indicated sooner. (See Section 9.4.3) For Month 1: Results must be evaluated within 7 days prior to study treatment.			
Vital Signs	X	X	X	Including BP, HR, and temperature. Obtain vital signs within 72 hours prior to first dose.
Physical Measurements (including performance status)	X	X	X	Weight and ECOG performance status within 72 hours prior to dosing. ECOG must be assessed prior to first dose on Cycle 1 Day 1 to re-confirm eligibility See Appendix 7 for ECOG Performance Status scale.
ECG	Participants will be evaluated within 7 days prior to C1D29 of treatment, and then as clinically indicated until discontinuation of treatment.			
Echocardiogram or MUGA	Evaluate LVEF within 7 days prior to C1D29 and C2D29, and then every 12 weeks thereafter until discontinuation of treatment.			
Adverse Events Assessment	Continuously			Adverse events will be graded according to the NCI-CTCAE (version 4.0).
Serious Adverse Event Assessment	Continuously			Serious adverse events will be graded according to the NCI-CTCAE (version 4.0).

Table 2-8: On-Treatment REDUCED ASSESSMENTS (Part 2 mCRC 3rd line, TRIPLET, [redacted] CA2099N9 Cohort 4) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 8 weeks)			Notes
	Day 1	C1D15 (required); C1D43 (optional)[b]	Day 29	
Review of Concomitant Medications	X	X	X	
Laboratory Tests	X	X	X	Local CBC, chemistry assessments, and thyroid panel should be done within 72 hours prior to D1 and D29 of each cycle through Cycle 6 (in addition to C1D15 and C1D43), and may be collected only prior to D1 of each cycle thereafter if deemed medically appropriate. Laboratory tests do not need to be repeated on C1D1 if screening labs results are deemed still clinically valid by the treating investigator. Lab assessments will include: • CBC w/differential and platelet count, • Chemistry panel including: AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine (if abnormal creatinine clearance should be reported), phosphate, Ca, Na, K, Mg, Cl, LDH, glucose, albumin • Urinalysis including protein, glucose, blood, leukocyte esterase, specific gravity, pHc,[c] • Coagulation including PT/INR and PTT (as clinically indicated) • If TSH is abnormal, refer to Appendix 5 for instructions on Free T4 and Free T3. (TSH is not required at C1D15 and C1D43 if not clinically indicated)

Table 2-8: On-Treatment REDUCED ASSESSMENTS (Part 2 mCRC 3rd line, TRIPLET, [redacted] CA2099N9 Cohort 4) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 8 weeks)			Notes
	Day 1	C1D15 (required); C1D43 (optional)[b]	Day 29	
				• CEA every 4 weeks CEA for all participants. For participants with elevated CA19-9 at screening, monitor CA19-9 AND CEA.
Pregnancy Test (WOCBP Only)	X		X	Serum or urine pregnancy test to be done within 24 hours prior to first dose, and then every 4 weeks (± 1 week) regardless of dosing schedule. See Appendix 4.
Efficacy Assessments				
Body Imaging	See notes			See Section 9.1.1. Imaging assessments will occur every 8 weeks (± 7 days) from the date of first dose until disease progression, end of trial, or withdrawal of consent, whichever occurs first. For participants who continue treatment beyond initial progression see Section 8.1.5. Tumor assessment scans should be submitted to the imaging vendor within 14 days of acquisition.
Brain Imaging	See notes			See Section 9.1.1. Participants with a history or clinical symptoms of brain metastasis should have surveillance MRI per local SOC (approximately every 12 weeks) or sooner if clinically indicated.
Other Imaging Bone Scan	See notes			As clinically indicated. See Section 9.1.1.2
Clinical Drug Supply				
Contact IRT	X		X	First dose should be administered within 3 calendar days of randomization.

Table 2-8: On-Treatment REDUCED ASSESSMENTS (Part 2 mCRC 3rd line, TRIPLET, [redacted] CA2099N9 Cohort 4) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 8 weeks)			Notes
	Day 1	C1D15 (required); C1D43 (optional)[b]	Day 29	
Administer Nivolumab (6 mg/kg)	X		X	Nivolumab dosing will occur every 4 weeks.
Administer Ipilimumab (1 mg/kg)	X			Ipilimumab dosing will occur every 8 weeks.
Administer Trametinib (1.5mg QD)	See notes			Trametinib dosing will occur once daily. Trametinib bottles will be dispensed at D1 and D29 of each cycle

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 regulation. If a dose is delayed, the procedures are to be delayed if deemed appropriate by treating physicians, except for tumor assessments that continue per schedule.

[b] Cycle 1 Day 15 assessments are required for the first cycle. C1 D43 and subsequent D15 and D43 assessments are optional and may be performed as clinically indicated at the investigator's discretion.

[c] Urinalysis should be assessed every 4 weeks for the first year of study treatment, and then every 8 weeks unless more frequent testing is clinically indicated. Urinalysis or urine dipstick. If blood, protein, or leukocytes esterase are positive on the dipstick, microscopic examination of the sediment is required.

Table 2-9: On-Treatment REDUCED ASSESSMENTS (Part 2 mCRC 3rd line, Regorafenib, [redacted] CA2099N9 [Cohort 5]) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 4 weeks)		Notes
	Day 1	C1 D15 (required); subsequent cycle D15 (if clinically indicated)[b]	
Safety Assessments			
Targeted Physical Examination	X	X	Targeted examination must include at a minimum the following body systems: Cardiovascular Gastrointestinal Pulmonary Neurological exam for participants with brain metastases
Vital Signs	X	See Note	Including BP[c], HR, and temperature. Obtain vital signs within 72 hours prior to dosing
Physical Measurements (including performance status)	X	See Note	Weight and ECOG performance status within 72 hours prior to dosing. ECOG must be assessed prior to first dose on Cycle 1 Day 1 to re-confirm eligibility. See Appendix 7 for ECOG Performance Status scale.
ECG	Participants will be evaluated within 7 days prior to C2D1 of treatment, and then as clinically indicated until discontinuation of treatment.		
Adverse Events Assessment	Continuously		Adverse events will be graded according to the NCI-CTCAE (version 4.0).
Serious Adverse Event Assessment	Continuously		Serious adverse events will be graded according to the NCI-CTCAE (version 4.0).
Review of Concomitant Medications	X	X	
Laboratory Tests	X	See Notes	Local CBC and chemistry assessments should be done within 72 hours prior to D1 of each cycle, and D15 of each cycle if clinically indicated (C1D15 is required). Laboratory tests do not need to be repeated on C1D1 if screening laboratory results are deemed still clinically valid by the treating investigator.

Table 2-9: On-Treatment REDUCED ASSESSMENTS (Part 2 mCRC 3rd line, Regorafenib, [redacted] CA2099N9 [Cohort 5]) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 4 weeks)		Notes
	Day 1	C1 D15 (required); subsequent cycle D15 (if clinically indicated)[b]	
			Lab assessments will include: • CBC w/differential and platelet count,[d] • Chemistry panel including: AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine (if abnormal creatinine clearance should be reported), phosphate, Ca, Na, K, Cl, Mg, LDH, glucose, albumin • Coagulation including PT/INR and PTT (as clinically indicated) • TSH every 4 weeks.[e] If TSH is abnormal, see Appendix 5 for instructions on Free T4 and Free T3. (TSH is not required at C1D15 if not clinically indicated). • CEA for all participants. For participants with elevated CA19-9 at screening, monitor CA19-9 AND CEA.[f] • Urine dipstick or urinalysis[g]
Pregnancy Test (WOCBP Only)	X		Serum or urine pregnancy test to be done within 24 hours prior to first dose, and then every 4 weeks (± 1 week) regardless of dosing schedule. See Appendix 4.
Efficacy Assessments			
Body Imaging	See notes		See Section 9.1.1. Imaging assessments will occur every 8 weeks (±7 days) from the date of first dose until disease progression, end of trial, or withdrawal of consent, whichever occurs first. Tumor assessment scans should be submitted to the imaging vendor within 14 days of acquisition.
Brain Imaging	See notes		See Section 9.1.1. Participants with a history or clinical symptoms of brain metastasis should have surveillance MRI per local SOC (approximately every 12 weeks) or sooner if clinically indicated.

Table 2-9: On-Treatment REDUCED ASSESSMENTS (Part 2 mCRC 3rd line, Regorafenib, [redacted] CA2099N9 [Cohort 5]) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 4 weeks)		Notes
	Day 1	C1 D15 (required); subsequent cycle D15 (if clinically indicated)[b]	
Other Imaging Bone Scan	See notes		As clinically indicated. See Section 9.1.1.2
Clinical Drug Supply			
IRT contact	X		First dose should be administered within 3 calendar days of randomization
Administer Regorafenib (160 mg)	See notes		Orally, once daily for the first 21 days (D1 to D21) of each cycle. See Section 7.1.4

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 regulation. If a dose is delayed, the procedures are to be delayed if deemed appropriate by treating physicians, except for tumor assessments that continue per schedule.

[b] Cycle 1, D15 clinic visit is required. Day 15 visits in the subsequent cycles are optional and should be performed as clinically indicated or per local institutional guidelines.

[c] Monitor BP more frequently as clinically indicated or per local institutional guidelines.

[d] Monitor coagulation more frequently for increased risk of bleeding per local institutional guidelines.

[e] Monitor TSH per local product label and/or institutional guideline.

[f] CEA at C1D1, C1D15, C2D1, C3D1, C4D1, C5D1, and then every 8 weeks thereafter or more frequent if clinically indicated. If CA19-9 is also monitored, follow same collection frequency as CEA.

[g] Urine dipstick or urinalysis to monitor urine protein per local product label and/or institutional guideline. Protocol recommended frequency is every 4 weeks.

Table 2-10: On-Treatment REDUCED ASSESSMENTS (Part 1B mCRC 2nd line, TRIPLET, [redacted], CA2099N9 [Cohort 6]) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 8 weeks)			Notes
	Day 1	C1D15 (required), C1D43 (optional)[b]	Day 29	
Safety Assessments				
Targeted Physical Examination	X	X	X	Targeted examination must include at a minimum the following body systems: Cardiovascular Gastrointestinal Pulmonary Neurological exam for participants with brain metastases
Ophthalmic Evaluation	Participants are required to have a standard ophthalmic examination conducted by an ophthalmologist at Month 1, Month 6, and then annually thereafter unless clinically indicated sooner. (See Section 9.4.3) For Month 1: Results must be evaluated within 7 days prior to study treatment.			
Vital Signs	X	X	X	Including BP, HR, and temperature. Obtain vital signs within 72 hours prior to first dose.
Physical Measurements (including performance status)	X	X	X	Weight and ECOG performance status within 72 hours prior to dosing. ECOG must be assessed prior to first dose on Cycle 1 Day 1 to re-confirm eligibility See Appendix 7 for ECOG Performance Status scale.
ECG	Participants will be evaluated within 7 days prior to C1D29 of treatment, and then as clinically indicated until discontinuation of treatment.			
Echocardiogram or MUGA	Evaluate LVEF within 7 days prior to C1D29 and C2D29, and then every 12 weeks thereafter until discontinuation of treatment.			
Adverse Events Assessment	Continuously			Adverse events will be graded according to the NCI-CTCAE (version 4.0).

Table 2-10: On-Treatment REDUCED ASSESSMENTS (Part 1B mCRC 2nd line, TRIPLET, [redacted], CA2099N9 [Cohort 6]) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 8 weeks)			Notes
	Day 1	C1D15 (required), C1D43 (optional)[b]	Day 29	
Serious Adverse Event Assessment	Continuously			Serious adverse events will be graded according to the NCI-CTCAE (version 4.0).
Review of Concomitant Medications	X	X	X	
Laboratory Tests	X	X	X	Local CBC, chemistry assessments, and thyroid panel should be done within 72 hours prior to D1 and D29 of each cycle through Cycle 6 (in addition to C1D15 and C1D43) and may be collected only prior to D1 of each cycle thereafter if deemed medically appropriate. Laboratory tests do not need to be repeated on C1D1 if screening labs results are deemed still clinically valid by the treating investigator. Lab assessments will include: • CBC w/differential and platelet count, • Chemistry panel including: AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine (if abnormal creatinine clearance should be reported), phosphate, Ca, Na, K, Mg, Cl, LDH, glucose, albumin • Urinalysis including protein, glucose, blood, leukocyte esterase, specific gravity, pH[c,d] • Coagulation including PT/INR and PTT (as clinically indicated) • TSH. If TSH is abnormal, see Appendix 5 for instructions on Free T4 and Free T3. (TSH is not required at C1D15 and C1D43 if not clinically indicated).

Table 2-10: On-Treatment REDUCED ASSESSMENTS (Part 1B mCRC 2nd line, TRIPLET, [redacted], CA2099N9 [Cohort 6]) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 8 weeks)			Notes
	Day 1	C1D15 (required), C1D43 (optional)[b]	Day 29	
				• CEA every 4 weeks for all participants. For participants with elevated CA19-9 at screening, monitor CA19-9 AND CEA.
Pregnancy Test (WOCBP Only)	X		X	Serum or urine pregnancy test to be done within 24 hours prior to first dose, and then every 4 weeks (± 1 week) regardless of dosing schedule. See Appendix 4.
Efficacy Assessments				
Body Imaging	See notes			See Section 9.1.1. Imaging assessments will occur every 8 weeks (± 7 days) from the date of first dose until disease progression, end of trial, or withdrawal of consent, whichever occurs first. For participants who continue treatment beyond initial progression see Section 8.1.5. Tumor assessment scans should be submitted to the imaging vendor within 14 days of acquisition.
Brain Imaging	See notes			See Section 9.1.1. Participants with a history or clinical symptoms of brain metastasis should have surveillance MRI per local SOC (approximately every 12 weeks) or sooner if clinically indicated.
Other Imaging Bone Scan	See notes			As clinically indicated. See Section 9.1.1.2
Clinical Drug Supply				
Contact IRT	X		X	First dose should be administered within 3 calendar days of treatment assignment.
Administer Nivolumab (6 mg/kg)	X		X	Nivolumab dosing will occur every 4 weeks.
Administer Ipilimumab (1 mg/kg)	X			Ipilimumab dosing will occur every 8 weeks.

Table 2-10: On-Treatment REDUCED ASSESSMENTS (Part 1B mCRC 2nd line, TRIPLET, [redacted], CA2099N9 [Cohort 6]) CLOSED FOR ENROLLMENT

Procedure[a]	Each Cycle (1 Cycle = 8 weeks)			Notes
	Day 1	C1D15 (required), C1D43 (optional)[b]	Day 29	
Administer Trametinib (1.5mg QD)	See notes			Trametinib dosing will occur once daily. Trametinib bottles will be dispensed at D1 and D29 of each cycle.

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 regulation. If a dose is delayed, the procedures are to be delayed if deemed appropriate by treating physicians, except for tumor assessments that continue per schedule.

[b] Cycle 1, Day 15 assessments are required. C1, D43 and subsequent D15 and D43 assessments are optional and may be performed as clinically indicated at the investigator's discretion.

[c] Urinalysis should be assessed every 4 weeks for the first year of study treatment, and then every 8 weeks unless more frequent testing is clinically indicated.

[d] Urinalysis or urine dipstick. If blood, protein, or leukocytes esterase are positive on the dipstick, microscopic examination of the sediment is required.

Table 2-11: Follow-Up Period REDUCED ASSESSMENTS (All treatment cohorts, CA2099N9)

Procedure[a]	Follow-Up, Visits 1 and 2[b]	Notes
Safety Assessments		
Targeted Physical Examination	X	To assess for potential late emergent study drug related issues, Targeted examination must include at a minimum the following body systems: • Cardiovascular • Gastrointestinal • Pulmonary • Neurological exam for participants with brain metastases
Ophthalmic Evaluation	X	To be performed at Follow Up Visit 1 only, and at any time a participant reports new or worsening visual disturbances (See Section 9.4.3). Not required for Cohort 5 unless clinically indicated.
Echocardiogram or MUGA	X*	*At Follow-up Visit 1 only, not required for Cohort 5 unless clinically indicated.
Adverse Events Assessment	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)
ECG	X	At Follow-up Visit 1 only
Review of Concomitant Medication	X	
Review of Subsequent Cancer Therapies	X	Additional subsequent cancer therapy details such as regimen, line of therapy, start date and end date of each regimen, best response to the regimen, and date of progression after additional line of therapy will be collected.

Table 2-11: Follow-Up Period REDUCED ASSESSMENTS (All treatment cohorts, CA2099N9)

Procedure[a]	Follow-Up, Visits 1 and 2[b]	Notes
Laboratory Tests	X	• Local testing: • CBC w/differential and platelet count, • Chemistry panel including: AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine (if abnormal creatinine clearance should be reported), phosphate, Ca, Na, K, Mg, Cl, LDH, glucose, albumin • Urinalysis including protein, glucose, blood, leukocyte esterase, specific gravity, pH[c] • Coagulation including PT/INR and PTT (as clinically indicated) • TSH. If TSH is abnormal, see Appendix 5 for instructions on Free T4 and Free T3. To be done at FU1. To be repeated at FU2 if study related toxicity persists.
Pregnancy Test (WOCBP only)	X	Serum or urine
Efficacy Assessments		
Body Imaging	See note	Only for participants without progression on study therapy. See Section 9.1.1. Imaging assessments will occur every 8 weeks (± 7 days) from the date of first dose until disease progression, end of study, or withdrawal of consent, whichever occurs first. For Part 1B and Part 2: Tumor assessment scans should be submitted to the imaging vendor within 14 days of acquisition.
Brain Imaging	See note	See Section 9.1.1. Participants with a history or clinical symptoms of brain metastasis should have surveillance MRI per local SOC (approximately every 12 weeks) or sooner if clinically indicated.

Table 2-11: Follow-Up Period REDUCED ASSESSMENTS (All treatment cohorts, CA2099N9)

Procedure[a]	Follow-Up, Visits 1 and 2[b]	Notes
Other Imaging: Bone Scan	See note	As clinically indicated. See Section 9.1.1.2.

[a] Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulation.

[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] Urinalysis or urine dipstick. If blood, protein, or leukocytes esterase are positive on the dipstick, microscopic examination of the sediment is required.

3 INTRODUCTION

3.1 Study Rationale

CA2099N9 (CHECKpoint pathway and nivoluMAb clinical Trial Evaluation [CHECKMATE] 9N9) is a Phase 1/2, open-label, multi-center trial of nivolumab in combination with trametinib, with or without ipilimumab for the treatment of proficient mismatch repair (pMMR)/microsatellite stable (MSS) metastatic colorectal cancer (mCRC). This trial provides an opportunity to evaluate nivolumab and ipilimumab in combination with trametinib for the treatment of later-line (3rd line plus [3L+]) (pMMR)/MSS mCRC participants who failed at least 2 prior lines of therapy (no more than 4 prior lines) for metastatic disease. Part 2 will include 2 treatment arms, including the triplet regimen and standard of care treatment (SOC) option (regorafenib). The objective of Part 2 is to further develop and optimize a [redacted] patient selection strategy for combination therapy of immune checkpoint inhibitors with a MEK inhibitor.

Additionally, the study presents an opportunity to validate the tolerability and preliminary efficacy and to further optimize a [redacted] patient selection strategy for nivolumab and ipilimumab in combination with trametinib in earlier line (2nd line [2L]) pMMR/MSS mCRC participants who failed only 1 prior line of therapy for metastatic disease (Part 1B).

3.1.1 Research Hypothesis

Combining MEK inhibition using trametinib with nivolumab and ipilimumab will improve the clinical activity in MSS metastatic CRC.

3.1.2 Rationale for the Combination of Nivolumab and Ipilimumab with Trametinib in MSS CRC Population

Nivolumab administered as monotherapy has demonstrated remarkable clinical benefit in several solid tumor types, including the microsatellite instable (MSI-H)-CRC. However, the MSS-CRC is highly immunosuppressive, and inhibits the activation of anti-tumor immune responses that allow T-cells to engage with the tumor.[1] Single-agent immunotherapies are largely ineffective in pMMR/MSS CRC, which represents approximately 85%-96% of the CRC patient population.[2,3,4]

Preclinical and clinical evidence suggests synergy between nivolumab and ipilimumab, which target distinct mechanisms to limit T-cell activation, PD-1, and CTLA-4, respectively. In vitro combinations of nivolumab plus ipilimumab increase IFN-γ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone.[5] The combination of nivolumab and ipilimumab has been shown to be more effective than either agent in monotherapy in the treatment of a variety of tumors including melanoma, lung, and renal cell carcinoma.[6,7,8,9] Most relevant, this combination has also demonstrated meaningful clinical efficacy (Checkmate 142) in MSI-H CRC of improved efficacy compared to IO monotherapy.

However, there was only modest activity observed for combination therapy in MSS CRC. The combination of durvalumab + tremelimumab only resulted in a median overall survival of

6.6 months (CI 90%, 6.0-7.4) and a HR of 0.66 (CI 90%, 0.48-0.89, p = 0.02) compared with best supportive care. [10,]This relative lack of response to immune therapies may be related to the MAP Kinase pathway. Recent published data have suggested combination therapy with a MEK inhibitor and antibody targeting PD-1 and CTLA-4 pathways were more efficacious in colon cancer model, CT26.[11] Therefore, targeting the CTLA-4 pathway in addition to PD-1 and MEK1/2 inhibition may enhance clinically effective anti-tumor immune response.

Immuno-oncologic approaches with checkpoint inhibition alone might not be sufficient in patients who have limited tumor immune cell infiltration like in MSS CRC tumors. In a fraction of patients who are resistant to anti-PD-L1 monoclonal Ab (mAb) therapy, $CD8^+$ T cells localize at the edge of the tumors, whereas they are found to accumulate in the tumor mass of patients who respond to PD-L1 blockade. This suggests that in addition to PD-L1 inhibition, strategies aimed at promoting T cell accumulation in the tumor mass are essential for the induction of therapeutic immunity.[12]

The mitogen-activated protein kinase (MAPK) pathway is one of the most frequently dysregulated pathways in cancer. The signaling molecule MEK (Mitogen/Extracellular signal regulated Kinase) is a key intermediate in the MAPK pathway. Two MEK isoforms (MEK1 and MEK2) are known, both of which phosphorylate ERK1 and/or ERK2 downstream of RAS and RAF. MEK has been well characterized as a critical mediator of the constitutively active mutant form of KRAS, KRASG12D, in many cancers.[13] The MEK pathway is presumed to be upregulated in a large fraction of colorectal tumors, due to mutation of several components of the pathway, most notably KRAS, NRAS, and BRAF. In addition to RAS and RAF mutations, many tumors are activated by amplification or overexpression of upstream pathway components.[14]

MEK is not only a critical signaling component for tumors with RAS mutation, it is also mediates TCR-mediated apoptosis. Mellman and colleagues demonstrated that MEK inhibition protected tumor-infiltrating $CD8^+$ T cells from death driven by chronic TCR stimulation while sparing cytotoxic activities.[13]

Importantly, there is likely a role of the activated MAPK/MEK pathway in immune evasion by tumors. It has been shown that tumor cells with an activated MAPK/MEK pathway produce factors including, but not limited to, interleukin (IL)-10, and IL-6, that inhibit dendritic cells. Signal transducer and activator of transcription 3 (STAT3) is also essential for immune evasion by human melanomas.[15] Pharmacologic intervention with a MEK inhibitor decreased production of immunosuppressive soluble factors from melanoma cells to levels comparable to STAT3 inactivation. Therefore, the MAPK/MEK pathway is a potential molecular target for overcoming tumor cell evasion of the immune system.[15]

The antigen presenting dendritic cells (DC) which are $CD103^+$ (the cross-presenting DC) are also critical for response to PD-1 pathway blockade and may also be modulated by MEK inhibition. In a mouse model, activated $CD103^+$ DC progenitors in the tumor enhanced responses to PD-L1 blockade and protected mice from tumor rechallenge. The DCs are also affected by the

MAPK/MEK pathway, which produces factors including, but not limited to, IL-10 and IL-6, that inhibit DC.[15]

Early experience in mCRC with MEK-inhibition has demonstrated no single-agent activity for this class of agents.[16,17] However, MEK inhibitors have been combined preclinically with anti-PD-1 to provide additional efficacy in mouse models.[18] Numerous preclinical studies have demonstrated that MEK inhibitors modulate the mechanisms of T cell mediated cell killing and MHC class I expression. In melanoma cell lines, the MEK inhibitor trametinib increased expression of HLA-I and/or II in 5 of 6 lines tested, and a similar effect was found in an in vivo mouse model which demonstrated that the combination of trametinib with anti–PD-1 increased tumor-infiltrating $CD8^+$ T cells in CT26 tumors and potentiated antitumor activity with PD-1 blockade.[18] MEK inhibition alone in immunocompetent mice harboring a colon carcinoma cell line with mutant KRASG12D who were treated with the potent and highly specific MEK inhibitor G-38963 resulted in intratumoral $CD8^+$T cell accumulation and class I MHC upregulation.[13] Observed increases ranged from 0- to almost 4-fold among several mouse and human tumor cell lines as determined by flow cytometry. In further experiments in preclinical models, MEK inhibition synergized with anti-PD-1 to promote durable tumor regression while promoting the effector phenotype and longevity of tumor-infiltrating $CD8^+$ T cells.[13]

However, the promising preclinical observations of combining MEK inhibition with PD-1 blockade have not been replicated in the clinic. To this point, the doublet treatment regimen of PD-(L)1 inhibition in combination with MEK inhibition has not exhibited significant clinical efficacy in MSS CRC. In the recent IMblaze370 Phase 3 trial, atezolizumab + cobimetinib failed to demonstrate improved overall survival versus regorafenib in later lines (3L or later) with a mOS 8.87 months, HR = 1.00 (0.73-1.38; p=0.99). [19] Similarly in a Phase 2 clinical study assessing the use of durvalumab plus trametinib in ≥ 2L MSS CRC, the combination only resulted in a partial response (PR) in 1 of 29 treated patients, and did not meet efficacy criteria to proceed with the second phase of the study.[10]

These clinical findings suggest that PD-(L)1 inhibition + MEKi doublet regimens do not provide meaningful improvement over existing treatment options, and triplet regimens may be needed to provide additional clinical efficacy. Additional combination strategies will be required to elicit the desired immunomodulatory effects to alter the tumor microenvironment, reduce immunosuppression, and allow for enhanced T-cell infiltration. Therefore, novel therapies using MEK inhibition with PD-1/PD-L1 and CTLA-4 antibodies as a triplet regimen may present a unique and much-needed opportunity to improve the effectiveness of this strategy in patients with MSS mCRC.

3.2 Background

3.2.1 Colon Cancer Background and Treatment Options

Worldwide, colon cancer (including rectal cancer) is the third most common form of cancer in men with 1,026,200 cases (11.6% of the total), and second most common in women with 823,300

cases (10% of the total) per year.[20] This disease predominately occurs in developed regions with the highest rates being found in Australia/New Zealand and Western Europe and to a lower extent in Africa and South-Central Asia. Each year, there are about 880,800 deaths from colon cancer, which is approximately 9% of all cancer deaths, making colon cancer the second most common cause of cancer death.[20] In 2020 in the United States (US), an estimated 147,950 new cases of CRC will be diagnosed, and an estimated 53,200 deaths.[21] At initial diagnosis, approximately 25% of patients present with metastatic disease and almost 50% of patients will develop metastasis which contributes to the high mortality rate reported in CRC patients.[22]

Treatment options for patients with metastatic colon or rectal cancer (mCRC) are predominantly 5-fluorouracil (5-FU) containing regimens in combination with either oxaliplatin or irinotecan (FOLFOX or FOLFIRI) with a biologic agent such as bevacizumab. The EGFR inhibitors, cetuximab and panitumumab, are also options if KRAS status is non-mutated.[23] Both chemotherapy regimens have demonstrated similar progression-free survival (PFS) benefit, a median first-line (1L) PFS of 8.5 months for FOLFIRI and 8 months for FOLFOX.[24]

In second-line therapy for those patients who had 1L therapy with FOLFOX or another 5-FU containing therapy, the median PFS for patients receiving FOLFIRI is approximately 4.5 months.[25, 26] Bevacizumab, ramucirumab, and ziv-afilbercept have indications for second-line treatment in combination with chemotherapy and have demonstrated improvement in median OS (mOS); for biologic agents, the improvement in mOS is less than 2 months: 13.5 months vs 12.06 months for bevacizumab,[27] 13.3 months vs 11.7 months for ramucirumab,[28] and 11.2 months vs 9.8 month for ziv-aflibercept.[29] In the chemorefractory setting, cetuximab also has demonstrated an improvement in mOS of less than 2 months in patients who have previously received chemotherapy, 6.1 months vs 4.6 months, when compared to best supportive care (BSC).[30] In later-line therapy, regorafenib, in patients who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild-type, an anti-EGFR therapy, has demonstrated an improvement in mOS- of less than 2 months, 6.4 months vs 5 months, when compared to BSC.[31] Similar results in mOS were demonstrated for trifluridine/tipiracil (as hydrochloride) (TAS-102), 7.1 months in TAS-102 group vs 5.3 months in BSC group.[32]

Despite the numerous initial treatment options for mCRC, the benefit of these therapies after 1L therapy is modest, and complete radiographic responses are rare, highlighting the need for more effective therapies.

3.2.2 RAS/BRAF Wild-type and RAS/BRAF Mutant CRC

Kirsten rat sarcoma (KRAS) and neuroblastoma rat sarcoma (NRAS) genes are two of the three human RAS genes that have been identified. The KRAS protein is one of the most pivotal effectors downstream of EGFR receptor tyrosine kinase activity. KRAS activates intracellular signaling cascades mediated by the RAF/MEK (mitogen-activated and extracellular signal regulated kinase)/ ERK(extracellular signal-regulated kinase) pathway, and PI3K (phosphatidylinositol 3-kinase)/

PDK1 (3-phosphoinositide-dependent protein kinase 1)/Akt pathways.[33] Constitutive activation of these pathways is achieved by point mutations in codons 12 or 13 of exon 2 of the KRAS gene; such mutations arise in approximately 33% to 48% of patients with mCRC.[34,35,36,37] Other relevant point mutations in the KRAS gene include those in codon 61 (exon 3) and codon 146 (exon 4).[51] Moreover, a high level of concordance exists between KRAS mutational status in patient-matched primary tumors and metastases, implying that KRAS mutations frequently occur early during the course of tumor evolution.[38]

The prognostic value of KRAS mutations in CRC (independent of anti-EGFR therapy) is unclear due to conflicting data from various meta-analyses across all disease stages. However, KRAS mutations are predictive for a lack of response and clinical benefit from anti-EGFR mAbs in patients with mCRC based on several large clinical trials, including CO.17, CRYSTAL, OPUS, and PRIME. In addition, retrospective analyses from several Phase 2 and 3 clinical trials of cetuximab and panitumumab have indicated that WT status in KRAS and NRAS exons 2 to 4 results in more pronounced treatment effects than the WT status of solely KRAS exon 2 (CALGB/SWOG 80405, CRYSTAL, FIRE-3, PEAK, and PRIME). Thereby increasing the proportion of patients ineligible for anti-EGFR therapy from approximately 45% to 55%. Consequently, DNA sequencing methods used for RAS testing have been introduced to capture hot spot-activating RAS (KRAS and NRAS) mutations in codons 12 and 13 (exon 2), 59 and 61 (exon 3), and 117 and 146 (exon 4).[51]

BRAF proto-oncogene kinase is an important player in the EGFR-mediated MAPK pathway. BRAF mutations have been recently reported in 5 to 15% of CRC cases.[39] Similar association between the BRAF mutations and resistance to EGFR-targeting agents in CRC patients has also been shown recently.[39] BRAF was reported to be mutated at several sites, however, the vast majority of mutated BRAF are V600E (1799T>A), representing up to 80% of all BRAF mutations.[40] Such mutations (V600) are associated with short progression-free and overall survival.[40] See Appendix 10 for KRAS, NRAS, and BRAF mutational testing suitable for this study.

The below table (Table 3.2.2-1) summarizes Response Rate, PFS, and OS of selected Standard of Care (SOC) treatment for ≥ 2L mCRC with KRAS wild-type (WT) and KRAS mutation (MT):

Table 3.2.2-1: Response Rate, PFS and OS for Patients with 2nd to 4th Line CRC treated with SOC

Line of therapy	KRAS status	Standard of Care (SOC)	RR	Median PFS (months)	Median OS (months)
2nd line	KRAS MT	FOLFOX or FOLFIRI + bevacizumab[41, 42] or aflibercept[43] or ramucirumab [39]	11-22%	6-7	12.9-13.5
	KRAS WT	FOLFOX or FOLFIRI + bevacizumab [52, 53] or ramucirumab [39] or panitumumab[44]	11-22%	6-7	12.9-14.5
≥ 3rd Line	KRAS WT/MT	Regorafenib[45]	1%	1.9	6.4
		TAS-102 [32]	1.6%	2.0	7.1

3.2.3 MSS/pMMR and MSI-H/dMMR CRC

Microsatellite stability (MSS) is the molecular fingerprint of a proficient mismatch repair system (pMMR). The term MSS is widely accepted as a surrogate for pMMR tumors. Approximately 85% of CRCs display MSS without novel microsatellite alleles.[46] Studies have confirmed that MSS identification can be prognostic in that MSS tumors have a worse prognosis than microsatellite instable CRC.[47]

There are well established methods to differentiate pMMR/MSS from deficient MMR/MSI-H or L that are incorporated into clinical practice. The NCCN recommends MSI testing for all patients with CRC.[48] There are several options for testing. The IHC MMR testing consists of staining of tumor tissue for loss of expression of the four mismatch repair proteins known to be mutated in Lynch syndrome: *MLH1*, *MSH2*, *MSH6*, and *PMS2*.[60] If at least one of these is not normally expressed, then the testing indicates the dMMR (MSI) phenotype. PCR amplification of a set of mono-and/or di-nucleotide repeats on tumor and normal DNA, followed by comparison of the peak patterns by capillary electrophoresis, can also assess for MSI with three categories: MSI-H, MSI-Low, and MSS. MSI-Low will be grouped together with MSS for this study as the clinicopathologic and most molecular characteristics in such tumors do not seem to differ from MSS tumors.[49]

Characterization of the molecular basis of MSI in CRC is underway and initial results show that mutations in genes encoding kinases and candidate genes with microsatellite tracts are over‑represented in MSI tumors.[50] Hypermethylation of *MLH1* can cause *BRAF* mutations in CRC

and are more frequent in sporadic MSI-H cases compared to hereditary cases.[51, 52] The strong local immune reaction observed in MSI-H CRC is characterized by peritumoral lymphoid nodules (Crohn's-like reaction) and a dense overall infiltration of the tumor with lymphocytes,[53] part of which are activated and cytotoxic.[54, 55] Frameshift mutations encountered in MSI-H CRC might lead to the generation of tumor-specific antigens.[56] In addition, it is known that antigens expressed in a noninflamed environment may induce tolerance rather than eliciting an antitumoral immune response[57]; however, the existence of T cell responses directed against a multiple tumor antigens in individuals with MSI-H CRC has been demonstrated in patients.[58, 59] This observation strongly suggests that antigenic structures are generated from coding DNA sequences carrying frameshift mutations in sufficient amounts to trigger antigen-specific T cell responses. The cytokine milieu encountered at the MSI-H tumor site initially tends to be proinflammatory and favoring T-cell response rather than contributing to tolerance induction.[60, 61] The mechanism by which immune tolerance is induced is not completely understood. This initial control of the MSI-H tumor by immune surveillance makes it hopeful that nivolumab, with its mechanism of action that abrogates immune tolerance, will have significant clinical activity in MSI-H CRC. In study CA209003, a Phase 1 trial of subjects with solid tumors, one trial subject with MSI-H metastatic CRC (mCRC) had a long-term complete response, suggesting the immune-modulatory approach warrants further evaluation.[62]

3.2.4 Consensus Molecular Subtypes

The CRC Subtyping Consortium (CRCSC) was formed to evaluate the presence of core subtype transcriptional patterns in patients with primary CRC.[63] This work led to the identification of four Consensus Molecular Subtypes (CMS1-4) with distinct molecular characteristics that consistently characterize primary and metastatic CRC tumors.[63,64] CMS subtyping in turn allows further segmentation of CRC patients to evaluate differential response to treatment and potential rationale for future patient selection.[63,65] The CMS1-4 subtypes are characterized below.

CMS1 (immune subtype) is observed in approximately 14% of CRC patients, and is primarily associated with BRAF mutations and MSI-H CRC. Compared to other subtypes, CMS1 is considered to be highly immunogenic as it is better infiltrated with CD8 and CD4 T cells and natural killer (NK) cells. CMS1 is also characterized by overexpression of cytotoxic lymphocyte and T helper cell (T_H1) specific genes.

CMS2 (canonical subtype) accounts for approximately 37% of CRC patients and is considered poorly immune-infiltrated epithelial tumors. This subtype is characterized by marked upregulation of canonical pathway genes and their downstream targets (WNT, MYC, MAPK, etc.).

CMS3 (metabolic subtype), another set of poorly immune-infiltrated epithelial tumors, has elevated expression of genes that are associated with metabolic dysregulation. This subtype is found in ~13% of CRC patients.

CMS4 (mesenchymal subtype) is a set of tumors which are distinguished by an inflamed tumor microenvironment with CD8 TILs, upregulation of T_H1 and cytotoxic T cell gene expression, but

are also infiltrated by immunosuppressive cells (eg, myeloid-derived suppressor cells [MDSC], T-regulatory cells [Tregs], T helper 17 cells [T_H17]). This subtype is also identified as stroma-enriched, with elevated gene expression of epithelial-mesenchymal transition (EMT), transforming growth factor- β (TGFβ), and fibroblast signaling. This subtype accounts for ~23% of early-stage CRC and found in approximately 30% of metastatic CRC tumors.[6366]

Retrospective analysis of clinical studies has explored the prognostic and/or predictive value of CMS in CRC patients receiving SOC therapies, chemotherapy +/- regorafenib;[6768] or regorafinib, in second- and third-line mCRC (Table 3.2.4-1).[66] Late line SOC, regorafenib monotherapy, resulted in a survival benefit in CMS2 and CMS4, but not CMS1 and CMS3, compared to placebo in the CORRECT trial.[66]

These clinical findings have demonstrated that efficacy outcomes are varied across CMS subtypes with available treatment regimens in later lines of therapy (2L+). Furthermore, these observations suggest that the underlying biology of these distinct molecular subtypes that characterize the TME may play a key role in response to therapy. The literature is sparse in context of IO therapy and combinations thereof.[69] Specifically, the association between CMS classification and efficacy following nivolumab + ipilimumab + trametinib needs further investigation to inform on potential patient selection strategies.

Table 3.2.4-1: 2L+ Clinical Data in CMS of mCRC

Treatment Regimen	CMS	Median OS	Median PFS
FOLFIRI +/- Regorafenib[70]	1 (n=8)	7.3 months	2 months
	2 (n=43)	12.3 months	5.5 months
	3 (n=3)	23.3 months	9.2 months
	4 (n=14)	10.9 months	5.8 months
Estimated Treatment Hazard Ratio: Regorafenib compared to Placebo			
Treatment Regimen	CMS	OS (CI 95%)	PFS (CI 95%)
Regorafenib[71]	1 (n=24)	HR=1.116 (0.290-4.690)	HR=0.850 (0.321-2.252)
	2 (n=140)	HR=0.779 (0.486-1.249)	HR=0.571 (0.387-0.842)
	3 (n=32)	HR=1.047 (0.399-2.749)	HR=0.287 (0.112-0.737)
	4 (n=85)	HR=0.672 (0.358-1.261)	HR=0.483 (0.286-0.814)

CI confidence interval; HR, hazard ratio; CMS, consensus molecular subtype; mCRC, metastatic colorectal cancer; PFS, progression free survival; OS, overall survival.

3.2.5 Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[71,72,73] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[74] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA 4, ICOS, and BTLA.[75] PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, interferon-γ (IFN-γ) and Bcl-xL. PD-1 expression also been noted to inhibit T cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[76] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a CMV re stimulation assay with human PBMC, the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[77]

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (immunoglobulin G4-S228P) that targets the PD-1 cluster of differentiation 279 cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, PD-L1 and PD-L2, results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary cells and is produced using standard

mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

Nivolumab (OPDIVO^{TM}) is approved for the treatment of several types of cancer in multiple regions including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).

3.2.6 Ipilimumab Mechanism of Action

Ipilimumab (BMS-734016, MDX010, MDX-CTLA4) is a fully human monoclonal immunoglobulin G1 kappa specific for human CTLA-4 (CD152), which is expressed on a subset of activated T cells. CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody (mAb) that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor-infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell (Treg) function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor response.

3.2.7 Nivolumab Combined with Ipilimumab Clinical Activity

Multiple clinical studies have evaluated nivolumab combined with ipilimumab at different doses and schedules. Based on Phase 3 data showing improved survival over standard of care therapies, nivolumab combined with ipilimumab has been approved in multiple countries for the treatment of patients with chemotherapy-naïve advanced nonsmall cell lung cancer (NSCLC), unresectable or metastatic melanoma, intermediate or poor risk, previously untreated advanced renal cell carcinoma (RCC), and microsatellite instability-high or mismatch repair deficient colorectal cancer. Details of the clinical activity in these various malignancies are provided in the United States Package Insert (USPI) and Summary of Product Characteristics (SmPC).

3.2.7.1 CA209012 in NSCLC

CA209012 was a multi-arm Phase 1b trial evaluating the safety and tolerability of nivolumab in patients with chemotherapy-naïve advanced NSCLC, as either a monotherapy or in combination with other agents including ipilimumab, at different doses and schedules. The primary endpoint of the study was safety with secondary endpoints of objective response rate (ORR) per RECIST 1.1 and 24-week progression-free survival (PFS). Participants were assigned to receive nivolumab 3 mg/kg Q2W + ipilimumab 1mg/kg Q12W (n=38), nivolumab 3mg/kg Q2W + ipilimumab 1 mg/kg Q6W (n=39) and nivolumab 3mg/kg Q2W (n=52). The confirmed ORR was 47% (N3 q2w + I1 q12w), 39% (N3 q2w + I1q6w) and 23% (N3 Q2W). The median duration of response (DOR) was not reached in any of these groups.

The rate of treatment-related adverse events (AEs) in the Q12W (82%) and Q6W (72%) arms were comparable to monotherapy (72%). In the study, Grade 3/4 adverse events were 37%, 33%, and 19% for the Q12W, Q6W, and nivolumab monotherapy arms, respectively. Treatment-related Grade 3-4 AEs led to discontinuation in 5% and 8% of participants in the Q12W and Q6W cohorts, respectively, and were similar to nivolumab monotherapy. There were no treatment-related deaths. The treatment-related select AEs in patients administered the optimized dosing schedule (3 mg/kg

of nivolumab Q2W plus 1 mg/kg of ipilimumab Q6W) were skin related (36%), gastrointestinal (23%), endocrine (20%), and pulmonary (5%) and there were ≤ 5% treatment related Grade 3 and Grade 4 AEs per category.[89]

3.2.7.2 CA209016 in mRCC

The combination of nivolumab with ipilimumab is being studied in the Phase 1 study CA209016. Subjects with metastatic RCC (mRCC) (Karnofsky performance status ≥ 80%; untreated or any number of prior therapies) were randomized to receive nivolumab 3 mg/kg + ipilimumab 1 mg/kg (arm N3 + I1) or nivolumab 1 mg/kg + ipilimumab 3 mg/kg (arm N1 + I3) IV Q3W for 4 doses followed by nivolumab 3 mg/kg IV Q2W until progression/toxicity. The primary objective was to assess safety/tolerability; secondary objective was to assess antitumor activity.

Subjects were randomized to N3 + I1 (n = 47) and N1 + I3 (n = 47). Approximately half (n = 46; 51%) had prior systemic therapy (N3 + I1: 22; N1 + I3: 26).

After a median follow-up of 22.3 months, the confirmed ORR per RECIST 1.1 was 40.4% (N = 47) in both Arms N3 + I1 and N1 + I3; 42.1% (n = 8) and 36.8% (n = 7) had an ongoing response, with a median DOR of 88.7 weeks (95% CI: 37.14, NA) and 85.9 weeks (95% CI: 35.14, NA), respectively. Median PFS was 7.7 months (95% CI: 3.71, 14.29) and 9.4 months (95% CI: 5.62, 18.63) in Arms N3 + I1 and N1 + I3, respectively. OS at 12 months was 80.9% and 85.0% in Arms N3 + I1 and N1 + I3, respectively, and at 24 months was 67.3% and 69.6%, respectively.

The safety of nivolumab combined with ipilimumab was assessed in study CA209016. Treatment-related AEs were seen in 88/94 pts (94%), including 43/47 (92%) in N3 + I1 and 45/47 (96%) in N1 + I3.–The most frequently reported drug-related AEs in N3 + I1 included fatigue (66%), cough (53.2%), and arthralgia (51.1%); the majority were Grade 1- 2. The most frequently reported drug-related AEs in N1 + I3 included fatigue (74.5%), nausea (55.3%), and diarrhea (53.2%). The majority were Grade 1-2.

Treatment-related AEs leading to discontinuation (31.9% versus 10.6%), and treatment-related serious adverse events (SAEs) (34% versus 23.4%) occurred more commonly in subjects in the N1 + I3 arm than in the N3 + I1 arm, respectively.[78]

3.2.7.3 CA209004 in Melanoma

In the Phase 1 study CA209004, ascending doses of nivolumab have been studied concomitantly with ascending doses of ipilimumab in participants with unresectable or metastatic melanoma. In each arm in this multi-arm study, ipilimumab was administered once every 3 weeks for 4 doses with nivolumab administered once every 3 weeks for 8 doses. Starting at week 24, ipilimumab and nivolumab were administered once every 12 weeks for 8 doses. The three initial dose-escalation cohorts consisted of Cohort 1 (nivolumab 0.3 mg/kg plus ipilimumab 3 mg/kg; n = 14), Cohort 2 (nivolumab 1.0 g/kg plus ipilimumab 3 mg/kg; n = 17) and Cohort 3 (nivolumab 3.0 mg/kg plus ipilimumab 3 mg/kg; n = 6). Later, the study was amended to include Cohort 2a which evaluated nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n = 16). The primary objective was to assess safety/tolerability; the secondary objective was to assess preliminary efficacy.

Of the 52 subjects evaluable for response as of the 15-Feb-2013 clinical cut-off in CA209004, of the 52 participants evaluable for response, 21 participants (40%) had an objective response by modified World Health Organization (mWHO) criteria. In an additional 2 participants (4%) there was an unconfirmed objective response. In Cohort 1 (0.1 mg/kg nivolumab + 3 mg/kg ipilimumab), 3 out of 14 evaluable participants had an objective response by mWHO (21%); 1 CR and 2 PRs with an additional PR by immune-related mWHO criteria (irPR).[80] In Cohort 2 (1 mg/kg nivolumab + 3 mg/kg ipilimumab), 9 out of 17 evaluable participants had an objective response by mWHO (53%; 3 CRs (18%), 6 PRs (35%) with two additional participants experiencing immune-related SD (irSD). In Cohort 2a (3 mg/kg nivolumab + 1 mg/kg ipilimumab), 6 out of 15 response evaluable participants had an objective response rate by mWHO (40%; 1 CR (7%), 5 PRs (33%) with 2 additional uPRs (13%) and 2 irSDs and 1 irPR). In Cohort 3 (3 mg/kg nivolumab + 3 mg/kg ipilimumab), 3 out of 6 evaluable participants had an objective response by mWHO (50%;3 PRs (50%) with 1 additional irPR and 1 irSD.

Preliminary analysis revealed 16 of the 52 evaluable participants (31%) had > 80% reduction in the size of target tumor lesions by the week 12 evaluation. This is compared to < 2% for 3 mg/kg ipilimumab monotherapy based on CA184020 (N = 540) and < 3% for nivolumab monotherapy based on CA209003 (N = 94, 0.1-10 mg/kg).

The following dose-limiting toxicities (DLTs) were observed in Cohort 1 - Grade 3 elevated AST/ALT (1 participant); in Cohort 2 - Grade 3 uveitis (1 participant) and Grade 3 elevated AST/ALT (1 participant) and in Cohort 3 - Grade 4 elevated lipase (2 participants) and Grade 3 elevated lipase (1 participant). Based on these data, Cohort 2 was identified as the maximum tolerated dose (MTD) and Cohort 3 exceeded the MTD.

A total of 53 melanoma participants were treated with nivolumab combined with ipilimumab in CA209004 across Cohorts 1, 2, 2a, and 3. At least one AE regardless of causality has been reported in 98% of participants treated. The most common (reported at > 10% incidence) treatment related AEs (any Grade %; Grade 3-4 %: 93; 53) are rash (55; 4), pruritus (47; 0), vitiligo (11; 0), fatigue (38; 0), pyrexia (21, 0), diarrhea (34; 6), nausea (21, 0), vomiting (11, 2), ALT increased (21; 11), AST increased (21; 13), lipase increased (19; 13), amylase increased (15, 6), headache (11, 0), and cough (13, 0).

The majority of AEs leading to discontinuation (regardless of causality) were Grade 3 or 4 (reported in 11 of 53 participants, 21%). Grade 3 events included lipase increased, ALT increased, AST increased, troponin I increased, colitis, diverticular perforation, pancreatitis, tachycardia, renal failure acute, choroiditis, autoimmune disorder, and pneumonitis. One participant each discontinued due to Grade 4 events of blood creatinine increased and AST increased. No drug-related deaths were reported.[79, 80]

3.2.8 Trametinib Mechanism of Action and Clinical Activity

Trametinib (Mekinist®) is a reversible and highly selective allosteric inhibitor of MEK1 and MEK2. MEK proteins are critical components of the MAPK pathway which is commonly hyperactivated in tumor cells. Oncogenic mutations in both BRAF and RAS signal through MEK1 or MEK2. Trametinib was first approved by the FDA on 2013 as a single-agent oral treatment for

unresectable or metastatic melanoma in adult patients with *BRAF* V600 mutations. Trametinib is currently also approved in the EU, Canada, and Australia and multiple other countries for the treatment of adult patients with unresectable or metastatic melanoma. The recommended dose of trametinib is 2 mg once daily (QD). Trametinib in combination with the BRAF inhibitor, dabrafenib, was first approved by the FDA in 2014 to treat unresectable or metastatic melanoma in adult patients with *BRAF* V600 mutations. The combination therapy is currently also approved in the EU, Australia, Chile, Canada, and multiple other countries.

Trametinib monotherapy has demonstrated a manageable safety profile in > 700 patients across all clinical trials. Across all completed studies for trametinib at the recommended dose of 2 mg daily, the most common AEs were rash, diarrhea, fatigue, edema peripheral, nausea, dermatitis acneiform, vomiting, constipation, anemia, pruritus, alopecia, hypertension, decreased appetite, dyspnea and dry skin. For more details, please refer to the most current trametinib Investigator's Brochure and the approved product information.

3.2.9 Nivolumab Monotherapy and Nivolumab and Ipilimumab Combination Therapy

Extensive details on the safety profile of nivolumab are available in the Investigator Brochure,[81] and will not be repeated herein.

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

A pattern of immune-related adverse events has been defined, for which management algorithms have been developed; these are provided in Appendix 5. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab IB.

The combination of nivolumab and ipilimumab has demonstrated increased benefit compared to both ipilimumab monotherapy and nivolumab monotherapy. The deep anti-tumor response observed in study CA209004 is described in Section 3.2.7 and is the basis for an ongoing randomized phase 3 study in advanced melanoma (CA209067). In Study CA209142, 55% of the participants with recurrent or metastatic MSI-H CRC treated with nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg Q3W had objective response. Seventy-nine percent (79%) of participants achieved disease control for ≥ 12 weeks. This durable and sustained response compares favorably to results with 3 mg/kg Q2W nivolumab monotherapy (Study CA209142).[82] Studies investigating the efficacy and safety of nivolumab in combination with ipilimumab are ongoing in NSCLC, RCC, and CRC.

The combination of nivolumab and ipilimumab has the potential for increased frequencies of adverse events compared to ipilimumab monotherapy or nivolumab monotherapy. The most common (reported at > 10% incidence) treatment related AEs are fatigue, rash, pruritus, diarrhea, lipase increased, pyrexia, ALT increase, AST increased, amylase increased and vitiligo. This class of AEs are expected for the combination of nivolumab and ipilimumab based on the known AE profile of each drug alone. In addition, many of the Grade 3-4 adverse events were laboratory in nature (ie, LFTs, lipase, amylase), were without clinical sequelae and have been manageable and reversible following intervention dose delays or with systemic steroid treatment. However, these AEs have the potential to be fatal if not detected early and managed per the established algorithm and fatal AEs have been reported for both ipilimumab and nivolumab monotherapy. Adverse drug reactions with fatal outcome in clinical trial participants treated with nivolumab monotherapy and nivolumab and ipilimumab combination therapy are listed in the current version of the nivolumab IB.[81]

3.3 Overall Benefit/Risk Assessment

Despite several therapies available for the treatment of mCRC, the incremental benefit of these treatments after treatment with a 1L regimen is small, as discussed in Section 3.2.1, and represents an area of unmet medical need.

The safety profiles of all agents proposed for the doublet and triplet combination are well defined as either monotherapy or in combination and the products are already commercially available for the treatment of several advanced and metastatic tumor types. The safety profile of the combination of nivolumab with ipilimumab (3 mg/kg) is well characterized and it is approved for treatment of unresectable or metastatic melanoma.[83] The toxicity profile of the nivolumab + ipilimumab combination has been shown to correlate with the ipilimumab dose: with increasing doses of ipilimumab, there has been an increase in frequency of adverse events and, potentially, the severity of these events; however, no novel toxicities have been demonstrated versus either agent alone.[84, 85, 86, 87, 88] In the current regimen for this protocol, the dose of ipilimumab will be cumulatively lower than the approved dose level for the combination for the treatment of advanced and metastatic melanoma. The toxicity profile with lower doses of ipilimumab has been established to be very similar to that of nivolumab monotherapy.[89]

Some potential overlapping toxicities are expected in the doublet (nivolumab + trametinib) and triplet (nivolumab + ipilimumab + trametinib) combination regimens, including, but not limited to, dermatologic toxicities, mucositis, pneumonitis, diarrhea, hepatitis/LFT elevation. For adverse events that may be related to both nivolumab and/or ipilimumab and trametinib, both Management Algorithms for nivolumab and ipilimumab (Appendix 5) AND trametinib Dose Modification guideline (Appendix 6) need to be carefully reviewed and followed. Where toxicity management guidelines differ between the two, the most stringent/conservative guideline should be followed.

Nivolumab in combination with ipilimumab has demonstrated efficacy in multiple tumor types including MSI-H CRC, as presented in Table 3.3.1-1. Recent clinical trials have also shown that PD-(L)1 inhibition in combination with CTLA-4 inhibition has led to improved survival in MSS

CRC.[10] Based on current pre-clinical and clinical data, there is scientific rationale (Section 3.1.2) to support the theory that a triplet combination of PD-(L)1 inhibition with CTLA-4 and MEK inhibition will elicit an improved immunomodulatory effect and improved clinical outcomes in MSS CRC.

3.3.1 Summary of Safety and Efficacy in Relevant Clinical Trials

Table 3.3.1-1 below summarizes the high level safety and efficacy data in some relevant clinical trials with nivolumab and ipilimumab in combination therapy, and trametinib in monotherapy. Study with cobimetinib and atezolizumab in combination therapy is also included for reference.

Table 3.3.1-1: Summary of Safety and Efficacy in Relevant Clinical Trials

Study	Treatment	Efficacy (n. of participants)	Safety (n. of participants)	Reference
CA209142 in MSI-H CRC	N3 + I1 Q3W (4 doses) then N3 Q2W	ORR: 46% DCR ≥ 12 weeks:66% DOR: Not Reached (n=84)	TRAE: 57% Grade 3/4 TRAE: 24% TRAE leading to discontinuation: 11%	Andre et al. J Clin Oncol 35, 2017 (suppl; abstr 3531)
CA209012 in NSCLC	N3 Q2W+ I1 Q12W	ORR: 47%; DOR: Not Reached (n=38)	TRAE: 82% Grade 3/4: 37% TRAE leading to discontinuation: 5% (n=38)	Nivolumab IB (v24Jun2016)
	N3 Q2W+ I1 Q6W	ORR: 39% DOR: Not Reached (n=39)	TRAE: 72% Grade 3/4: 33% TRAE leading to discontinuation: 8% (n=39)	
	N3 Q2W	ORR: 23% DOR: Not Reached (n=52)	TRAE: 72% Grade 3/4: 19% TRAE leading to discontinuation: similar to combo (n=52)	
CA209016 in mRCC	N3+I1 Q3W then N3 Q2W	ORR: 43% DOR: 4.1+ to 42.1+ weeks (n=21)	TRAE: 83% TRAE leading to discontinuation: 21% (n=47)	Nivolumab IB (v24Jun2016)
	N1+I3 Q3W then N3 Q2W	ORR: 48% DOR: 12.1+ to 35.1 weeks (n=23)	TRAE: 94% TRAE leading to discontinuation: 11% (n=47)	
CA209004 in Melanoma	N0.3 Q3W + I3 Q3W then Q12W	ORR: 21% (n=14)	TEAE: 98%	Nivolumab IB (v24Jun2016)

Table 3.3.1-1: Summary of Safety and Efficacy in Relevant Clinical Trials

Study	Treatment	Efficacy (n. of participants)	Safety (n. of participants)	Reference
	N1 Q3W + I3 Q3W then Q12W	ORR: 53% (n=17)	>30% incidence (all grade; grade 3-4): rash (55%; 4%), pruritus (47%; 0), fatigue (38%; 0), diarrhea (34%; 6) (n=53)	
	N3 Q3W + I1 Q3W then Q12W--- MTD	ORR: 40% (n=16)		
	N3 Q3W + I3 Q3W then Q12W --- Exceeded MTD	ORR: 50% (n=6)		
Melanoma (BRAF-Mutated)	Trame 2mg QD	ORR: 22% DOR: 5.5 mon (n=214)	TEAE: >99% >30% incidence (all grade; grade 3-4): rash (57%; 8%), diarrhea (43%, 0%) (n=211)	Flaherty et al., N Engl J Med. 2012;367:107–14.
Melanoma (BRAF-Mutated, previously treated)	Trame 2mg QD	BRAF inhibitor previously treated: ORR: 0%; DCR: 28% (n=40) BRAF inhibitor naive: ORR: 25%; DCR: 75% (n=57)	TRAE: 97% Grade 3/4: 27% >30% incidence (all grade; grade 3): rash/dermatitis acneiform (75%; 9%), diarrhea (52%, 4%) (n=97)	Kim et al. J Clin Oncol. 2013;31(4):482-9.
IMBlaze 370 mCRC 3rd line and above (up to 5% MSI-H)	Cobi 60mg (21 days on/7 days off) +atezo 840mg Q2W	Median OS: 8.87 months - HR vs regorafenib: 1.00 (95% CI 0.73-1.38) Median PFS: 1.91 months-HR vs regorafenib: 1.25 (95% CI 0.94-1.65) ORR: 3% DCR: 26%	TRAE: 100% Grade 3/4 TRAE: 39% AEs leading to discontinuation: 17% (cobi only)	Eng et al., Lancet Oncol 2019; 20:849-61
CCTG CO.26 Trial: Advanced mCRC (3L+)	Durvalumab 1500 mg Q4W + tremelimumab Q4W (For 4 Cycles)	Median OS: 6.6 months – HR vs BSC: 0.72; (90% CI, 0.54-0.97; p=.07) HR vs BSC in MSS mCRC: 0.66 (CI 90%, 0.48-0.89, p=0.02) Median PFS: 1.8 months – HR vs. BSC:	TRAE: 100% Grade 3 / 4 TRAE: 64%	Chen et al., JAMA Oncol. 2020 Jun; 6(6): 831-838.

Table 3.3.1-1: Summary of Safety and Efficacy in Relevant Clinical Trials

Study	Treatment	Efficacy (n. of participants)	Safety (n. of participants)	Reference
		1.01 (90% CI, 0.76-1.34)		

Abbreviations: AE, adverse event; atezo: atezolizumab; BSC, best supportive care; CCTG, Canadian Cancer Trials Group; CI, confidence interval; cobi: cobimetinib; CRC, colorectal cancer; DCR, disease control rate; DOR, duration of response; HR, hazard ratio; I, ipilimumab; IB, Investigator's Brochure; I1, ipilimumab 1 mg/kg; mCRC, I3, ipilimumab 3 mg/kg; metastatic colorectal cancer; mRCC, metastatic renal cell carcinoma; MSI-H, microsatellite instability high; MSS, microsatellite stable; MTD, maximum tolerated dose; N, nivolumab; N0.3, nivolumab 0.3 mg/kg; N3, nivolumab 3 mg/kg; NSCLC, nonsmall cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; Q6W, every 6 weeks; Q13W, every 13 weeks; QD, once daily; TEAE, treatment-emergent adverse event; TRAE, treatment related adverse event; trame, trametinib; 3L(+): 3rd line (plus).

3.3.2 Safety Monitoring on Study Treatment

The following safety measures have been employed to ensure safety of the participants in this current study:

- A 3+3 design was used to evaluate safety and dose limiting toxicities (DLT) in both doublet and triplet regimens. Safety/DLT evaluation phase was performed to determine the recommended Phase 2 dose (RP2D) for metastatic CRC.
- Intense toxicity monitoring for dose optimization cohorts will help to ensure the participant safety, including frequent safety conference calls with investigators and representatives of the sponsor and collaborator (as needed).
- A BMS medical safety team (MST) routinely reviews safety signals across the entire nivolumab program, including all ongoing combinations with ipilimumab or other agents like MEK-inhibitor that are applicable for this study.

In summary, safety evaluations will be carried out by the Sponsor/BMS Medical Monitor (or designee) and investigators throughout the study to determine whether dose modification, additional safety measures, or termination of the study treatment combination is required at any time. Treatment of AEs will follow institutional guidelines and local prescribing information as applicable. Study specific toxicity management guidelines include investigator brochures for each study treatment component,[90,91] and dose modification and discontinuation guidelines as stated in protocol Sections 7.4 and 8.1, and Appendix 5 and Appendix 6. The most stringent toxicity management must be applied in cases where the study specific guideline and local treatment guideline differ.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints: Parts 1 and 1A

Objectives	Endpoints
Primary	
• To characterize the safety and tolerability of combination therapies	• DLTs in Part 1 and Part 1A, only, observed for 1 treatment cycle (4 weeks for the doublet regimen and 8 weeks for the triplet regimen)
• To establish recommended dosing regimen for the combination (nivolumab plus ipilimumab plus trametinib OR nivolumab plus trametinib)	• Safety (including but not limited to): AEs, SAEs, deaths, and clinical laboratory abnormalities per CTCAE (version 4.0)
Secondary	
• To evaluate preliminary efficacy	• ORR DCR, DOR, TTR, and PFS by investigator per RECIST v1.1 • OS
[redacted]	

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DLTs, dose limiting toxicities; DOR, duration of response; [redacted]; ORR, objective response rate; OS, overall survival; PFS, progression free survival; [redacted]; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; TTR, time to response.

Table 4-2: Objectives and Endpoints: Parts 1B and 2

Objectives	Endpoints
Primary	
• To evaluate the ORR in all participants treated with nivolumab plus ipilimumab and trametinib in the 2L and 3L+[a] setting (Parts 1B and 2, respectively) and regorafenib in 3L+[a] (Part 2 only)	• ORR by investigator [b]
Secondary	
• To evaluate efficacy in all participants treated with nivolumab plus ipilimumab and trametinib in the 2L and 3L+[a] setting (Parts 1B and 2, respectively); and regorafenib in 3L+[a] (Part 2 only) [redacted]	• BOR, DCR, DOR, TTR, and PFS by investigator[b] • OS
• To characterize the safety and tolerability of combination therapies	• Safety (including but not limited to): AEs, SAEs, deaths, and clinical laboratory abnormalities per CTCAE (version 4.0)

[redacted]

Table 4-2: Objectives and Endpoints: Parts 1B and 2

Objectives	Endpoints
[redacted]	

AE, adverse event; [redacted], BOR, best overall response; [redacted]; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate;; DOR, duration of response; [redacted]; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PFS2, time to second objective disease progression; [redacted]; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; TTR, time to response; [redacted]; 2L, second line; 3L+, third line plus.

[a] No more than 4 prior lines of therapy

[b] Per RECIST v1.1

5 STUDY DESIGN

5.1 Overall Design

This is a Phase 1/2 open-label, multi-center trial of nivolumab in combination with trametinib, with or without ipilimumab, to evaluate the safety profile and clinical activity of these regimens in participants with metastatic colorectal cancer (mCRC).

Participants were dosed in the dose optimization phases of the study (Parts 1 and 1A) with either the doublet (nivolumab + trametinib) or triplet (nivolumab + ipilimumab + trametinib) regimen. Decisions regarding dosages of trametinib to be used in Parts 1B and 2 were based on observed safety and efficacy signals in Parts 1A and 1. The recommended Phase 2 dose was determined to be the triplet regimen for Parts 1b and 2 (nivolumab 6 mg/kg Q4W + ipilimumab 1 mg/kg Q8W + trametinib 1.5 mg continuous QD). Assessment of the preliminary benefit/risk based on the safety and efficacy profile for the doublet and triplet regimens used in the non-randomized parts of the study was reviewed along with additional emerging safety and efficacy data from other relevant trials to determine the optimal dose of trametinib to be used in Part 2 and Part 1B in combination with nivolumab and ipilimumab (Figure 5.1-1). Participants in each part of the study will be treated until progression, unacceptable toxicity, withdrawal of consent, or a maximum of 2 years. Maximum treatment duration is not applicable to participants receiving SOC therapy in Part 2, Cohort 5, which may be continued until progression of disease or unacceptable toxicity.

Per Protocol Amendment 04, due to early study closure the last participant last treatment (LPLT) date on CA209-9N9 study will occur approximately 9 months after last participant first treatment (LPFT); and last participant last visit (LPLV) date will occur approximately 12 months after LPFT. When this LPLV date is reached, participants follow-up will be ceased, and all participants will complete the study. Any participant still on treatment after LPLT date who continue to demonstrate clinical benefit will be eligible to receive treatment outside of this study in accordance with Protocol Section 7.8. For Cohort 4 and Cohort 6 participants the total maximum duration of treatment will be 2 years, including the treatment duration on CA209-9N9. For participants in Cohort 5, the treatment will be administered as per the local standard of care. In the event alternative means of supplying study treatment as described in Section 7.8 is not accessible, the study may remain open until such means become available or last participant ends treatment and completes follow-up visits 1 and 2 in accordance with Table 2-8, Table 2-9, Table 2-10, and Table 2-11.

In the **initial dose optimization phase of the study,** which is now completed, both the doublet regimen (Part 1, 3L mCRC) and triplet regimen (Part 1A; 2L mCRC) employed "3+3" design for observation of DLT. The dose-limiting toxicities (DLT) observation period was one cycle for both treatment regimens, ie, 4 weeks for the doublet regimen; 8 weeks for the triplet regimen. DLT observations are described in Section 5.1.1.1. Dose optimization phase of the study (Part 1 and Part 1A) has been completed. Enrollment is closed in Part 1 and Part 1A cohorts. No further evaluations of DLT will be conducted.

Participants were allocated to treatment as follows:

- Part 1: Participants with 3L mCRC were assigned to receive doublet therapy as nivolumab 480 mg Q4 week plus trametinib 1.5 mg QD (continuous dosing, Cohort 1 Group)
- Part 1A: Participants with 2L mCRC were assigned to receive the triplet therapy of either:
  - 6 mg/kg nivolumab (Q4W) plus ipilimumab 1 mg/kg (Q8W) plus trametinib 1.5 mg QD (continuous dosing, Cohort 2 Group), OR
  - 6 mg/kg nivolumab (Q4W) plus ipilimumab 1 mg/kg (Q8W) plus trametinib 1.5 mg QD (2 week ON/2 week OFF, Cohort 3 Group)

Only pMMR/MSS participants were enrolled in Part 1 and Part 1A.

Trametinib 1.5 mg QD was the starting dose selected for Cohort 1, 2, and 3 groups. In Part 1, trametinib continuous doing regimen were investigated initially in Cohort 1, with dose de-escalation and escalation scheme built in for trametinib intermittent dosing regimen, 2 week ON/2 week OFF (Cohort 1 Group). In Part 1A, both trametinib continuous dosing and intermittent dosing was investigated initially in two separate Cohort Groups (Cohort 2 Group and Cohort 3 Group). Specifications regarding trametinib dosing in dose optimization phase can be found in Section 5.1.1.

The totality of the safety data was reviewed, and decision on dose escalation, de-escalation or discontinuation of a particular dosing regimen were made by the study team in conjunction with treating physicians and documented accordingly.

- For [redacted] **(Part 1B) phase**, further evaluations of safety and efficacy will be conducted in Part 1B (triplet regimen; 2L pMMR/MSS mCRC) of the study. Participants who have failed 1 prior line of therapy will be allocated to:
  - Part 1B Cohort 6: One cohort will be initiated in Part 1B to further characterize the safety and preliminary efficacy profile of the triplet regimen. Participants with 2L pMMR/MSS mCRC will be assigned to receive: 6 mg/kg nivolumab (Q4W) plus ipilimumab 1 mg/kg (Q8W) plus trametinib 1.5 mg continuous QD (Cohort 6)

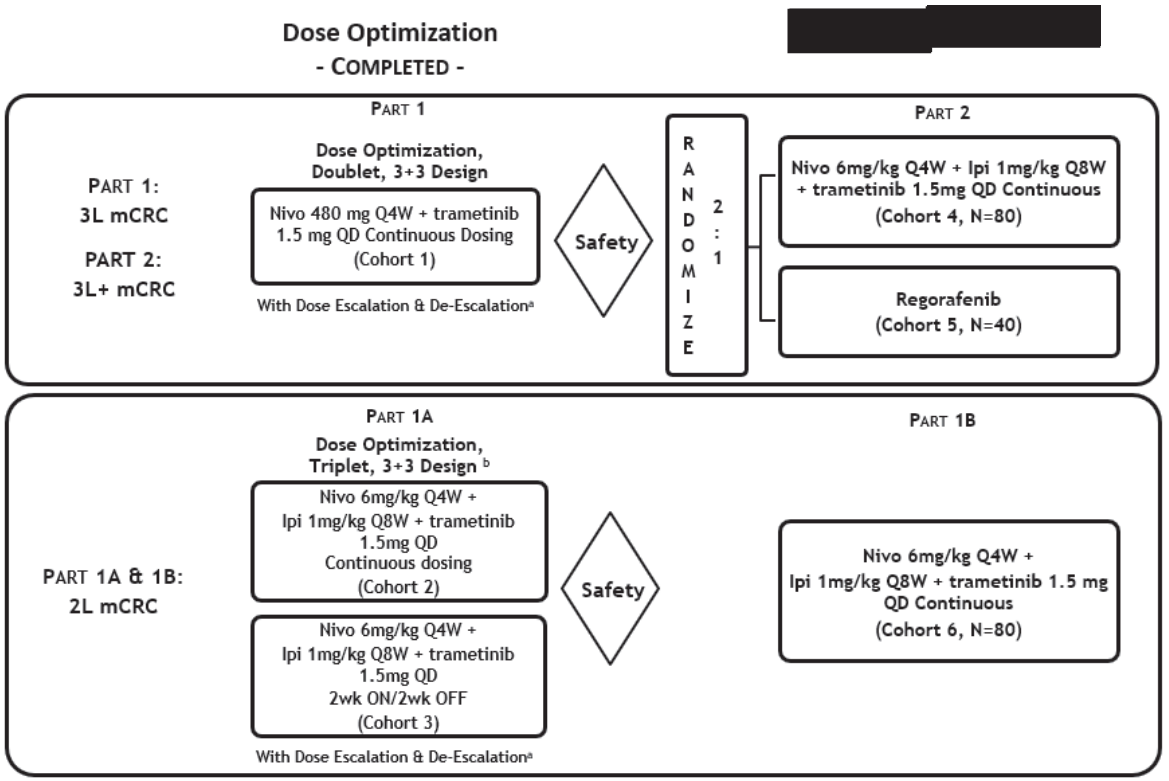
- For [redacted] **(Part 2) phase**, the efficacy and safety of the investigational triplet regimen versus SOC regimen (regorafenib) in 3L+ (no more than 4 prior lines of therapy) pMMR/mCRC will be evaluated in Part 2, the randomized controlled portion of the trial.
  - Participants will be randomized at 2:1 ratio to receive nivolumab 6 mg/kg Q4W plus ipilimumab 1 mg/kg Q8W plus trametinib 1.5 mg continuous QD (Cohort 4), OR regorafenib in the SOC arm (Cohort 5).

For Part 1B (Cohort 6) and Part 2 (Cohorts 4 and 5), the proportion of participants with RAS mutations will be monitored on an ongoing basis. The IRT system will be set up to notify the Sponsor once the pre-defined number of RAS mutant participants have been enrolled. The target will be approximately 65% mutant, 35% wild type. If accrual diverges significantly from this goal, accrual in a cohort may be paused after discussion between the Sponsor and the investigators. Patients with BRAF V600 mutation are not eligible for the study.

Interim analysis will be performed to evaluate preliminary safety and efficacy per Section 10.3.7.

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

Figure 5.1-1: Study Design Schematic



Ipi, ipilimumab; mCRC, metastatic colorectal cancer; MSS, microsatellite stable; Nivo, nivolumab; pMMR, proficient mismatch repair, QD, quaque die, once daily; Q4W, every 4 weeks; Q8W, every 8 weeks; wk, week; 2L, second line; 3L, third line; 3L+, third line plus.

[a] See Table 7.2-1 for unique cohort numbers for dose escalation and de-escalation.

[b] Participants in Part 1A were assigned to each treatment cohort on an alternating basis in IRT (interactive response technology). NOTE: Enrollment is closed in Part 1 and Part 1A cohorts.

NOTE: Participants in each part of the study will be treated until progression, unacceptable toxicity, withdrawal of consent, or a maximum of 2 years. Maximum treatment duration is not applicable to standard of care therapy (regorafenib).

5.1.1 Part 1 and Part 1A: Dose Optimization

The dose optimization phase of the study has completed. Enrollment is closed in all Part 1 and Part 1A cohorts. There will be ongoing safety data review, but no further DLT evaluations.

The DLT observation period will be one cycle for both treatment regimens, i.e., 4 weeks for the doublet regimen (Part 1); 8 weeks for the triplet regimen (Part 1A).

Following 3+3 design in Part 1 (doublet regimen) and Part 1A (triplet regimen), trametinib dosing regimen could be either escalated or de-escalated for the next treatment cohort based on the number of DLT's observed from previous cohort. Table 5.1.1-1 describes dose escalation or de-escalation plan for trametinib as a general rule. However, the totality of the safety data observed, not only the adverse events that meet the DLT definition, will be considered when making decisions for dose escalation or de-escalation. Such decisions will be made and documented in conjunction with treating physicians and collaborator at the end of the DLT observation period.

Table 5.1.1-1: Dose Escalation and De-Escalation Plan Per 3+3 Design

Number of Participants with DLT at a Given Dose Level	Escalation And De-Escalation Plan
0 out of 3, or < 2 out of 6	May Enter 3 additional patients at the next higher dose level.
1 out of 3	Enter 3 additional patients at the same dose level.
2-3 out of 3, or ≥ 2 out of 6	Enter 3 additional patients at the next lower dose level

Part 1 Doublet Regimen, Cohort 1 Group

Trametinib dose levels are detailed below with starting daily dose at 1.5 mg with dose escalation and de-escalation scheme following 3 + 3 design for the doublet regimen (Part 1; Table 5.1.1-2). (See Table 7.2-1 for cohort identification by trametinib dose level)

Table 5.1.1-2: Dose Escalation and De-Escalation for Trametinib ONLY in Part 1 (DOUBLET Regimen [Nivolumab + Trametinib])[a]

Trametinib DOSE LEVEL (DL)	Trametinib plus Nivolumab 480 mg Q4W 1 cycle = 4 weeks
DL+2	2 mg continuous
DL+1	2 mg 2wk on/2wk off[b]
starting	1.5 mg continuous
DL-1	1.5 mg 2 wk on/2 wk off[b]
DL-2	1 mg 2 wk on/2 wk off[b]

[a] No dose de-escalation for nivolumab is permitted. Dose modification for individual participants during DLT observation period is not permitted.

[b] Trametinib is administered on Day 1 through Day 14 of each cycle.

Part 1A Triplet Regimen, Cohort 2 and 3 Groups

Trametinib dose levels are detailed below with starting daily dose at 1.5 mg with dose escalation and de-escalation scheme following 3+3 design for the triplet regimens (Part 1A; Table 5.1.1-3). No dose escalation or de-escalation for nivolumab or ipilimumab is permitted. Participants with 2L mCRC will be assigned to treatment cohorts in Part 1A on an alternating basis in IRT. (See Table 7.2-1 for Cohort identification by trametinib dose level.)

Table 5.1.1-3: Dose Escalation and De-Escalation for Trametinib ONLY in Part 1A (TRIPLET Regimen [Nivolumab + Ipilimumab + Trametinib])[a]

Trametinib DOSE LEVEL (DL)	Trametinib Continuous Dosing Arm NIVO (6 mg/kg) Q4W/ IPI (1mg/kg) Q8W 1 cycle = 8 weeks	Trametinib Intermittent Dosing Arm (2 Week ON/2 week OFF [b]) NIVO (6 mg/kg) Q4W/ IPI (1mg/kg) Q8W 1 cycle = 8 weeks
DL+1	2 mg cont	2 mg 2wk/2wk off
starting	1.5 mg cont	1.5 mg 2wk on/2wk off
DL-1	1 mg cont	1 mg 2wk on/2wk off

cont, continuous; DL, Dose Level.

[a] No dose escalation or de-escalation for nivolumab or ipilimumab is permitted in either arm. Dose modification for individual participants during DLT observation period is not permitted.

[b] Trametinib is administered on Day 1 through Day 14 of each cycle.

Part 1 and Part 1A, All Cohorts: ENROLLMENT CLOSED

All participants will start at the same trametinib dose level and frequency (daily in continuous regimen vs. intermittent regimen) within a particular cohort throughout the first cycle (doublet and triplet regimens). No dose escalation or de-escalation within a particular cohort is permitted once study treatment starts during the first cycle (doublet and triplet regimens) for DLT observation. If participants don't tolerate the study treatment at the pre-specified starting dose during the first cycle/DLT observation period, study treatment must be permanently discontinued*. After the DLT observation period, the daily dose of trametinib may be modified to manage participants' adverse events (see Section 7.4.4). Modification of trametinib dosing frequency is not permitted throughout treatment duration, except dosing delay per dose modification guidelines (Appendix 6).

Toxicities will be considered DLTs only if they occur in Cycle 1 for the doublet and triplet regimens. Participants are required to complete Cycle 1 (≥ 50% of the planned cumulative dose) to be considered evaluable unless discontinuation occurred due to a DLT.

DLTs are specified in Section 5.1.1.1 below.

*Under rare circumstances, participants may resume study treatment at a lower dose level for trametinib if deemed medically appropriate by investigators. BMS Medical Monitor or designee

should be consulted before resuming study treatment. Dose modification should be approved by BMS on a case by case basis (refer to Sections 7.4 and 8). Participants will be analyzed based on initial cohort assignment regardless of dose modification received.

Part 1B and Part 2: ENROLLMENT CLOSED

Per Revised Protocol 02, Part 2 ([redacted] phase for triplet regimen including SOC arm) and Part 1B ([redacted] for triplet regimen) will be initiated based on the totality of safety data observed from this study and relevant ongoing clinical studies. The observed benefit/risk profile from Part 1 and 1A has determined a recommended Phase 2 dose to be the triplet regimen of nivolumab 6 mg/kg Q4W + ipilimumab 1 mg/kg Q8W + trametinib 1.5 mg continuous QD. There will be ongoing safety data review, but no further DLT evaluations.

5.1.1.1 Dose Limiting Toxicity

As Part 1 and Part 1A are completed, there will be ongoing safety data review, but no further DLT evaluations.

For the purpose of guiding dose regimen, DLTs will be defined based on the incidence, duration and grade of AEs for which no alternate cause can be identified. Adverse events will be evaluated according to the NCI CTCAE (version 4.0). DLT(s) during the first cycle of treatment (the DLT evaluation period) will be observed for the first 4 weeks for the doublet regimen and first 8 weeks for the triplet regimen. Every attempt must be made to assign relationship to the individual study treatment, if possible, or to the combination regimen, nivolumab/ipilimumab/trametinib combination or nivolumab/trametinib combination. To meet criteria for dose limiting toxicity, adverse events have to be at least possibly related to study treatment, and not to disease progression, be clinically relevant and a clinically relevant shift from baseline.

Participants who withdraw from the study during the DLT evaluation interval for reasons other than a DLT may be replaced at the same dose of the study treatment.

Dose limiting toxicities can include the following adverse events (meeting the preceding criteria):

1) **Hepatic DLT**
   a) Any of the following events will be considered a hepatic DLT (Note that this special category of DLT uses ULN rather than Common Toxicity Criteria Grade for definition.):
      i) For participants with normal baseline AST and ALT values: AST or ALT > 8× ULN
      ii) For participants with normal baseline Total bilirubin (TBIL) value: TBIL > 5× ULN
      iii) For participants with normal baseline AST and ALT and normal baseline bilirubin values: AST or ALT > 3× ULN and concurrent total bilirubin > 2× ULN without initial findings of cholestasis (elevated serum alkaline phosphatase ≥ 2× ULN) or other reasons to explain the combination of increased aminotransferases and TBIL
      iv) For participants with abnormal baseline AST or ALT or abnormal baseline bilirubin values: [AST or ALT > 2× baseline AND >8× ULN], combined with [TBIL > 2× baseline AND > 2× ULN] without initial findings of cholestasis (elevated serum alkaline phosphatase ≥ 2× ULN) or other reasons to explain the combination of increased aminotransferases and TB,

2) Nonhepatic Nonhematologic DLT

a) Any of the following events will be considered a nonhepatic nonhematologic DLT:

i) Grade 2 ocular toxicities, including episcleritis, uveitis, iritis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment

ii) Any clinical evidence of congestive heart failure or ≥ Grade 3 cardiac event that is symptomatic or requires medical intervention

iii) Grade 3 pneumonitis, bronchospasm, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction

iv) Grade 3 hypertension if it persists > 7 days despite optimal anti-hypertensive treatment or grade 4 hypertension of any duration

v) Any Grade 3 or greater nondermatologic, nonhepatic, nonhematologic toxicity will be considered a DLT with the following specific EXCEPTIONS:

(1) Grade 3 electrolyte or laboratory abnormalities that are not complicated by associated clinical adverse experiences, last less than 48 hours, and either resolve spontaneously or respond to conventional medical intervention. The maximum allowable time limit for correction of electrolyte abnormalities to ≤ Grade 1 is 72 hr.

(2) Grade 3 nausea, vomiting, or diarrhea that lasts less than 48 hours and either resolves spontaneously or responds to medical intervention.

(3) Isolated Grade 3 or Grade 4 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis

(4) Isolated Grade 3 fever not associated with hemodynamic compromise (eg, hypotension, clinical or laboratory evidence of impaired end-organ perfusion).

(5) Grade 3 endocrinopathy that is well-controlled by hormone replacement

(6) Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to site of known or suspected tumor)

(7) Grade 3 fatigue

(8) Grade 3 infusion reaction that returns to Grade 1 in less than 6 hours

3) Dermatologic DLT

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

b) Grade 4 rash of any duration

4) Hematologic DLT

a) Grade 4 neutropenia ≥ 7 consecutive days in duration

b) Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding, or any requirement for platelet transfusion

c) Grade 4 anemia not explained by underlying disease

d) Grade ≥ 3 febrile neutropenia for 48 hours

e) Grade ≥ 3 hemolysis (ie, requiring transfusion or medical intervention such as steroids) or any clinically relevant hemolysis as follows:
   i) Any clinically meaningful laboratory evidence of hemolysis and Grade 2 creatinine elevation
   ii) Any clinically meaningful laboratory evidence of hemolysis and Grade 3 thrombocytopenia
   iii) Any clinically meaningful laboratory evidence of hemolysis with more than a 3gm/dL drop in hemoglobin (or CTCAE hemoglobin level ≥ Grade 3).

5) Any toxicity requiring dose delay of study treatment during cycle 1 resulting in:
   a) Delay of > 4 weeks in initiating Cycle 2
   b) Participant receives less than 50% of intended total dose of any study drug treatment
   c) Participant only receives one dose of nivolumab in the triplet regimen

5.1.1.2 Toxicity Management during DLT Observation

Optimal medical management must be implemented for all participants in this study, including the DLT observation phase in Part 1 and Part 1A. As Part 1 and Part 1A are completed, there will be ongoing safety data review, but no further DLT evaluations.

Adequate patient education and frequent follow-up with participants by investigator site staff must be performed to manage treatment emergent toxicities. Refer to Section 3.3.2 for AE management guidelines. Prophylaxis/prevention measures relating to trametinib related skin toxicities and diarrhea are described below and in Appendix 6:

- Rash: Rash prophylaxis/prevention is recommended for the first 6 weeks of study treatment with trametinib. Participants who develop rash/skin toxicities should be seen by a qualified physician and should receive evaluation for symptomatic/supportive care management.
- Diarrhea: Loperamide or other anti-diarrheal treatment should be accessible prior to start of study treatment with trametinib so loperamide or other anti-diarrheal administration can begin at the first signs of diarrhea, if clinically indicated.

5.1.2 Part 1B: [redacted] The Triplet Regimen

Preliminary safety, efficacy, [redacted] data from Parts 1 and 1A were analyzed in a predetermined interim analysis to select the optimal dosing regimen of nivolumab 6 m/kg Q4W plus ipilimumab 1 mg/kg Q8W plus trametinib 1.5 mg continuous QD for Part 1B. Approximately 80 participants (Cohort 6) will be treated in Part 1B to further assess the safety and preliminary efficacy of the combination regimen. The totality of the safety data and preliminary efficacy data from Part 1B will be reviewed on an ongoing basis.

5.1.3 Part 2: [redacted] the Triplet Regimen and Standard of Care Arm

Preliminary safety, efficacy, [redacted] data from Part 1 and Part 1A were analyzed in a predetermined interim analysis to determine the optimal regimen for Part 2. Part 2 of the study for

the triplet regimen will consist of 1 cohort (Cohort 4) to investigate the safety and clinical activity of nivolumab 6 mg/kg Q4W plus ipilimumab 1 mg/kg Q8W plus trametinib 1.5 mg continuous QD. A SOC arm with regorafenib will also be initiated (Cohort 5). Participants will be randomized according to a 2:1 ratio (approximately 80 participants to receive the triplet regimen and 40 participants to receive the SOC therapy, regorafenib).

Participants who have failed at least 2 prior lines of therapy (no more than 4 prior lines) will be randomized to receive the triplet regimen OR regorafenib. No crossover will be permitted between the 2 treatment arms upon discontinuation of study treatment.

5.1.4 Data Monitoring Committee and Other External Committees

A data monitoring committee (DMC) will not be utilized for this Phase 1/2 study.

5.1.4.1 Blinded Independent Central Review

A blinded independent central review (BICR) may be utilized in Part 2 and Part 1B of this study [redacted]. Details of BICR procedures will be specified in a BICR Charter. Refer to Section 9.1.1 Imaging Assessment for the Study for further details.

5.2 Number of Participants

Part 1 and Part 1A followed a 3+3 design, with potential dose escalation and de-escalation based on DLT observations, with intention to treat up to approximately 18 and 24 participants, respectively. Part 1 and Part 1A (dose optimization phase) have completed. Part 1B, will treat approximately 80 participants. Part 2 will randomize approximately 120 participants into 2 arms (nivolumab + ipilimumab + trametinib and regorafenib) in a 2:1 ratio. See Section 10.1 for sample size determination.

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) for the last participant. Study completion is defined as the final date on which data for the primary endpoint is expected to be collected.

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for 2 year treatment duration for Immunotherapy (Nivolumab + Ipilimumab)

The optimal duration of immunotherapy is an important question and continues to be investigated. Clinical trials across different tumor types in the nivolumab and ipilimumab development program indicate that most of the responses occur early, with a median time to response of 2 to 4 months, and emerging data suggests that benefit can be maintained in the absence of continued treatment. A recent analysis in a melanoma study suggests the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment.[92] Furthermore, a limited duration of ipilimumab (at doses up to 10 mg/kg), including

only 4 induction doses, resulted in long term survival in patients with metastatic melanoma, with a sustained plateau in survival starting around 2 years after the start of treatment.[93]

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long term benefit. CA209-003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with previously treated advanced solid tumors (including 129 subjects with NSCLC), specified a maximum treatment duration of 2 years. Among 16 subjects with NSCLC who discontinued nivolumab after completing 2 years of treatment, 12 subjects were alive > 5 years and remained progression-free without any subsequent therapy. In the CA209-003 NSCLC cohort, the OS curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years.[94] These survival outcomes are similar to Phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2 year OS rates of 23% and 29%, and 3 year OS rates of 16% to 18% for squamous and non-squamous NSCLC, respectively).[95]

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

In contrast, a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated patients with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153, patients with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 patients still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in progression-free survival (PFS) compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached vs 10.3 months, respectively; HR = 0.42 (95% CI, 0.25 to 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for patients on continued treatment to live longer (OS HR = 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (ie, 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years.[96]

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

For these reasons, in study CA2099N9, nivolumab and ipilimumab treatment will be given for up to 2 years in the absence of disease progression or unacceptable toxicity for the doublet and triplet regimens. There is no maximum treatment duration for the SOC arm (regorafenib) in Part 2, Cohort 5, which may be continued until progression of disease or unacceptable toxicity. Please refer to Section 7.8.

5.4.2 Rationale for Choice of Standard of Care Treatment in Part 2

Regorafenib is a standard late line therapy for mCRC patients who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and anti-EGFR therapy (if KRAS wild type). Regorafenib is approved by regulatory authorities in many regions of the world for patients with mCRC who have failed at least 2 prior lines of therapy (no more than 4 prior lines).

Regorafenib was chosen to be the SOC treatment in Part 2, in accordance with current clinical expert guidance that advises that regorafenib may provide benefit when used in the 3L+ setting. Prior TAS-102 is allowed as it is often well-tolerated and equally effective whether or not patients have received regorafenib.[97,98,99,100]

5.4.3 Rationale for Stratification in Part 2

Two stratification factors, primary tumor location (right vs left sided tumor) and extended RAS mutation status (wild-type vs mutant) were chosen for the evaluation of the triplet regimen (nivolumab plus ipilimumab plus trametinib) with SOC therapy (regorafenib) in 3L+ (no more than 4 prior lines of therapy) mCRC.

Right vs Left Sided Tumor:

In a systemic review and meta-analysis with more than 1.4 million colon cancer participants, a significant prognostic impact of primary tumor location on overall survival (OS) was observed with a 20% reduced risk of death for cancers arising on the left side.[101] Such a survival benefit seen in the left side primary tumor was independent of disease stage (II, III, and IV), and Stage IV disease showed a significantly greater survival benefit compared with Stage II and III disease. Recent meta-analysis based on data from 6 randomized clinical trials in mCRC (Stage IV), CRYSTAL, PRIME, PEAK, FIRE-3, CALGB 80405 and 20050181, also demonstrated predictive favorable effect on OS and PFS in patients with left-sided tumors.[102] Five of the aforementioned studies were in 1L mCRC patient population, and Study 20050181 was in the 2L mCRC patient population.

Thus, the right versus left sided tumor is chosen as one of the 2 stratification factors. Specifically, primary tumors originating in the appendix, cecum, ascending colon, hepatic flexure, and transverse colon will be classified as right-sided. Primary tumors originating in the splenic flexure, descending colon, sigmoid colon, rectosigmoid junction, and rectum will be classified as left-sided. If tumors were located in both left-sided and right-sided locations and the origin could not be ascribed to either side, these tumors will be stratified as right-sided (Appendix 13).

Participants with unknown primary tumor location or primary tumor located in both sides will be stratified to the right-sided stratum. Such participants are not expected to exceed 2% to 5%.

Extended RAS/BRAF Wild-type vs Mutant:

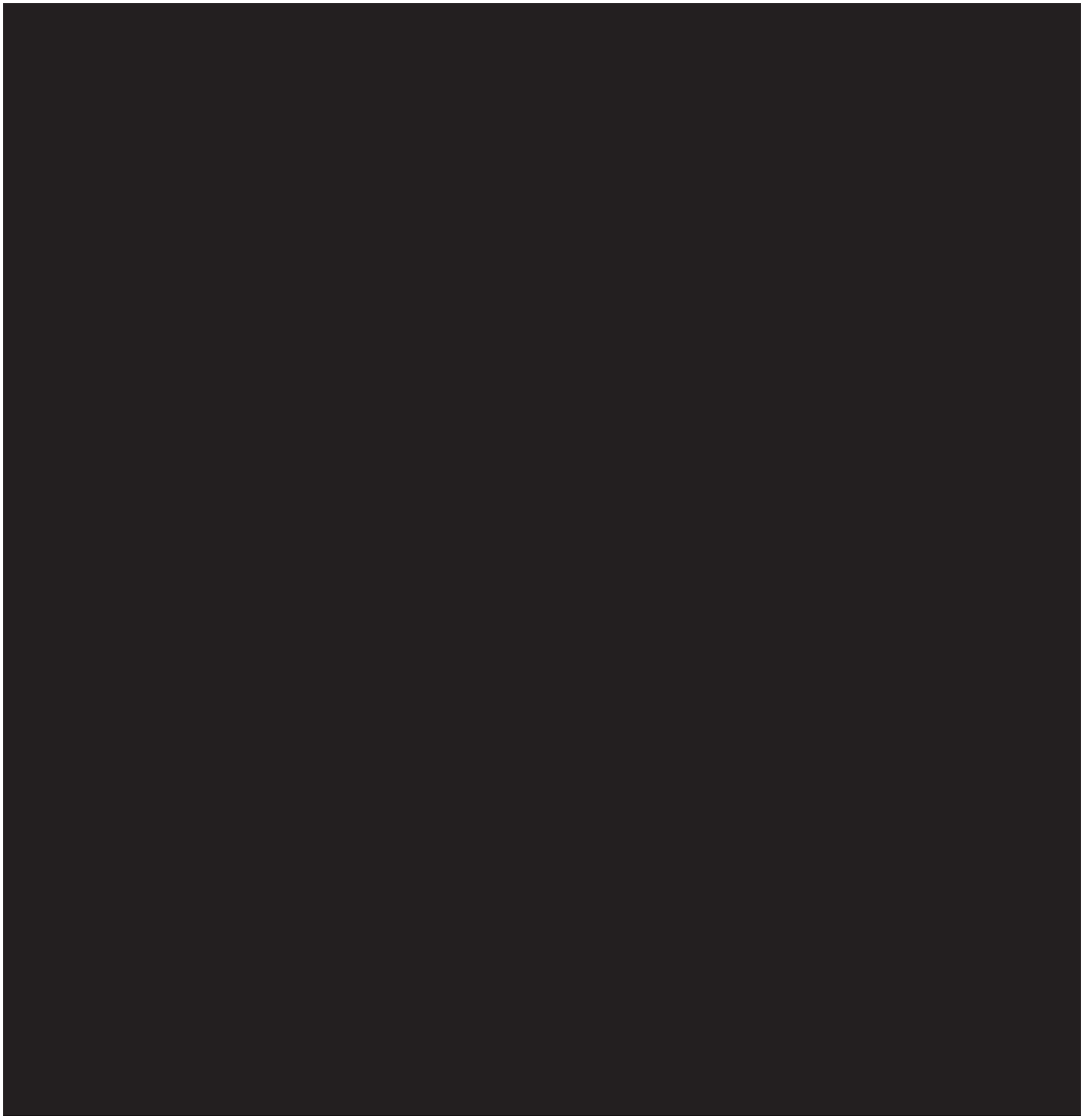
Extended RAS (KRAS and NRAS) and BRAF mutation status testing is standard practice in guiding treatment decisions in mCRC. As discussed in Section 3.2.2, the prognostic value of KRAS mutations in mCRC (independent of anti-EGFR therapy) is unclear due to conflicting data from various meta-analyses across all disease stages. It is also uncertain which mutation status will benefit more from the triplet (nivolumab + ipilimumab + trametinib). Based on current available data, preliminary anti-cancer efficacy using PD-L1 antibody in combination with MEKi was observed only in KRAS mutant participants, recognizing 20 out of 23 participants treated were KRAS mutant (refer to Section 3.1.2 for updated results).[103] In addition, the CORRECT[45] and RECOURSE trial results also indicated that both regorafenib and TAS-102 improved OS over best supportive care numerically higher in the KRAS wild-type population than in the KRAS mutant population, although not statistically significant. In order to keep balanced distribution of each treatment stratum for both cohorts (Cohort 4 and Cohort 5), extended RAS mutation status will also be utilized as a stratification factor in Part 2. Coexistence of both RAS and BRAF mutation is very rare. Thus participants whose tumors are wild-type for extended RAS vs. participants whose tumors are extended RAS mutant will be stratified into 2 groups, RAS wild-type vs mutant. Capping for wild-type (extended RAS) status will be implemented per study design (Section 5.1). BRAF mutations are observed in 5% to 10% of CRC, with 80% to 90% of BRAF mutations being V600E.[40,104] Given the poor prognosis associated with BRAF V600 mutations, these patients will be excluded.[40]

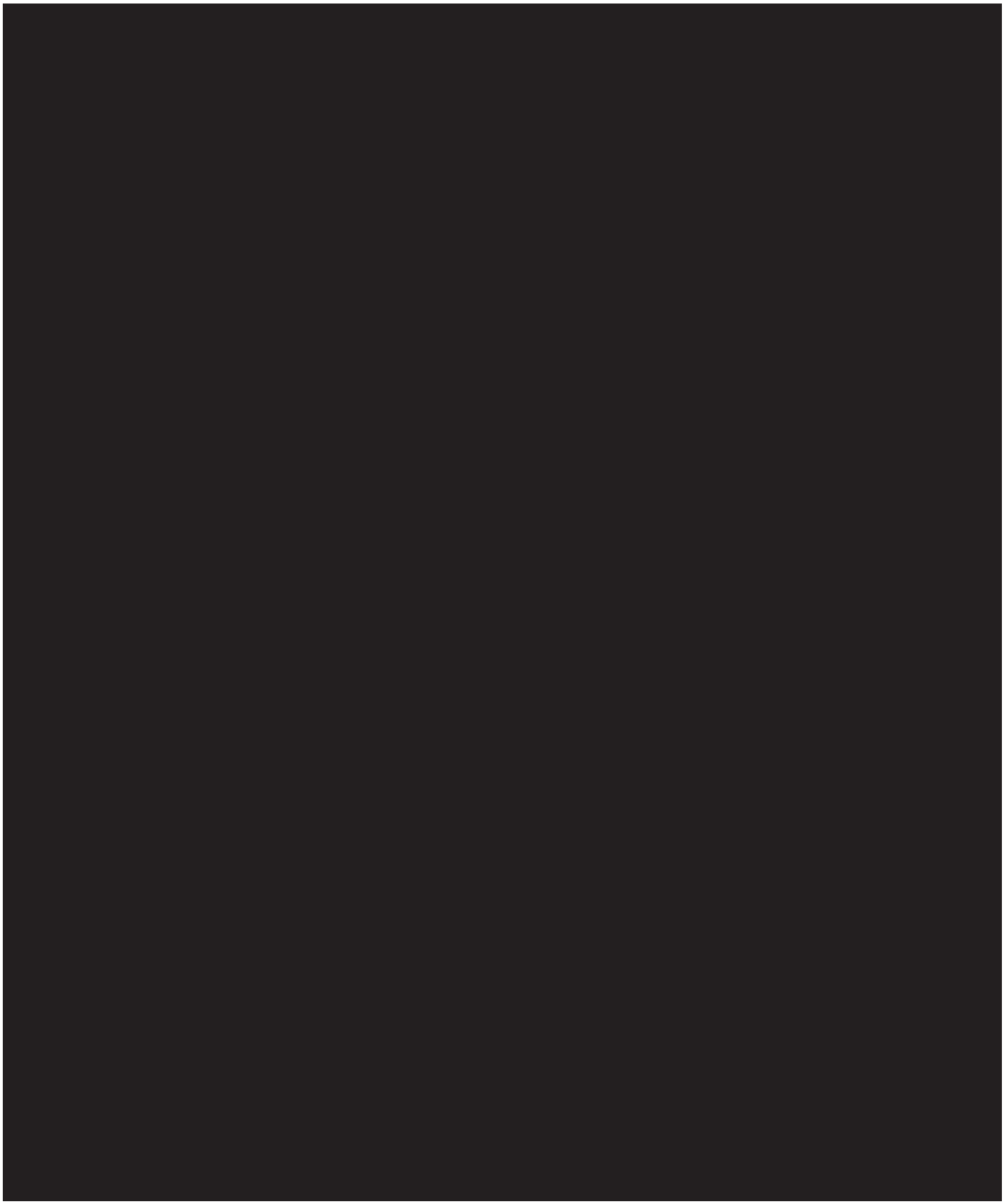
5.5 Justification for Dose

5.5.1 Rationale for Dose Selection of Nivolumab and Ipilimumab

5.5.1.1 Rationale for Nivolumab Dosing

Nivolumab monotherapy has been extensively studied in multiple tumor types, including melanoma, NSCLC, renal cell carcinoma (RCC), classical Hodgkin's lymphoma (cHL), head and neck (H&N) and urothelial carcinoma (UC), using body weight normalized dosing (mg/kg), and has been safely administered at doses up to 10 mg/kg Q2W. Nivolumab is currently approved for the treatment of various tumors, including melanoma, NSCLC, RCC, cHL, SCCHN, and UC, using a regimen of either nivolumab 240 mg Q2W or nivolumab 3 mg/kg Q2W.





5.5.1.2 Rationale for Ipilimumab Dosing

In CA209012, ipilimumab 1 mg/kg using Q6W and Q12W schedules were assessed and were found to be safe in combination with nivolumab 3 mg/kg Q2W.

5.5.2 Rationale for the Dose of Trametinib

The FDA and EMA approved dose of trametinib as single agent and in combination with dabrafenib is 2 mg QD for unresectable and metastatic melanoma.

[redacted]

5.5.3 Rationale for Shorter Infusion Time

Long infusion times place a burden on patients and treatment centers. [redacted]

[redacted]

5.5.4 Rationale for Dose Selection of Regorafenib in 3rd line MSS/mCRC

Recommended starting dose for regorafenib is selected based on approved product labels across various regions. Local product label and institutional guidelines for regorafenib starting dose can be considered in consultation with BMS Medical Monitor/designee (see Table 7.1.4.2-1).

6 STUDY POPULATION

For entry into the study, the following criteria MUST be met. As of 30-Nov-2022, enrollment into this study was closed.

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 or cytologically confirmed previously treated metastatic colorectal cancer with adenocarcinoma histology and in Stage IV per American Joint Committee on Cancer (Edition 7.0) at study entry.

b) Microsatellite status should be performed per local standard of practice, IHC and/or PCR. If IHC results are equivocal, PCR is required for determining microsatellite status, MSS or MSI-H.

i) **Not applicable per Protocol Amendment 03**: Part 1 (3L setting), Part 1A and Part 1B (2L setting) and Part 2 (3L setting): only participants with pMMR/MSS mCRC are eligible

ii) **No longer applicable per Revised Protocol 02.** Part 2 (≥ 3L setting): Both participants with pMMR/MSS and dMMR/MSI-H mCRC are eligible. dMMR/MSI-H enrollment will be capped at 5% in each treatment arm.

iii) Part 1 (3L setting), Part 1A and Part 1B (2L setting) and Part 2 (3L+ setting): only participants with pMMR/MSS mCRC are eligible.

c) KRAS and NRAS (extended RAS) and BRAF mutation status should be verified based on available local testing results as part of medical history prior to study treatment. Refer to Appendix 10 for local testing methodology permitted by the study. Participants with colorectal cancers that are RAS wild-type or mutant may be enrolled.

i) In Parts 1B and 2, the proportion of participants with RAS mutations and wild-type will be monitored on an ongoing basis, as specified in Section 5.1.

d) Prior lines of therapies:

i) **Not applicable per Protocol Amendment 03:** Participants with 3L mCRC in Part 1 and Part 2 must have progressed or been intolerant to two prior lines of chemotherapy in the metastatic disease setting, which must include at least a fluoropyrimidine and oxaliplatin- and irinotecan-containing regimens.

ii) Participants with 2L mCRC in Part 1A and 1B must have progressed or been intolerant to one prior line of chemotherapy in the metastatic disease setting, which must include at least a fluoropyrimidine and oxaliplatin- or irinotecan-containing regimens.

iii) For participants who received systemic therapy in the adjuvant or neoadjuvant setting, progression must occur at least 6 months after the last dose of the adjuvant or neoadjuvant therapy, except for Part 2.

iv) Adjuvant/neoadjuvant therapy or maintenance therapy will NOT be considered as one line of prior therapy for study entry. See criterion below for Part 2 on adjuvant/neoadjuvant therapy.

v) **Not applicable per Protocol Amendment 03:** Participants who received FOLFOXIRI (or equivalent) in the 1L setting may be considered for enrollment in the third line setting (Part 1 or Part 2) but not the second-line setting (Part 1A or Part 1B).

vi) Prior therapies containing anti-VEGF agents and/or anti-EGFR agents are permitted.

vii) **No longer applicable per Revised Protocol 02**. Participants with ≥ 3L mCRC in Part 2 must have progressed or been intolerant to at least 2 prior lines of chemotherapy in the metastatic setting, which must include at least a fluoropyrimidine and oxaliplatin- and irinotecan-containing regimens.

viii) **Not applicable per Protocol Amendment 03**: Participants with 3L mCRC in Part 2 disease recurrence within 6 months after the last dose of the adjuvant/neoadjuvant therapy is permitted and will be considered as 1 line of prior therapy for study entry. Disease recurrence beyond 6 months after the last dose of the adjuvant/neoadjuvant therapy is also permitted but will NOT be considered as 1 line of prior therapy for study entry.

ix) **Not applicable per Protocol Amendment 03**: Participants with 3L mCRC in Part 2: disease progression must have occurred during or within 3 months following the last dose of approved standard therapies.

x) Participants with 3L mCRC in Part 1 and 3L+ mCRC in Part 2 must have progressed or been intolerant to 2 prior lines or at least 2 prior lines (no more than 4 prior lines) of therapy, respectively, in the metastatic disease setting, which must include at least a fluoropyrimidine and oxaliplatin- and irinotecan-containing regimens.

xi) Participants who received FOLFOXIRI (or equivalent) in the 1L setting may be considered for enrollment in the 3L setting (Part 1) or 3L+ setting (Part 2) but not the second line setting (Part 1A or Part 1B).

xii) Participants with 3L+ mCRC in Part 2: disease recurrence within 6 months after the last dose of the adjuvant/neoadjuvant therapy is permitted and will be considered as 1 line of prior therapy for study entry. Disease recurrence beyond 6 months after the last dose of the adjuvant/neoadjuvant therapy is also permitted but will NOT be considered as 1 line of prior therapy for study entry.

xiii) Participants with 3L+ mCRC in Part 2: disease progression must have occurred during or within 3 months following the last dose of approved standard therapies.

e) Participants must have measurable disease per RECIST 1.1 (Appendix 8). Participants with lesions in a previously irradiated field as the sole site of measurable disease will be permitted to enroll provided the lesion(s) have demonstrated clear progression and can be measured accurately.

[redacted]

g) ECOG Performance Status of 0-1 at screening and on C1D1. See Appendix 7 for ECOG Performance Status scale.

h) Re-enrollment: This study permits the re-enrollment of a participant who 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.

[redacted]

[redacted]

3) Age and Reproductive Status

a) Men and women, 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 drug.

c) Women must not be pregnant or breastfeeding.

d) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of study treatment and 5 months after the last dose of study treatment {i.e., 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo approximately five half-lives. See Appendix 4. For participants randomized to treatment with regorafenib (Part 2: Cohort 5) institutional guidelines apply.

e) **Not Applicable per Protocol Amendment 03:** Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment and 7 months after the last dose of study treatment (ie, 90 days [duration of sperm turnover] plus the time required for the investigational drug to undergo approximately five half-lives.) In addition, male participants must be willing to refrain from sperm donation during this time. See Appendix 4. For participants randomized to treatment with regorafenib (Part 2: Cohort 5) institutional guidelines apply.

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

g) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment and 4 months after the last dose of study treatment {i.e., 90 days (duration of sperm turnover) plus the time required for the investigational drug to undergo approximately five half-lives.} In addition, male participants must be willing to refrain from sperm donation during this time. See Appendix 4. For participants randomized to treatment with regorafenib (Part 2: Cohort 5) institutional guidelines apply.

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 WOCBP and male participants who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% per year when used consistently and correctly.

At a minimum, participants must agree to use one highly effective method of contraception. See Appendix 4 for recommended methods of contraception.

6.2 Exclusion Criteria

1) Target Disease Exceptions

a) Participants with BRAF V600 mutant colorectal cancer are NOT eligible for this study.

i) Verify BRAF V600 mutation status based on available local testing results as part of medical history prior to study treatment. Refer to Appendix 10 for local testing methodology permitted by the study. All other BRAF variants, except V600, are eligible for this study.

b) 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. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 14 days prior to study drug administration.

2) Medical History and Concurrent Diseases

a) 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.

b) **Not applicable per Protocol Amendment 03**: Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.

c) 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.

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

e) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways, including prior therapy with anti-tumor vaccines or other immuno-stimulatory antitumor agents.

f) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE [version 4.0]) or baseline before administration of study drug. Participants with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enroll.

g) Toxicities from the prior anti-cancer treatment have not been resolved to Grade 1 (NCI CTCAE version 4.0) at the time of study entry or participants have not completed prior treatment as specified below:

   i) Received chemotherapy and other approved SOC within 14 days prior to first dose

   ii) Received investigational product(s) (IPs) within 28 days or 5 half-lives prior to first dose

   iii) Prior major surgery within 28 days prior to first dose. Any surgery-related AE(s) must have resolved at least 14 days prior to first dose.

   iv) Received radiation therapy with curative intent within 28 days prior to first dose. Prior focal palliative radiotherapy must have been completed at least 14 days prior to first dose.

h) Current use of a prohibited medication. 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 first dose of study treatment. Refer to Section 7.7 for prohibited therapies.

i) Prior treatment with any MEK inhibitor

j) History of interstitial lung disease or pneumonitis.

k) Inability to take oral medication or significant nausea and vomiting, malabsorption, external biliary shunt, significant bowel resection that would preclude adequate absorption of oral medication.

l) Psychological, familial, or sociological condition potentially hampering compliance with the study protocol and follow-up schedule.

m) Additional criteria for Part 2 only: Note: criterion vii) below applies to both Part 1b and Part 2:

   i) Prior treatment with regorafenib

   ii) Severe hepatic impairment (Child-Pugh C)

   iii) Any evidence of active bleeding, or hemorrhage or bleeding event ≥ NCI-CTCAE version 4.0 Grade 3 within 4 weeks prior to the start of study medication

   iv) Prior or current gastrointestinal perforation or fistula

   v) Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism within 6 months before the start of study medication (except for adequately treated catheter-related venous thrombosis occurring more than 1 month before the start of study medication)

vi) Non-healing wound, non-healing ulcer, or non-healing bone fracture

vii) Active infection (ie, body temperature ≥ 38°C due to infection): Applies to Parts 1B and Part 2.

n) Participants who have received a live/attenuated vaccine within 30 days of randomization (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]).

o) Prior malignancy active within the previous 2 years prior to randomization except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.

3) 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 > 50 mL/min (measured or calculated using the Cockcroft-Gault formula)

g) AST and/or ALT: > 3.0 ×ULN

i) Part 2 ONLY: Participants with documented liver metastases with AST and ALT > 5.0 ×ULN will be excluded.

h) Total bilirubin > 1.5 ×ULN

i) Participants with Gilbert's Syndrome who have a total bilirubin level of > 3.0 ×ULN will be excluded.

i) Albumin < 3.0 g/dL

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

k) History or evidence of cardiovascular risk including any of the following:

i) LVEF <LLN or < 50%, whichever is lower by ECHO (preferred) or MUGA. NOTE: same method used at baseline must be used throughout the study.

ii) A QT interval corrected for heart rate using the Bazett's formula (QTcB) ≥ 480 msec;

iii) History or evidence of current clinically significant uncontrolled arrhythmias

iv) Clarification: Participants with atrial fibrillation controlled for > 30 days prior to dosing are eligible.

v) History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to dosing.

vi) History or evidence of current ≥ Class II congestive heart failure as defined by New York Heart Association (NYHA; Appendix 11).

vii) Treatment refractory hypertension defined as a blood pressure of systolic >140mmHg and/or diastolic > 90 mm Hg, which cannot be controlled by anti-hypertensive therapy

viii) Participants with intra-cardiac defibrillators.

l) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally. Please see Appendix 12.

m) Participants with serous retinopathy or retinal vein occlusion (RVO) noted on ophthalmological evaluation, or participants with a history of serous retinopathy or retinal vein occlusion.

Note: Study required laboratory testing results (refer to Table 2-1) should be obtained within 28 days prior to first dose, and reviewed to confirm eligibility. Screening laboratory values must meet the above criteria without continuous supportive treatment such as growth factor administration, blood transfusion, coagulation factors and/or platelet transfusion, or albumin transfusion.

4) Allergies and Adverse Drug Reaction

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

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

c) Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to study drug, or excipients or to dimethyl sulfoxide (DMSO).

5) Other Exclusion Criteria

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

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

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.

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the study treatment(s) that may impact participant eligibility is provided in the most recent Investigator Brochure for each study treatment components (nivolumab, ipilimumab, trametinib). Refer to local product label and institutional guidelines for regorafenib.

6.3 Lifestyle Restrictions

Not applicable for nivolumab, ipilimumab, or trametinib. Refer to local product label and institutional guidelines for regorafenib.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently entered in the study or 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 screen failure. If re-enrolled, the participant must be re-consented and assigned a new participant number from IRT.

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

The most current result prior to enrollment 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/designee may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

7 TREATMENT

Study treatment is defined as any investigational treatment(s), 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
- Ipilimumab
- Trametinib
- Regorafenib

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 CA2099N9

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Nivolumab Solution for Injection	100 mg (10 mg/mL)	IP	Open label	Vial	Refer to the label on container and/or pharmacy manual.
Ipilimumab Solution for Injection	200 mg 50 mg (5 mg/mL)	IP	Open label	Vial	Refer to the label on container and/or pharmacy manual.
Trametinib Tablet[a]	0.5 mg and various strengths	IP	Open label	Various packing configurations	Refer to label on container or package insert/summary of product characteristics
Regorafenib Tablet[a]	40 mg and various strengths	IP	Open label	Various packing configurations	Refer to label on container or package insert/summary of product characteristics

[a] 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

7.1.1 Nivolumab and Ipilimumab Infusion

There will be no dose escalations or reductions of nivolumab or ipilimumab allowed in any part of the study. Participants should begin study treatment within 3 calendar days of treatment assignment. There is ± 3 day window for dose administration subsequent to the first dose. Premedications are not recommended for the first dose of nivolumab and ipilimumab.

Participants should be carefully monitored for infusion reactions during nivolumab and ipilimumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.2.

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

Doses of nivolumab or ipilimumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed.

Please refer to the current versions of the nivolumab or ipilimumab Investigator Brochures and/or pharmacy manual for complete storage, handling, dispensing, and infusion information for nivolumab and ipilimumab.

7.1.2 Trametinib Dosing

Trametinib should be taken as follows:

- Trametinib should be administered under fasted conditions, either 1 hr before or 2 hrs after a meal with approximately 120-240 mL of water.
- Participants should be instructed to take trametinib in the morning, at approximately the same time every day.
- On visits when participants are to receive nivolumab and/or ipilimumab, participants should bring their trametinib to scheduled visit and withhold until after medical assessments. After participants are confirmed to be eligible to continue with study treatment, participants should take trametinib first, then receive infusion.
- If a participant vomits after taking trametinib, the participant should be instructed not to retake the dose and wait for the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted in the AE section of the eCRF.
- If a participant misses a dose, he/she should be instructed not to double the next regularly scheduled dose. However, participant may take the missed dose immediately if the next scheduled dose is at least 12 hours later for trametinib. Participant may then take the next dose at the scheduled time.

7.1.3 Part 1 (Completed) (Doublet Regimen, Cohort 1 Group: Enrollment Closed)

Participants should receive nivolumab at a dose of 480 mg as a 30-minute infusion on Day 1 of each treatment cycle, in combination with trametinib 1.5 mg QD (starting dose for the initial/first cohort) until progression, unacceptable toxicity, withdrawal of consent, completion of 2 years of treatment, or the study ends, whichever occurs first. Participants should begin study treatment within 3 calendar days of treatment assignment.

Table 7.1.3-1: Dose Schedule of Nivolumab and Trametinib in Part 1 (Cohort 1 Group)

Trametinib Dosing Regimen	Study Treatment	Every Cycle until End of Treatment (28 day/4 week per cycle)
Trametinib Continuous	Nivolumab 480mg IV + Trametinib 1.5 mg PO[a]	Nivolumab on Day 1 only; Trametinib QD Day 1 through Day 28
Trametinib Intermittent (2 weeks on/2 weeks off)[b]	Nivolumab 480mg IV + Trametinib 1.5mg PO[a]	Nivolumab on Day 1 only; Trametinib QD Day 1 through D14 only

[a] Trametinib 1.5 mg is the starting dose for the initial/first cohort. Refer to Section 5.1.1 for trametinib daily dose to be administered in Cohort 1 Group.

[b] Trametinib intermittent regimen will be initiated for the next new cohort in case of dose de-escalation.

Treatment cycles should be given every 4 weeks. Following first nivolumab dose, subsequent nivolumab dosing will be based on the actual date of administration of the previous dosing. Participants may be dosed within a ± 3-day window of scheduled dose due to scheduling conflict. A treatment cycle is complete if nivolumab infusion has been administered and the next cycle is triggered by the next infusion. Maintain dosing regimen for trametinib and capture the dosing in the appropriate treatment cycle anchored by nivolumab infusion. In case of trametinib dosing delay, synchronize re-initiation of trametinib dosing to fit in the treatment cycle whenever possible if deemed medically appropriate by the investigator.

Participants are not permitted to continue with only one of the study treatment components if either nivolumab or trametinib needs to be discontinued.

See Section 8.1 Discontinuation Criteria for further detail.

Initiation of the Next Treatment Cycle:

- Infusion with nivolumab initiates Day 1 of the next cycle. If nivolumab is delayed, the cycle is delayed. Maintain trametinib dosing regimen during the current cycle. Cycle is not skipped, only delayed.
- If a decision is made to permanently discontinue nivolumab, trametinib must be permanently discontinued as well.

7.1.4 Part 2 (Triplet Regimen, Cohort 4 and Standard of Care (SOC) Arm, Cohort 5) Enrollment Closed

In Part 2 [redacted], 2 cohorts of participants will be enrolled.

7.1.4.1 Cohort 4 Triplet Regimen

In Cohort 4, participants should receive nivolumab at a dose of 6 mg/kg as an approximately 30-minute IV infusion on Day 1 and Day 29 of each treatment cycle (every 4 weeks). If needed, flush the IV line with an appropriate amount of diluent (eg, 0.9% sodium chloride or 5% dextrose in water) to ensure that the complete dose is administered over approximately 30 minutes. Ipilimumab should be administered at a dose of 1 mg/kg as about a 30-minute IV infusion on Day 1 of each treatment cycle (every 8 weeks), plus trametinib 1.5 mg continuous QD until progression, unacceptable toxicity, withdrawal of consent, completion of 2 years of treatment, or the study ends, whichever occurs first. Participants should begin study treatment within 3 calendar days of treatment randomization.

Table 7.1.4.1-1: Dose Schedule of Nivolumab + Ipilimumab and Trametinib in Part 2 (Cohort 4)

Study Treatment	Every Cycle until End of Treatment (56 day/8 week per cycle)
Nivolumab 6 mg/kg IV + Ipilimumab 1 mg/kg IV + Trametinib 1.5 mg PO	Nivolumab on Day 1 and Day 29; Ipilimumab on Day 1 only; Trametinib QD Day 1 through Day 56

Treatment cycles should be given every 8 weeks. Following first nivolumab dose, subsequent nivolumab dosing will be based on the actual date of administration of the previous dosing. Participants may be dosed within a ± 3 day window of scheduled dose due to scheduling conflict. Following, the first ipilimumab dose, subsequent ipilimumab dosing will be synchronized with the first dosing of nivolumab in the next cycle. For weight-based dosing, dosing calculations should be based on the body weight assessed at baseline. It is not necessary to re-calculate subsequent doses if the participant's weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up or to the nearest milligram per institutional standard. Participants should begin study treatment within 3 calendar days of treatment assignment.

A treatment cycle is complete if 2 nivolumab infusions have been administered, OR, 1 nivolumab infusion has been administered and at least 8 weeks have passed from the first infusion to the next infusion, whichever occurs earlier. Maintain dosing regimen for trametinib and capture the dosing in the appropriate treatment cycle anchored by nivolumab infusion. If any of the investigational drugs of the triplet regimen (nivolumab, ipilimumab, or trametinib) need to be permanently discontinued, then the patient should discontinue all study treatment.

Initiation of the Next Treatment Cycle:

- The next treatment cycle starts if 2 nivolumab infusions have been administered or the next infusion is at least 8 weeks apart from the first infusion, whichever is shorter in duration. Cycle is not skipped, only delayed.
- When study treatments nivolumab and ipilimumab are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study treatment and will start after the infusion line has been flushed, filters changed, and the participant has been observed to ensure no infusion reaction has occurred.
- When nivolumab and ipilimumab are scheduled to be dosed on the same day, if dosing is delayed, both nivolumab and ipilimumab must be delayed together. If dosing is resumed after a dose delay, both nivolumab and ipilimumab must be resumed on the same day if the next scheduled day includes both nivolumab and ipilimumab administration.

7.1.4.2 Cohort 5 Regorafenib

In Cohort 5, participants will receive regorafenib at the approved dose per local product label until progression, unacceptable toxicity, withdrawal of consent, whichever occurs first. Participants should begin study treatment within 3 calendar days of treatment randomization.

Table 7.1.4.2-1: Recommended Dose of Regorafenib in Part 2 (Cohort 5)

Study Treatment	Every Cycle till the End of Treatment (28 day/4 week per cycle)
Regorafenib 160 mg [a]	Orally, once daily for the first 21 days of each 28-day cycle

[a] The recommended dose of regorafenib is 160 mg. Refer to local product label and institution guidelines.

7.1.4.3 Regorafenib Dosing

Please refer to local product label and institutional guidelines for further details.

The recommended dose of regorafenib is 160 mg (four 40 mg tablets) taken orally once daily for the first 21 days of each 28-day cycle. Continue treatment until disease progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

The participant should take regorafenib at the same time each day. Swallow tablet as a whole with water after a low-fat meal that contains less than 600 calories and less than 30% fat. The participant should not take 2 doses of regorafenib on the same day to make up for a missed dose from the previous day. Any missed doses reported by the participant should be recorded in the participant's source documents and in the participant's diary.

Initiation of the Next Treatment Cycle:

- The next cycle will be initiated every 4 weeks with regorafenib dosing as specified in Table 7.1.4.2-1.

- If regorafenib dosing is delayed, the next cycle will start if at least 4 weeks have passed from the first dose in the current cycle to dosing re-initiation.
- The next treatment cycle may be initiated within a ± 3-day window of scheduled dose due to scheduling conflict.

7.1.5 Part 1A Completed (Triplet Regimen, Cohort 2 Group and Cohort 3 Group: Closed for Enrollment)

The dose optimization phase of the study (Parts 1 and 1A) are completed. Enrollment is closed in Part 1 and Part 1A cohorts.

In Part 1A, participants should receive nivolumab at a dose of 6 mg/kg as an approximately 30-minute IV infusion on Day 1 and Day 29 of each treatment cycle (every 4 weeks). If needed, flush the intravenous line with an appropriate amount of diluent (eg, 0.9% sodium chloride or 5% dextrose in water) to ensure that the complete dose is administered over approximately 30 minutes. Ipilimumab should be administered at a dose of 1 mg/kg as about a 30-minute IV infusion on Day 1 of each treatment cycle (every 8 weeks), plus trametinib 1.5 mg QD (starting dose for the initial/first cohorts, either continuously, or 2 week on/2 week off dosing) until progression, unacceptable toxicity, withdrawal of consent, the study ends or up to a maximum of 2 years whichever occurs first (see Table 7.1.5-1). Dosing calculations should be based on the body weight assessed at baseline. It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up or to the nearest milligram per institutional standard. Participants should begin study treatment within 3 calendar days of treatment assignment.

Table 7.1.5-1: Dose Schedule of Nivolumab, Ipilimumab and Trametinib in Part 1A (Cohort 2 Group and Cohort 3 Group)

Trametinib Dosing Regimen	Study Treatment	Every Cycle till End of Treatment (56 day/8 week per cycle)
Cohort 2 Group: Trametinib Continuous	Nivolumab 6 mg/kg IV + Ipilimumab 1 mg/kg IV + Trametinib 1.5 mg PO[a]	Nivolumab on Day 1 and Day 29; Ipilimumab on Day 1 only; Trametinib QD Day 1 through Day 56
Cohort 3 Group: Trametinib Intermittent (2 weeks on/2 weeks off)	Nivolumab 6 mg/kg IV + Ipilimumab 1 mg/kg IV + Trametinib 1.5 mg PO[a]	Nivolumab on Day 1 and Day 29; Ipilimumab on Day 1 only; Trametinib QD Day 1 through D14; Day 29 through Day 42

[a] Trametinib 1.5 mg is the starting dose for the initial/first cohorts. Refer to Section 5.1.1 for trametinib daily dose to be administered in Cohort 2 and 3.

Treatment cycles should be given every 8 weeks. Following first nivolumab dose, subsequent nivolumab dosing will be based on the actual date of administration of the previous dosing.

Participants may be dosed within a ± 3 day window of scheduled dose due to scheduling conflict. Following first ipilimumab dose, subsequent ipilimumab dosing will be synchronized with the first dosing of nivolumab in the next cycle. A treatment cycle is complete if two nivolumab infusions have been administered, OR, one nivolumab infusion has been administered and at least 8 weeks have passed from the first infusion to the next infusion, whichever occurs earlier. Maintain dosing regimen for trametinib and capture the dosing in the appropriate treatment cycle anchored by nivolumab infusion. In case of trametinib dosing delay, synchronize re-initiation of trametinib dosing to fit in the treatment cycle whenever possible if deemed medically appropriate by the investigators. If any of the investigational drugs of the triplet regimen (nivolumab, ipilimumab, or trametinib) need to be permanently discontinued, then the participant should discontinue all study treatment.

Initiation of the Next Treatment Cycle:

- The next treatment cycle starts if two nivolumab infusions have been administered or the next infusion is at least 8 weeks apart from the first infusion, whichever is shorter in duration. Cycle is not skipped, only delayed.
- When study treatments nivolumab and ipilimumab are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study treatment and will start after the infusion line has been flushed, filters changed, and the participant has been observed to ensure no infusion reaction has occurred.
- When nivolumab and ipilimumab are scheduled to be dosed on the same day, if dosing is delayed, both nivolumab and ipilimumab must be delayed together. If dosing is resumed after a dose delay, both nivolumab and ipilimumab must be resumed on the same day if the next scheduled day includes both nivolumab and ipilimumab administration.

7.1.6 Part 1B (Triplet Regimen, Cohort 6) Enrollment Closed

In Part 1B of the study, participants will receive nivolumab at a dose of 6 mg/kg as an approximately 30-minute IV infusion on Day 1 and Day 29 of each treatment cycle (every 4 weeks). If needed, flush the intravenous line with an appropriate amount of diluent (eg, 0.9% sodium chloride or 5% dextrose in water) to ensure that the complete dose is administered over approximately 30 minutes. Ipilimumab should be administered at a dose of 1 mg/kg as about a 30-minute IV infusion on Day 1 of each treatment cycle (every 8 weeks), plus trametinib 1.5 mg QD, until progression, unacceptable toxicity, withdrawal of consent, the study ends, or up to a maximum of 2 years, whichever occurs first (see Table 7.1.6-1). For weight-based dosing, dosing calculations should be based on the body weight assessed at baseline. It is not necessary to re-calculate subsequent doses if the participant's weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up or to the nearest milligram per institutional standard. Participants should begin study treatment within 3 calendar days of treatment assignment.

Table 7.1.6-1: Dose Schedule of Nivolumab, Ipilimumab, and Trametinib in Part 1B (Cohort 6)

Nivolumab Dosing Regimen	Study Treatment	Every Cycle till End of Treatment (56 day/8 week per cycle)
Cohort 6: Nivolumab weight-based dosing	Nivolumab 6 mg/kg IV + Ipilimumab 1 mg/kg IV + Trametinib 1.5 mg	Nivolumab on Day 1 and Day 29; Ipilimumab on Day 1 only Trametinib 1.5 mg QD (continuous)

Treatment cycles should be given every 8 weeks. Following first nivolumab dose, subsequent nivolumab dosing will be based on the actual date of administration of the previous dosing. Participants may be dosed within a ± 3-day window of scheduled dose due to scheduling conflict. Following the first ipilimumab dose, subsequent ipilimumab dosing will be synchronized with the first dosing of Nivolumab in the next cycle. A treatment cycle is complete if two nivolumab infusions have been administered, OR, one nivolumab infusion has been administered and at least 8 weeks have passed from the first infusion to the next infusion, whichever occurs earlier. Maintain dosing regimen for trametinib and capture the dosing in the appropriate treatment cycle anchored by nivolumab infusion. In case of trametinib dosing delay, synchronize re-initiation of trametinib dosing to fit in the treatment cycle whenever possible if deemed medically appropriate by the investigators.

Initiation of the Next Treatment Cycle:

- The next treatment cycle starts if two nivolumab infusions have been administered or the next infusion is at least 8 weeks apart from the first infusion, whichever is shorter in duration. Cycle is not skipped, only delayed.
- When study treatments nivolumab and ipilimumab are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study treatment and will start after the infusion line has been flushed, filters changed, and the participant has been observed to ensure no infusion reaction has occurred.
- When nivolumab and ipilimumab are scheduled to be dosed on the same day, if dosing is delayed, both nivolumab and ipilimumab must be delayed together. If dosing is resumed after a dose delay, both nivolumab and ipilimumab must be resumed on the same day if the next scheduled day includes both nivolumab and ipilimumab administration.

7.2 Method of Treatment Assignment

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

All participants must be assigned a participant number upon providing signed written informed consent. For Part 1 and 1A, contact Sponsor for treatment allocation authorization before registering participants in IRT (Parts 1 and 1A are now closed for enrollment). The Sponsor will implement an IRT to assign participant numbers, study treatment group and dose level, as well as

manage treatment supply. During the screening visit, the investigative site will register the participant by an IRT designated by BMS for assignment of a 5-digit participant number that will be unique across all sites.

The participant identification number (PID) will ultimately be composed of the site number and participant number. For example, the first participant screened (eg, enrolled) at site number 1, will have a PID [redacted]. For Parts 1, and 1A, the digit [redacted] will be dependent on which cohort group the participant has been screened to (see Table 7.2-1). Specific instructions for using the IRT will be provided to the investigational sites in a separate instruction manual.

Unique cohort numbers are assigned to individual treatment arms and trametinib dose levels. See Table 7.2-1 below.

Table 7.2-1: Unique Cohort Numbers in Part 1, 1A, 1B and 2

Part 1 and Part 1A (Completed)			
Trametinib Dose Level (DL)	**Trametinib Dose in Doublet Regimen[a] -- Cohort Number**	**Trametinib Dose in Triplet Regimen[b]- Continuous Dosing --- Cohort Number**	**Trametinib Dose in Triplet Regimen[b] Intermittent Dosing --- Cohort Number**
DL+2	2 mg continuous in Part 1---- Cohort 1D	NA	NA
DL+1	2 mg 2 wk on/2 wk off in Part 1----Cohort 1B	2 mg continuous in Part 1A ----Cohort 2B	2mg 2wk/2 wk off in Part 1A --- Cohort 3B
starting	1.5 mg continuous in Part 1 --Cohort 1	1.5 mg continuous in Part 1A ---Cohort 2	1.5 mg 2 wk on/2 wk off in Part 1A --- Cohort 3
DL-1	1.5 mg 2 wk on/2 wk off in Part 1--- Cohort 1A	1 mg continuous in Part 1A ----Cohort 2A	1 mg 2 wk on/2 wk off in Part 1A --- Cohort 3A
DL-2	1 mg 2 wk on/2 wk off in Part 1 ---Cohort 1C	NA	NA

Table 7.2-1: Unique Cohort Numbers in Part 1, 1A, 1B and 2

Part 1 and Part 1A (Completed)			
Trametinib Dose Level (DL)	**Trametinib Dose in Doublet Regimen[a] -- Cohort Number**	**Trametinib Dose in Triplet Regimen[b]- Continuous Dosing --- Cohort Number**	**Trametinib Dose in Triplet Regimen[b] Intermittent Dosing --- Cohort Number**
Parts 2 and 1B			
Trametinib Dose Level (DL)	**Regorafenib**	**Trametinib Dose in Triplet Regimen[b]- Continuous Dosing --- Cohort Numbers**	
N/A		Part 2 1.5 mg continuous --- Cohort 4 Part 1B 1.5 mg continuous --- Cohort 6	
SOC without trametinib	Part 2 with regorafenib --- Cohort 5	NA	

DL= dose level; SOC=standard of care; wk=week.

[a] Doublet regimen: nivolumab + trametinib. Refer to Section 7.1.3 and 7.1.4 for nivolumab dosing.

[b] Triplet regimen: nivolumab + ipilimumab + trametinib. Refer to Sections 7.1.5 and 7.1.6 for nivolumab and ipilimumab dosing.

Part 2 is a randomized open-label study with 2 treatment arms, nivolumab + ipilimumab + trametinib versus regorafenib. Enrollment is closed for Part 2.

- Once enrolled in IRT, participants who have met all eligibility criteria for Part 2 will be randomized in a 2:1 ratio to nivolumab + ipilimumab + trametinib (Cohort 4) or regorafenib (Cohort 5). The following stratification factors will be applied:
  - Primary tumor sidedness (left vs right) (Appendix 13). Participants with unknown primary tumor location or primary tumor located in both sides will be allocated to the right sided stratum. Such participants are not expected to exceed 2% to 5%.
  - Extended RAS mutation status (wild-type vs mutant). Please refer to Section 5 for details on proportion of participants with RAS mutation status monitoring. Patients with unknown RAS/BRAF status will not be eligible. Patients with BRAF V600 mutation are not eligible for the study.

7.3 Blinding

This is an open label Phase 1/2. However, Part 2 of the study is randomized/ open-label, and the specific treatment to be taken by a participant will be assigned using an IRT. Access to treatment codes will be restricted from select BMS personnel prior to database lock.

Part 1B is non-randomized, open-label. The site will contact the IRT prior to the start of study treatment administration for each participant in Part 1B. The site will record the treatment assignment on the applicable case report form, if required. Part 1B is now closed to enrollment.

Part 1 and 1A are closed to enrollment.

For Part 2, designated staff of BMS Research & Development may obtain the randomization codes prior to database lock to facilitate the bioanalytical analysis [redacted]. A bioanalytical scientist in the Bioanalytical Sciences department of BMS Research & Development (or a designee in the external central bioanalytical laboratory) may obtain the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples. BMS will not generate any aggregated reports until pre-specified interim or final analyses. Part 2 is now closed to enrollment.

7.4 Dosage Modification

For participants in Part 1 and Part 1A who complete DLT observation period (first cycle), and participants in Part 1B and Part 2, study treatment may be modified to manage toxicity. Adverse events should be graded and managed according to NCI CTCAE (version 4.0) guidelines. There are no dose modifications for nivolumab or ipilimumab, except treatment delay. Trametinib dosing will be adjusted as described in Section 7.4.4. 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, nivolumab/ipilimumab/trametinib combination or nivolumab/trametinib combination.

- For adverse events that are deemed to be related to trametinib ONLY by the treating physician, dose modification criteria for trametinib must be followed as described in Section 7.4.4 and Appendix 6
- For adverse events that are deemed to be related to nivolumab or nivolumab in combination with ipilimumab ONLY by the treating physician, dose modification criteria for nivolumab/ipilimumab must be followed as described in Section 7.4.1 and Appendix 5
- For adverse events that are possibly related to the combination regimen, either nivolumab + trametinib or nivolumab + ipilimumab + trametinib, the most conservative toxicity management guidelines must be followed. Refer to Section 7.4.3 and Appendix 6 for trametinib, and Section 7.4.1 and Appendix 5 for nivolumab + ipilimumab.
- For adverse events that are deemed to be related to regorafenib by the investigator, refer to local product label and institution guidelines for further detail in addition to the recommendation provided in Section 7.4.6.

7.4.1 Nivolumab/Ipilimumab Dose Delay

Nivolumab or ipilimumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related adverse event, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT, and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related adverse event

- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation (see Section 8.1.1)
- 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/ipilimumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab/ipilimumab dosing when re-treatment criteria are met.

Further detail on immune related adverse event management algorithm is described in Appendix 5 for the following categories:

- GI Adverse Event
- Renal Adverse Event
- Pulmonary Adverse Event
- Hepatic Adverse Event
- Endocrinopathy Management
- Skin Adverse Event
- Neurological Adverse Event
- Myocarditis Adverse Event

7.4.2 Criteria to Resume Treatment with Nivolumab or Ipilimumab

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

- Participants may resume treatment in the presence of Grade 2 fatigue;
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity;
- 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/designee;
- Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor/designee. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

7.4.3 Treatment of Nivolumab- or Ipilimumab-related Infusion Reactions

Since nivolumab and ipilimumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, 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 4.0) 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 drug 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 medication 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 and/or ipilimumab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or 4 symptoms: (severe reaction, Grade 3: prolonged [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 drug. Begin an IV infusion of normal saline and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a

1:1000 solution for 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 drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.

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

7.4.4 Trametinib Dose Delay/Modifications

7.4.4.1 General Guidelines for Trametinib Related Toxicities

General guidelines regarding management and dose reduction for adverse events that are considered by the investigator to be related to trametinib are provided in Table 7.4.4.1-1. The severity of adverse events will be graded utilizing the CTCAE v 4.0. Guidelines for specific trametinib related toxicities as listed in Section 7.4.4.2 are provided in Appendix 6.

Table 7.4.4.1-1: Dose Delay and Modification for Events Considered Related to Trametinib (excluding pyrexia)

CTCAE Grade	Action and Dose Modification
Grade 1	• Continue trametinib at current dose level • Monitor closely • Provide supportive care according to institutional standards
Grade 2	• Interrupt trametinib if clinically indicated • Monitor closely • Provide supportive care according to institutional standards • When toxicity resolves to Grade 1 or baseline, restart trametinib at current dose level
Grade 3	• Interrupt trametinib if clinically indicated • Monitor closely • Provide supportive care according to institutional standards • When toxicity resolves to Grade 1 or baseline, restart trametinib reduced by one dose level • If the Grade 3 toxicity recurs, interrupt trametinib • When toxicity resolves to Grade 1 or baseline, restart trametinib reduced by another dose level
Grade 4	• Interrupt trametinib • Monitor closely • Provide supportive care according to institutional standards • If event resolves to Grade 1 or baseline discuss potential continuation of trametinib with the Medical Monitor/designee; if continuation of treatment agreed then restart trametinib at dose reduced by one dose level

Table 7.4.4.1-1: Dose Delay and Modification for Events Considered Related to Trametinib (excluding pyrexia)

CTCAE Grade	Action and Dose Modification
	• If event does not resolve permanently discontinue trametinib
Note: Approval from the Medical Monitor/designee is required to restart study treatment after ≥21 days of interruption. Note: In participants who experience retinal vein occlusion, trametinib treatment should be permanently discontinued.	

7.4.4.2 Guidelines for Specific Trametinib-related Toxicities

Trametinib dose modification guidelines for specific clinically significant toxicities and common toxicities that may be related to trametinib are outlined in Appendix 6:

- Rash
- Diarrhea
- Ejection fraction changes
- Hypertension
- Pneumonitis
- Visual changes
- Liver chemistry elevation.
- Hand and foot syndrome
- Pyrexia

Refer to the relevant sections of Appendix 6 for dose modification guidelines for these specific adverse events as listed above.

7.4.4.3 Dose Modification for Trametinib

Table 7.4.4.3-1 describes the dose /schedule to be used for any necessary dose modifications for trametinib.

- For Grade 2 or 3 laboratory abnormalities that are considered unrelated to the study treatment or those that are reversible in <48 hrs (except for liver enzymes) such as electrolyte abnormalities may continue without dose reductions. Modification of trametinib dosing frequency is not permitted, except dose delay to manage toxicity per dose modification guideline (Appendix 6).
- A maximum of 2 trametinib dose level reductions are allowed for Part 1 and Part 1A. For Parts 1B and 2, a maximum of 1 trametinib dose level reduction is allowed If a third dose level/frequency reduction is required for Part 1 or Part 1A, second for Parts 1B and 2, treatment will be permanently discontinued.

- If a dose reduction of trametinib is required (Parts 1B and 2), but the toxicity resolves and no additional toxicities are seen after 4 weeks of treatment, the dose of trametinib may be re-escalated but should not exceed 1.5 mg once a day or the dose determined from dose optimization evaluation, whichever is lower. Dose re-escalation may NOT be permitted for specific toxicities as described in Appendix 6.
- The minimum daily dose of trametinib that is permissible on study is 1.0 mg. If participants require a dose reduction below 1.0 mg, they should be permanently discontinued from trametinib.

Table 7.4.4.3-1: Potential Trametinib Dose Levels in Part 1B and Part 2

Daily Dose Level	Dose/Day
Maximum	1.5 mg once a day
Minimum	1.0 mg once a day

7.4.5 Criteria to Resume Treatment with Trametinib

Treatment with trametinib may be delayed for up to 21 days to allow resolution of toxicity, or based on investigator discretion (eg, scheduling issues). If the investigator and the Medical Monitor/designee conclude that continued treatment will benefit a participant who has experienced a treatment delay > 21 days, then the participant may continue treatment with the approval of the Medical Monitor/designee. If a dose delay continues for 10 weeks or more, then trametinib should be permanently discontinued for toxicities considered related to study drug.

7.4.6 Dose Modification for Regorafenib

If dose modifications are required, reduce the dose in 40 mg (1 tablet) increments; the lowest recommended daily dose of regorafenib is 80 mg daily. The following dose modification is provided as a recommendation. Local product labels and/or institutional guidelines should be followed if they are more conservative than the recommendations below.

Interrupt regorafenib for the following:

- Grade 2 hand-foot skin reaction (HFSR) [palmar-plantar erythrodysesthesia (PPES)] that is recurrent or does not improve within 7 days despite dose reduction; interrupt therapy for a minimum of 7 days for Grade 3 HFSR (refer to Table 7.4.6-2 for additional requirements)
- Symptomatic Grade 2 hypertension
- Any Grade 3 or 4 adverse reaction
- Worsening infection of any grade
- Reduce the dose of regorafenib to 120 mg:
  - For the first occurrence of Grade 2 HFSR of any duration (refer to Table 7.4.6-2 for additional requirements)
  - After recovery of any Grade 3 or 4 adverse reactions except infection

– For Grade 3 AST/ALT elevation, only resume if the potential benefit outweighs the risk of hepatotoxicity (refer to Table 7.4.6-1 for additional requirements)

Reduce the dose of regorafenib to 80 mg:

- For re-occurrence of Grade 2 HFSR at the 120 mg dose (refer to Table 7.4.6-2 for additional requirements). After recovery of any Grade 3 or 4 adverse reaction at the 120 mg dose (except hepatotoxicity or infection)

Table 7.4.6-1: Recommended Measures and Dose Modifications in Case of Drug-related Liver Function Test Abnormalities

Observed Elevations of ALT and/or AST	Occurrence	Recommended Measures and Dose Modification
≤ 5 times ULN (maximum Grade 2)	Any occurrence	Continue regorafenib treatment. Monitor liver function weekly until transaminases return to < 3 times ULN (Grade 1) or baseline.
> 5 times ULN ≤ 20 times ULN (Grade 3)	1st occurrence	Interrupt regorafenib treatment. Monitor transaminases weekly until they return to < 3 times ULN or baseline. Restart: If the potential benefit outweighs the risk of hepatotoxicity, re-start regorafenib treatment, reduce dose by 40 mg (1 tablet), and monitor liver function weekly for at least 4 weeks.
	Re-occurrence	Discontinue treatment with regorafenib permanently.
> 20 times ULN (Grade 4)	Any occurrence	Discontinue treatment with regorafenib permanently.
> 3 times ULN (Grade 2 or higher) with concurrent bilirubin > 2 times ULN	Any occurrence	Discontinue treatment with regorafenib permanently. Monitor liver function weekly until resolution or return to baseline. Exception: Patients with Gilbert's syndrome who develop elevated transaminases should be managed as per the above outlined recommendations for the respective observed elevation of ALT and/or AST.

Source: Modified from Table 2 of regorafenib SmPC

Table 7.4.6-2: Recommended Dose Modifications and Measures for HFSR

Skin Toxicity Grade	Occurrence	Recommended Dose Modification and Measures
Grade 1	Any	Maintain dose level and immediately institute supportive measures for symptomatic relief.
Grade 2	1st occurrence	Decrease dose by 40 mg (1 tablet) and immediately institute supportive measures. If no improvement occurs despite dose reduction, interrupt therapy for a minimum of 7 days, until toxicity resolves to Grade 0-1. A dose re-escalation is permitted at the discretion of the physician.
	No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (1 tablet). A dose re-escalation is permitted at the discretion of the physician.
	3rd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (1 tablet). A dose re-escalation is permitted at the discretion of the physician.
	4th occurrence	Discontinue treatment with regorafenib permanently.
Grade 3	1st occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (1 tablet). A dose re-escalation is permitted at the discretion of the physician.
	2nd occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (1 tablet).
	3rd occurrence	Discontinue treatment with regorafenib permanently.

Source: Modified from Table 1 of regorafenib SmPC

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.

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

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

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

7.5.1 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability, and review of dosing diary cards. Drug accountability should be reviewed by the site study staff at each visit to confirm treatment compliance. Sites should discuss discrepancies with the participant at each on-treatment study visit.

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, 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.
- Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) within 100 days post last dose of nivolumab without or with ipilimumab.
- Non-live Coronavirus Disease 2019 (COVID-19) vaccination is considered a simple concomitant medication within the study. However, the safety and efficacy of non-live vaccines (including non-live COVID-19 vaccines) in participants receiving nivolumab, ipilimumab, or trametinib are unknown.

The potential for overlapping toxicities with radiotherapy and nivolumab with or without ipilimumab in combination with trametinib is not known currently. Therefore, radiotherapy is not

permitted while receiving study treatment. If radiotherapy is required, participants should discontinue study treatment. Palliative radiotherapy for participants in the SOC arm receiving regorafenib may be administered per local product label and institutional guidelines.

- Refer to local product labels/institution guidelines for additional prohibited and/or restricted treatments for participants receiving regorafenib.

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 treatment assignment/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.

Any prescription or herbal product which is not prescribed by the investigator or licensed physician for treatment of a specific clinical condition is prohibited.

- Refer to local product labels/institution guidelines for additional restrictions and precautions for participants receiving regorafenib.

7.7.2.1 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. Should a participant have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis may be obtained.

Specific to MRI, participants with severe renal insufficiency (ie, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this participant population. In addition, participants are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. The ultimate decision to perform MRI in an individual participant in this study rests with the site radiologist, the investigator and the standard set by the local Ethics Committee.

7.7.3 Permitted Therapies

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

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

Hormone replacement therapy: Participants may continue to receive hormonal replacement therapy if initiated prior to treatment assignment/randomization.

Supportive Care: For participants receiving regorafenib, follow local product label, institutional guidelines, or relevant regional guidelines (eg, ASCO or ESMO) to manage expected toxicities. Supportive care includes, but is not limited to, hematologic support and management of diarrhea, nausea/vomiting, skin toxicities, as well as prophylactic or therapeutic administration of appropriate therapies.

7.8 Treatment After the End of the Study

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study treatment **for the maximum treatment duration specified in protocol Section 5.4.1.** 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 study drugs 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. Adverse events should be graded and managed according to NCI CTCAE (version 4.0) guidelines.
- 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. (Note: Under specific circumstances, and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)

- Documented radiographic disease progression per RECIST v1.1.
  - Note: For 2L and 3L+ mCRC participants in Cohorts 4 and 6, treatment beyond progression is permitted. See Section 8.1.5.
- Criteria listed in Section 8.1.1 thru 8.1.4.
- Requiring treatment as listed in Section 7.7.

Any criteria leading to the discontinuation of nivolumab, ipilimumab, or trametinib as part of the triplet investigative regimen in Parts 1B and 2 will require discontinuation of the entire regimen.

Discontinuation of the study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined in the protocol (Section 8.1, Appendix 5, and Appendix 6) or if the investigator believes that it is in best interest of the participant.

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

In the case of pregnancy, the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the BMS Medical Monitor/designee of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Refer to Section 9.2.5 Pregnancy.

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.

The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of ipilimumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.

If a participant in any of the nivolumab/ipilimumab combination arms meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the participant should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study.

Participants are permitted to continue with nivolumab in combination with trametinib if deemed medically appropriate by the treating physician to manage toxicity, and in consultation with Medical Monitor/designee. Continuation with ipilimumab in combination with trametinib is not

permitted. For participants in Part 1A or Part 1, changes in study treatment are not permitted during the DLT observation period. See Section 7.1.2 trametinib dosing for further detail.

8.1.1 Nivolumab Dose Discontinuation (Part 1 Only)

For participants who receive nivolumab without ipilimumab, 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 (s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment(s), 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/designee.

- Any event that leads to delay in dosing lasting > 10 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 > 10 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor/designee.
  - Prior to re-initiating treatment in a participant with a dosing delay lasting >10 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 4 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 Nivolumab and Ipilimumab Dose Discontinuation

For participants who receive nivolumab in combination with ipilimumab and trametinib, study treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, or recurs, with the following exceptions for laboratory abnormalities, diarrhea, colitis, neurologic toxicity, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related diarrhea, colitis, neurologic toxicity, uveitis, pneumonitis, bronchospasm, 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
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require 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(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment(s), 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/designee.
- Any event that leads to delay in dosing lasting > 10 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 > 10 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor/designee. Prior to re-initiating treatment in a participant with a dosing delay lasting > 10 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 4 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 + ipilimumab dosing.

Any criteria leading to the discontinuation of nivolumab, ipilimumab, or trametinib as part of the triplet investigative regimen in Parts 1B and 2 will require discontinuation of the entire regimen.

8.1.3 Trametinib Dose Discontinuation

A maximum of 2 trametinib dose level reductions are allowed for Part 1 and Part 1A. Only 1 dose level reduction is permitted for Parts 1B and 2. If a third dose level reduction is required for Part 1 or 1A, or dose reduction below 1.0 mg per day is required, study treatment should be permanently discontinued. In addition, discontinue trametinib permanently for the following:

- Any event that leads to delay in dosing for > 10 weeks from the previous dose requires discontinuation with the following exception:
  - Dosing delays > 10 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor. Prior to re-initiating treatment in a subject with a dosing delay lasting > 10 weeks, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued treatment

Any criteria leading to the discontinuation of nivolumab, ipilimumab, or trametinib as part of the triplet investigative regimen in Parts 1B and 2 will require discontinuation of the entire regimen.

Refer to Appendix 6 for additional dose discontinuation criteria.

8.1.4 Regorafenib Dose Discontinuation

Discontinue regorafenib permanently for any of the following (local product label and institutional guidelines should be followed if they are more conservative):

- Failure to tolerate 80 mg dose
- Any occurrence of AST or ALT > 20× ULN
- Any occurrence of AST or ALT > 3× ULN with concurrent bilirubin > 2× ULN, except in participants with Gilbert's syndrome
- Re-occurrence of AST or ALT > 5× ULN despite dose reduction to 120 mg
- Gastrointestinal perforation or fistula
- Severe or life-threatening hemorrhage
- Reversible posterior leukoencephalopathy syndrome
- Wound dehiscence
- For any Grade 4 adverse reaction; only resume if the potential benefit outweighs the risks
- Any event that leads to delay in dosing for > 10 weeks from the previous dose requires discontinuation with the following exception:
  - Dosing delays > 10 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor. Prior to re-initiating treatment in a subject with a dosing delay lasting > 10 weeks, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued treatment

8.1.5 Treatment Beyond Progression

Participants in Cohorts 4 and 6 only, will be permitted to continue treatment beyond initial RECIST 1.1 defined progressive disease (PD), as assessed by the investigator, as long as the following criteria are considered:

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

Radiographic assessment/scan(s) should continue in accordance with the Section 2 Schedule of Activities for the duration of the treatment beyond progression and should be submitted to the central imaging vendor.

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

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

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

8.1.6 Post Study Treatment Study Follow-up

Post study treatment 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 until the LPLV on the study.

8.2 Discontinuation from the Study

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

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

8.3 Lost to Follow-Up

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

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities (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, 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 treatment assignment/randomization. The

investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on site/local labs until all study 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.[90]

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

9.1 Efficacy Assessments

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

9.1.1 Imaging Assessment for the Study

9.1.1.1 Methods of Measurements

- 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 a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis and other known/suspected sites of disease may be obtained.
- 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.
- PET alone will not be considered for the disease assessment. Complementary CT and/or MRI or biopsy must be performed in such cases. Note: Use of CT component of a PET/CT scanner: Combined modality scanning, such as with 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 1.1 (Appendix 8) 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.

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

Table 9.1.1.1-1: Acceptable Imaging Assessment Methods for Different Anatomical Areas

Anatomic Region	Preferred Method	Alternative Methods
Chest, abdomen, and pelvis Note: Scan must cover lung apices to diaphragm, diaphragm through entire liver, and to below the pubic symphysis	CT with IV contrast	**For chest:** • CT without contrast can be used only if the participant has a clinical contraindication for iodine-based IV contrast (e.g., hypersensitivity, renal insufficiency) **For abdomen and pelvis:** • MRI with gadolinium-based IV contrast is the first alternative method if the participant has a clinical contraindication for iodine-based IV contrast • CT without contrast can be used as the second alternative method only if the participant has a clinical contraindication for both contrast-enhanced CT and MRI.
Brain	MRI with IV contrast	• CT with IV contrast is the first alternative method if IV gadolinium is clinically contraindicated. • MRI without contrast can be used as a second alternative method if a participant has clinical contraindications for both contrast-enhanced CT and MRI

Notes:

1. CT scans must be performed with slice thickness of ≤ 5 mm. The reconstruction interval should be equal to slice thickness to avoid gap.
2. The same modality for a given anatomical coverage and the same scanning procedure (most importantly: reconstruction slice thickness, anatomic coverage, use of IV contrast) should be consistent between baseline and all subsequent follow-up scanning. If possible, the same scanner or an equivalent scanners should be used throughout the study.
3. For abdomen and pelvis CT scans, oral contrast is recommended as per institutional standards.
4. MRI should include T1 and T2-weighted sequences with T1-weighted at both pre- and post-contrast.
5. All scans generated should be exportable in electronic format (DICOM) to enable secure and rapid electronic transmission to the designated central imaging laboratory.

9.1.1.2 Imaging Schedule and Assessment

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

At Screening, MRI of the brain without and with contrast will be performed for participants with a history or clinical symptoms of brain metastasis. Participants with history or clinical symptoms of brain metastasis should have surveillance MRI per local SOC (approximately every 12 weeks) or sooner if clinically indicated.

First imaging assessment post-baseline should be performed Week 8 (± 7 days) following date of first dose. Subsequent assessments should include chest, abdomen, pelvis, and all known sites of disease and should use the same imaging method as was used at baseline. Irrespective of whether subsequent treatment is given, held, or discontinued, imaging assessment should occur for all participants who have received at least one dose of study treatment at every 8 weeks (± 7 days) until whichever of the following occurs first:

- Radiological disease progression
- Withdrawal of consent
- Death
- End of Trial

For all participants who continue treatment beyond initial progression (Section 8.1.5), scans should continue at every 8 weeks until treatment discontinuation criteria are met (Section 8).

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.

9.1.1.3 Tumor Assessment by Investigator Sites

Investigator sites must review baseline images to confirm the participant has measurable disease using RECIST (Response Evaluation Criteria in Solid Tumor) 1.1 criteria (Appendix 8). Tumor assessments for ongoing study treatment decisions will be completed by the local investigator sites using RECIST 1.1 criteria. Tumor assessments are to continue for all participants on the protocol schedule irrespective of whether treatment is given, held, or discontinued. Study treatment decisions should be made by the investigator based on local read results and clinical assessment.

Per RECIST 1.1, partial or complete response should be confirmed by a repeat tumor imaging assessment, preferably at the next scheduled imaging visit, and not less than 4 weeks from the date the response was first documented. A Best Overall Response (BOR) of SD requires a minimum of 49 days from first dose (Day 1) to the date of the first imaging assessment.

[redacted] may undergo blinded independent central review (BICR) at any time during the study. Prior to [redacted] first participant, sites should be qualified and understand the [redacted] provided by the central imaging vendor.

For Part 1B and Part 2, tumor assessment scans should be submitted to the vendor within 14 days of acquisition.

[redacted]

[redacted]

9.2 Adverse Events

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

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

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

Contacts for SAE reporting specified in Appendix 3

Immune-Mediated Adverse Events

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.

Trametinib Adverse Event of Special Interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the Investigator Brochure, and a list of Medical Dictionary for Regulatory Activities (MedDRA) preferred terms to flag as AESI's will be included in the Data Presentation plan.

AESI for trametinib include:

- Skin related toxicities
- Ocular events
- Cardiac related events
- Hepatic disorders
- Pneumonitis/interstitial lung disease
- Bleeding events
- Hypertension
- Hypersensitivity
- Venous thromboembolism

Warnings and Precautions for Regorafenib

Refer to local product labels for safety profile, including Warnings and Precautions.

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).

Sections 5.6.1 and 5.6.2, in the 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 discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

For participants assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assignment.

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

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

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

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 AEs and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known AEs when appropriate for the program or protocol.

Every adverse event must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's case report form.

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 9.2.4 and Appendix 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

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

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

9.2.4 Regulatory Reporting Requirements for SAEs

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

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

9.2.5 Pregnancy

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

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/designee within 24 hours of awareness of the pregnancy (see Section 8.1).

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

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to 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 worsens from baseline and 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/delayed, or dose reduced
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy or intervention
- Any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition, are not to be reported as AEs or SAEs.

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

9.2.7 Potential Drug Induced Liver Injury (DILI)

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

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

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

For participants with elevated AST or ALT or Total bilirubin at baseline, potential DILI is defined as (Appendix 6):

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

9.3.1 Nivolumab or Ipilimumab Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 9.2.4).

9.3.2 Trametinib Overdose

In the event of a trametinib overdose, defined as administration of more than 3.0 mg once daily, the investigator should contact the Medical Monitor/designee immediately and closely monitor the participant for AEs/SAEs and laboratory abnormalities. There is no specific treatment recommended by the marketing authorization holder for trametinib overdose. The investigator will use clinical judgment to treat any overdose.

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

[redacted]

Information regarding the quantity of the excess dose as well as the duration of the overdosing should be documented in the eCRF.

9.3.3 Regorafenib Overdose

Refer to local product label.

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 in Section 2.

9.4.2 Vital signs

Refer to Schedule of Activities in Section 2.

9.4.3 Ophthalmic Examination

Participants are required to have a standard ophthalmic examination conducted by an ophthalmologist at screening prior to randomization (7-day window does not apply at C1D1), Week 4/Month 1 (within 7 days prior to study treatment.), Month 6 from the first dose date, then annually thereafter unless clinically indicated sooner on treatment. In addition, there will be an

exam at follow-up visit 1. Ophthalmic examination will be performed at the time points indicated in the Schedule of Activities in Section 2. The exam will include visual acuity (best corrected), tonometry (intraocular pressure measurement), visual field examination, slit lamp biomicroscopy of the anterior segment (with special attention to inflammation) and the posterior segment, and indirect fundoscopic examination with special attention to possible retinal abnormalities. Optical coherence tomography is strongly recommended at scheduled visits, with special attention to retinal abnormality that are predisposing factors for Retinal Vein Occlusion (RVO) or Central Serous Retinopathy (CSR). In participants with clinical suspicion of RVO or CSR, additional color fundus photographs, as well as fluorescein angiography and/or optical coherence tomography were recommended, if clinically indicated.

Ophthalmic examination during treatment and Follow-Up periods is not required for Cohort 5 participants, unless clinically indicated.

9.4.4 Electrocardiograms

Refer to Schedule of Activities in Section 2.

9.4.5 Echocardiogram/MUGA

Decreases of the LVEF have been observed in participants receiving trametinib. Echocardiograms (ECHOs) will be performed to assess cardiac ejection fraction and cardiac valve abnormalities. ECHOs will be performed at the time points indicated in the Schedule of Activities in Section 2. The evaluation by the echocardiographer should include an evaluation for LVEF and an assessment of the right and left-sided heart valves. The procedure (ECHO) to document the participant's baseline LVEF status must be used consistently throughout the study. If possible, it is also preferred that interpretation of LVEF status be performed consistently by the same reviewer throughout the study.

9.4.6 Clinical Safety Laboratory Assessments

Local laboratories are being utilized to analyze clinical safety samples. Investigators must document their review of each laboratory safety report.

Results of clinical laboratory tests performed at screening must be available and meet eligibility criteria prior to first dosing. For subsequent infusion, clinical laboratory tests must be performed within 72 hours prior to next infusion (with results available to support continuation with study treatment). Continuation of trametinib dosing will be also assessed within 72 hours prior to initiation of the subsequent cycle, and as needed throughout the cycle.

For participants with normal or clinically stable thyroid function results from previous test, study treatment can resume with pending laboratory results if participants meet all other requirements for continuing study treatment. Results must be reviewed promptly once available to confirm dosing decision and medical management.

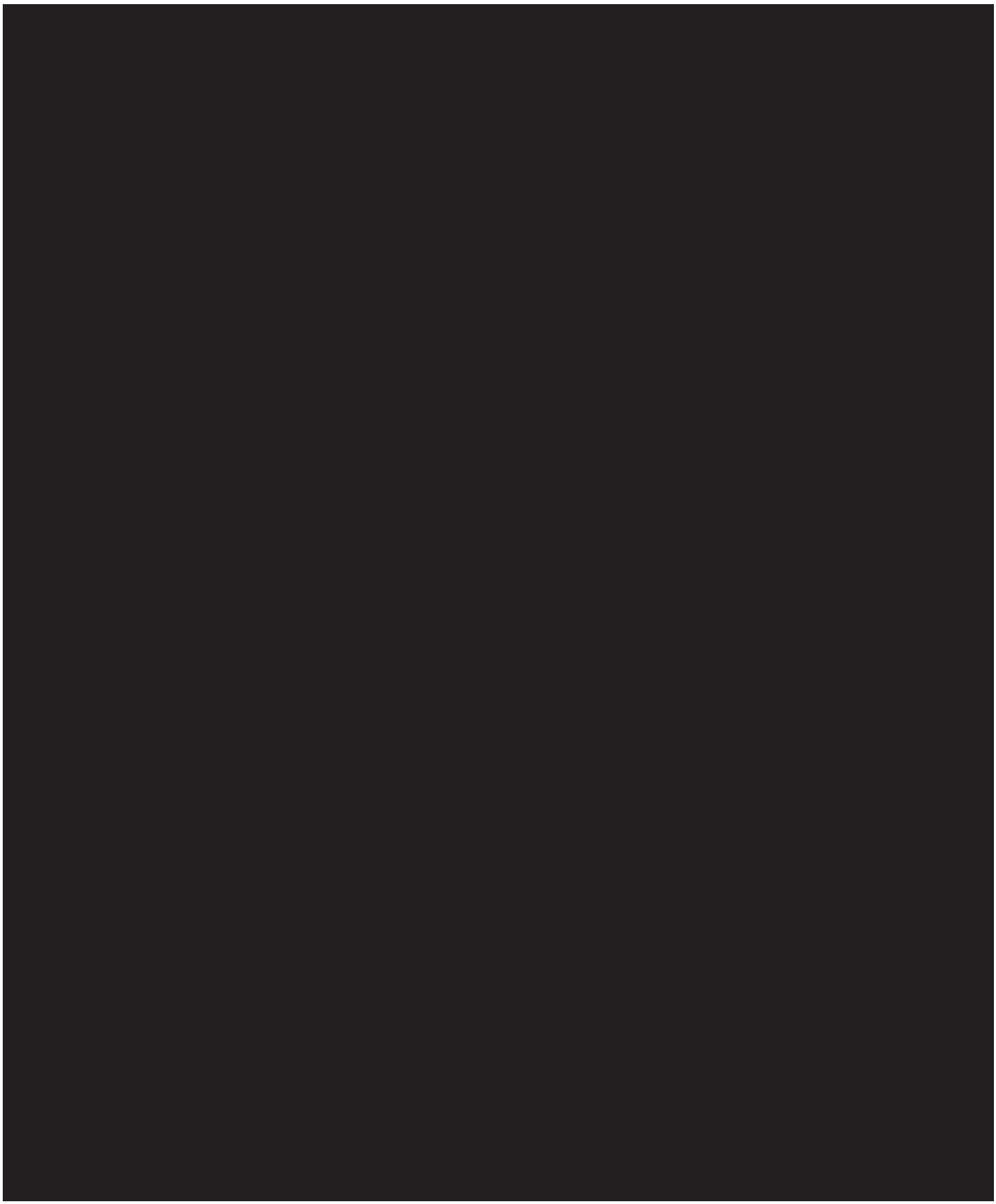
See Schedule of Activities (Section 2).

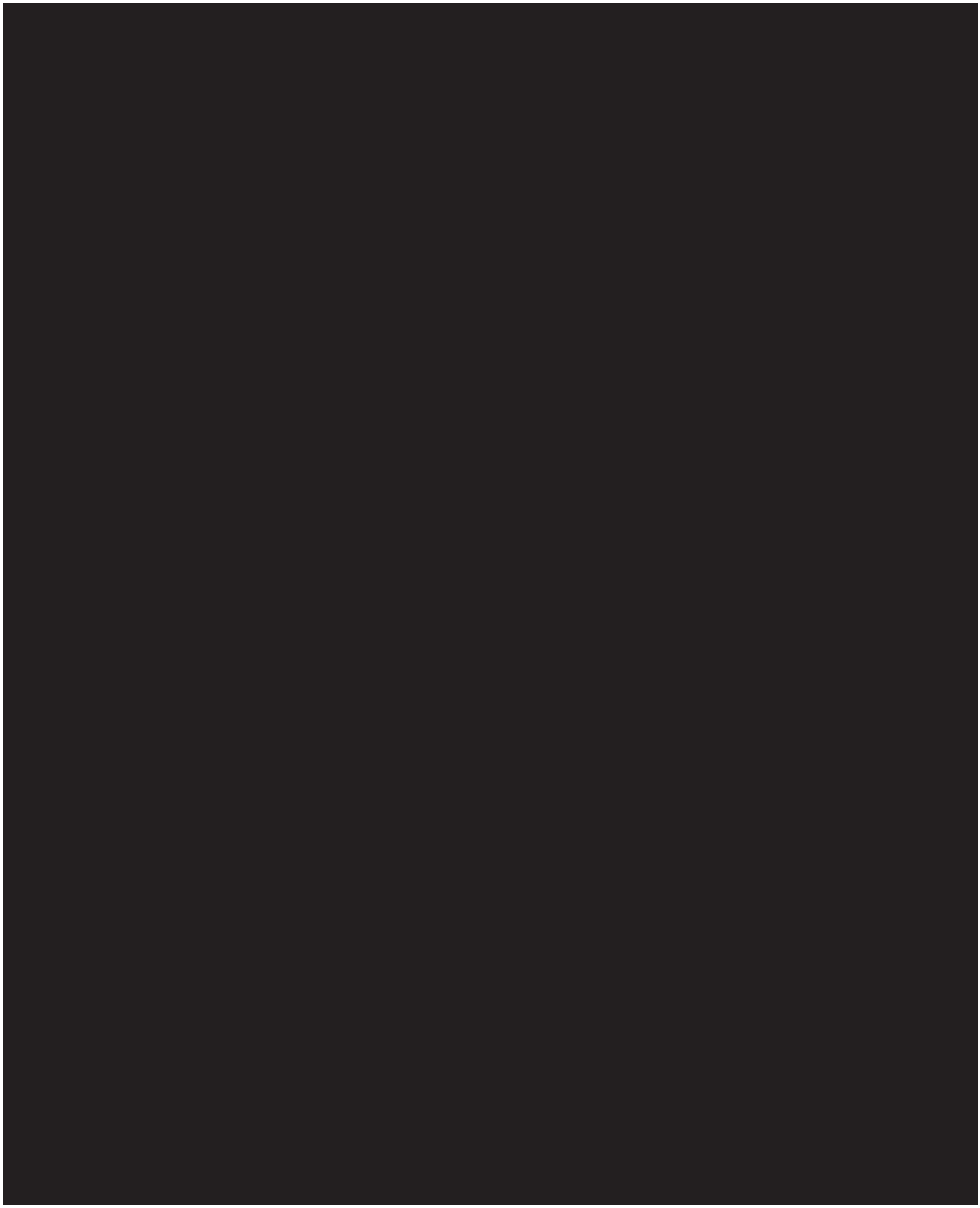
9.4.7 Imaging Safety Assessment

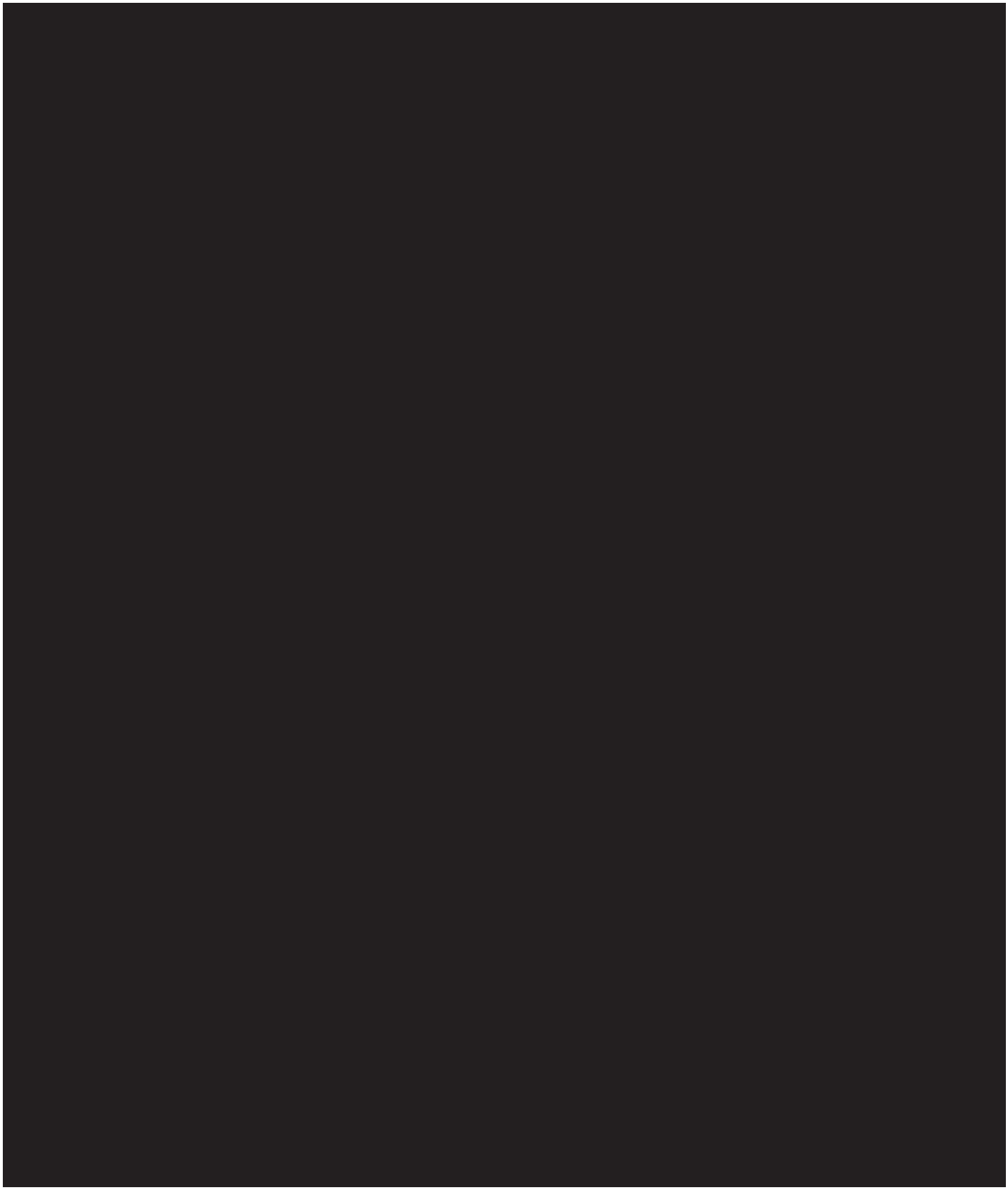
Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

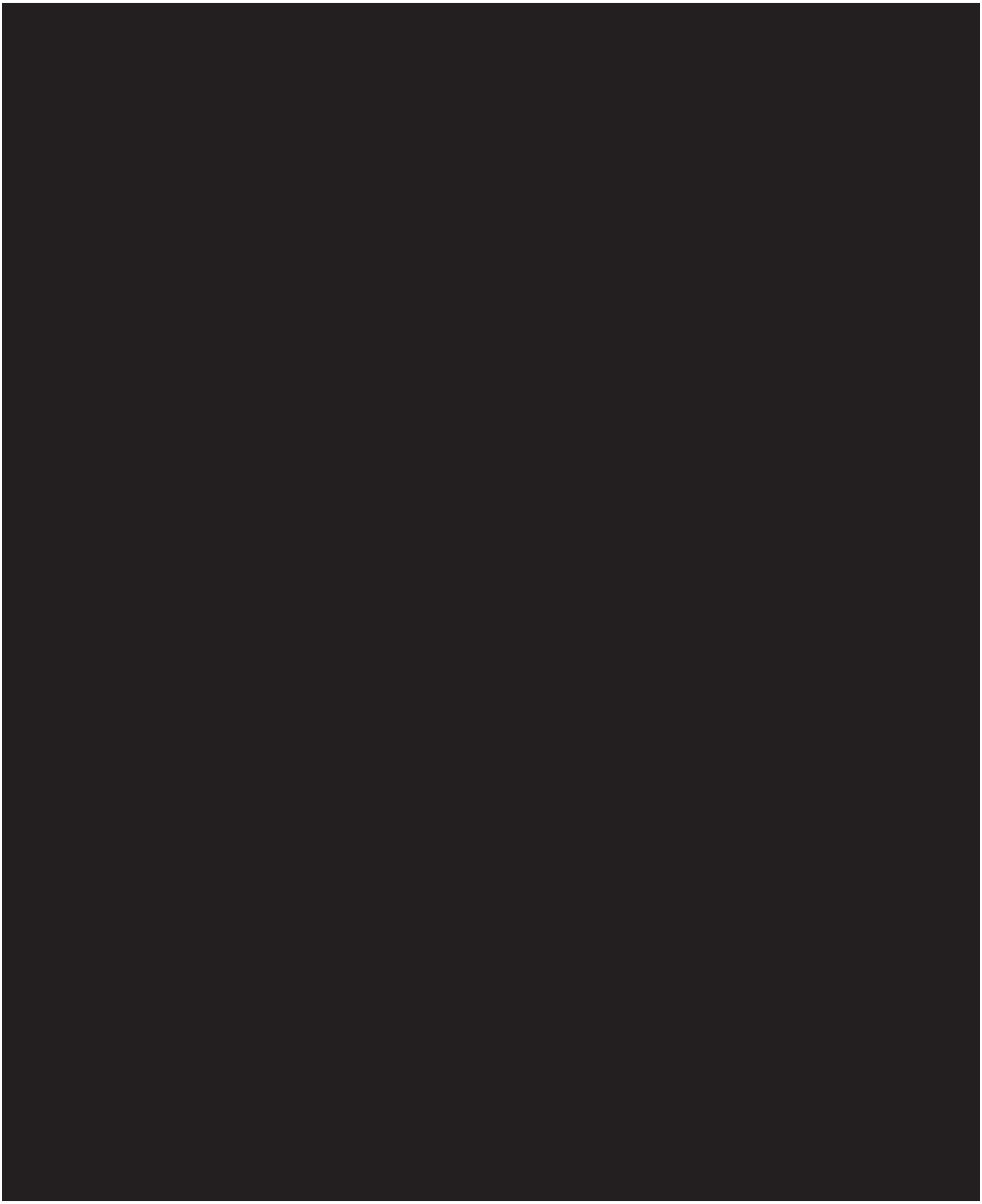
[redacted]

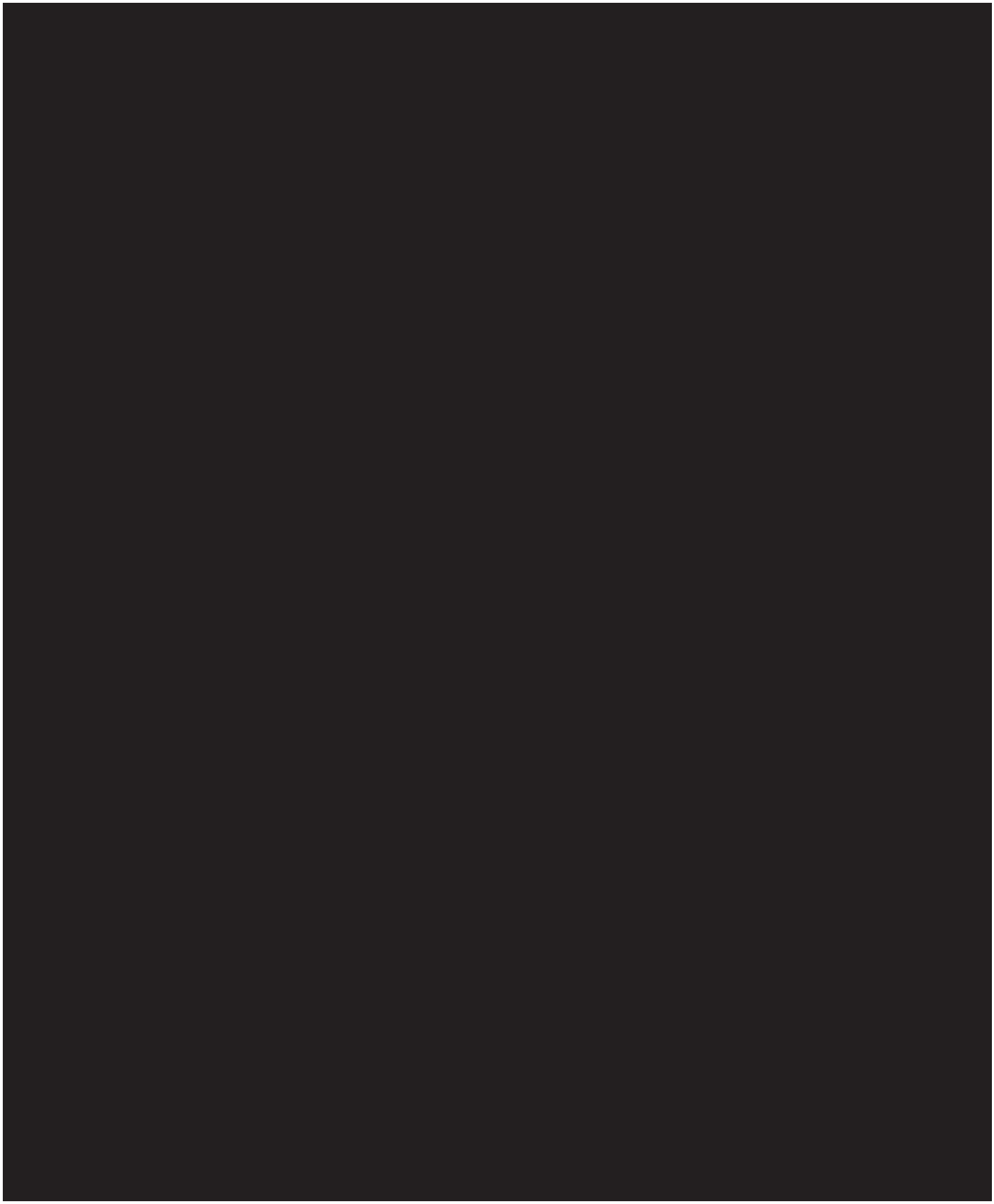
[redacted]

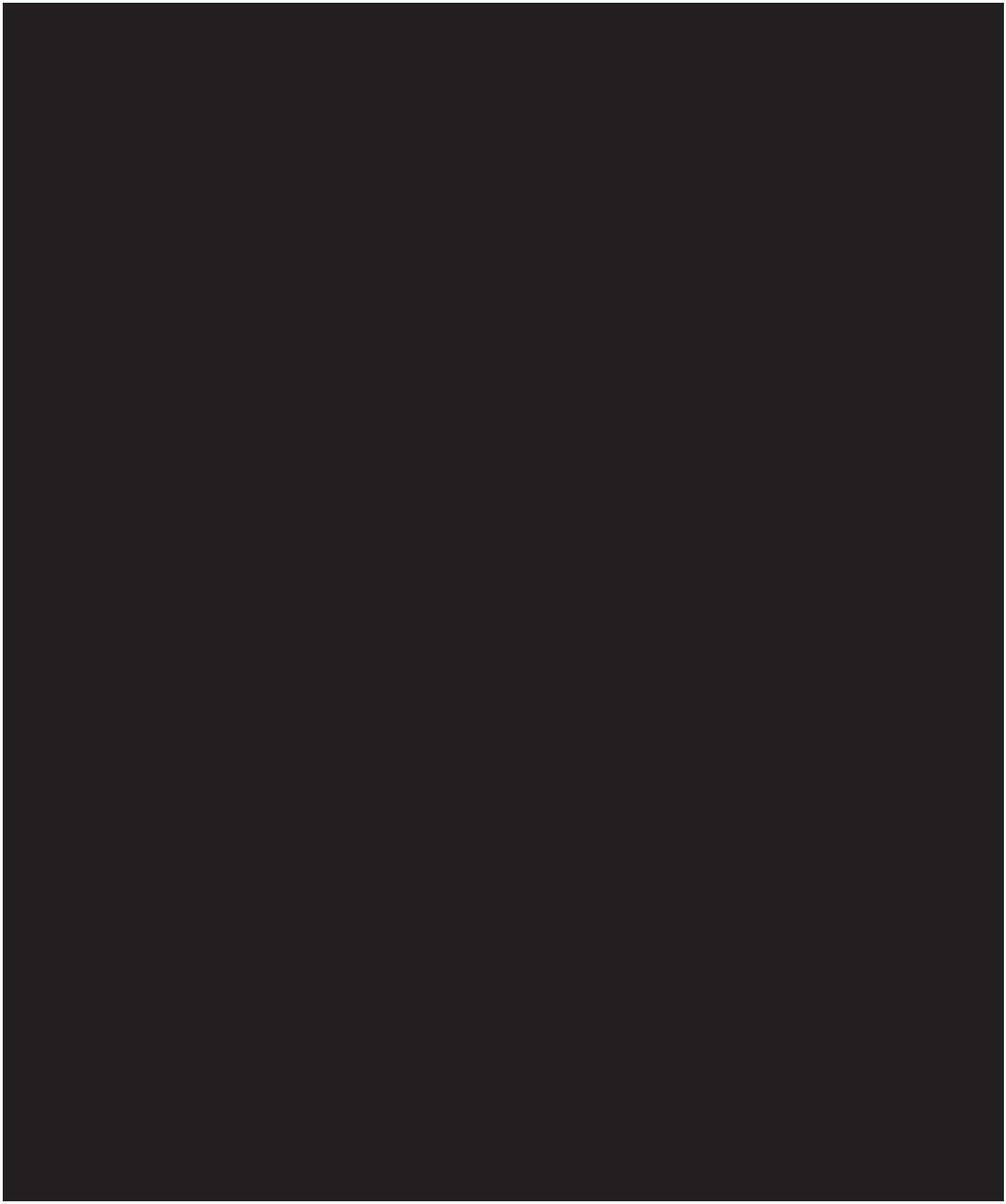


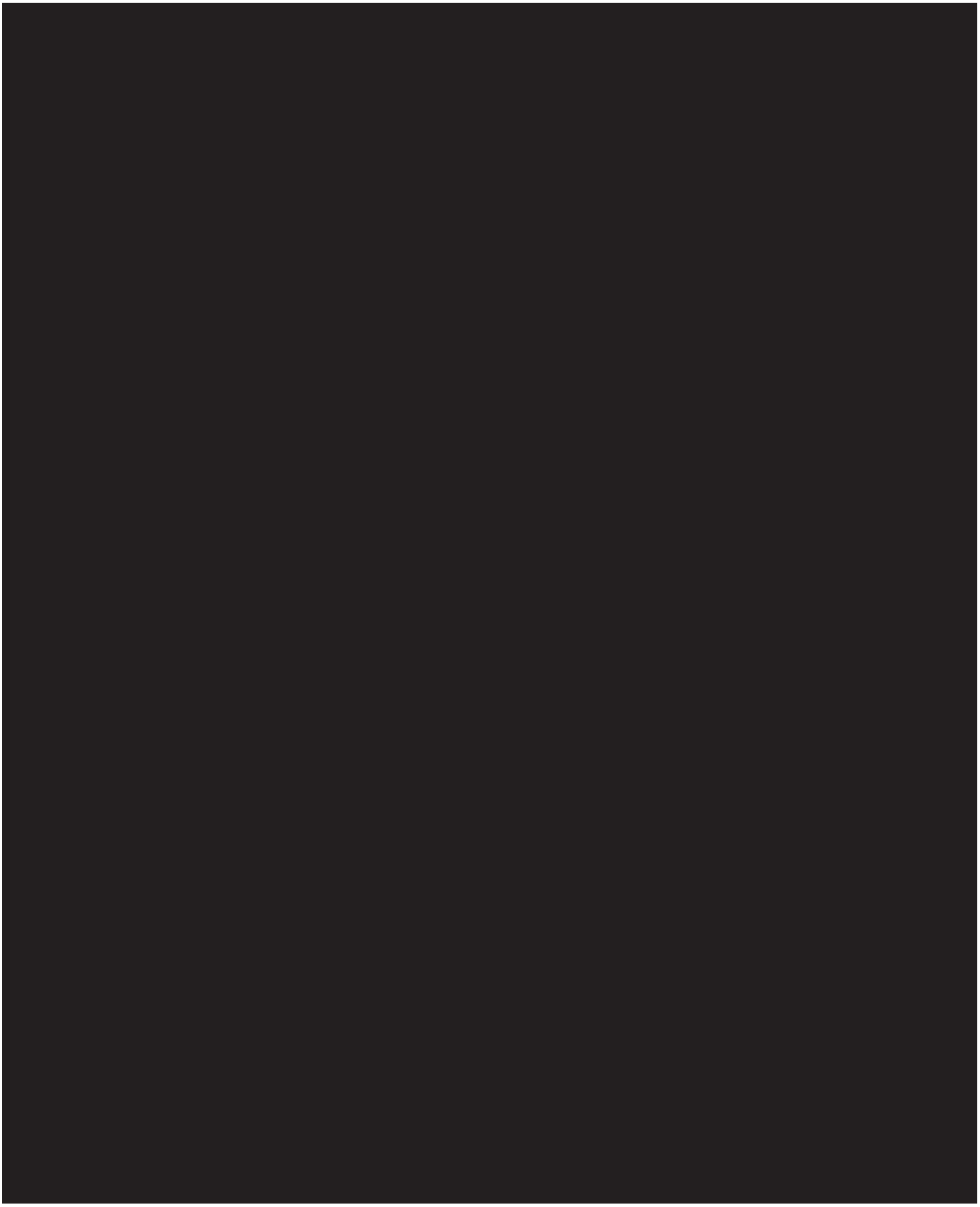












[redacted]

9.9 Health Economics OR Medical Resource Utilization and Health Economics

In addition to the aforementioned [redacted], health care resource utilization data will be collected for Part 2 participants using an internal case report form eCRF developed for use in previous trials. The form, which is completed by study staff, records information about hospital admissions, including number of days spent in various wards and discharge diagnosis, as well as non-protocol specified visits related to study therapy, including date of visit, reason for visit, and type of visit. The health care resource utilization data will be used to support subsequent economic evaluations.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

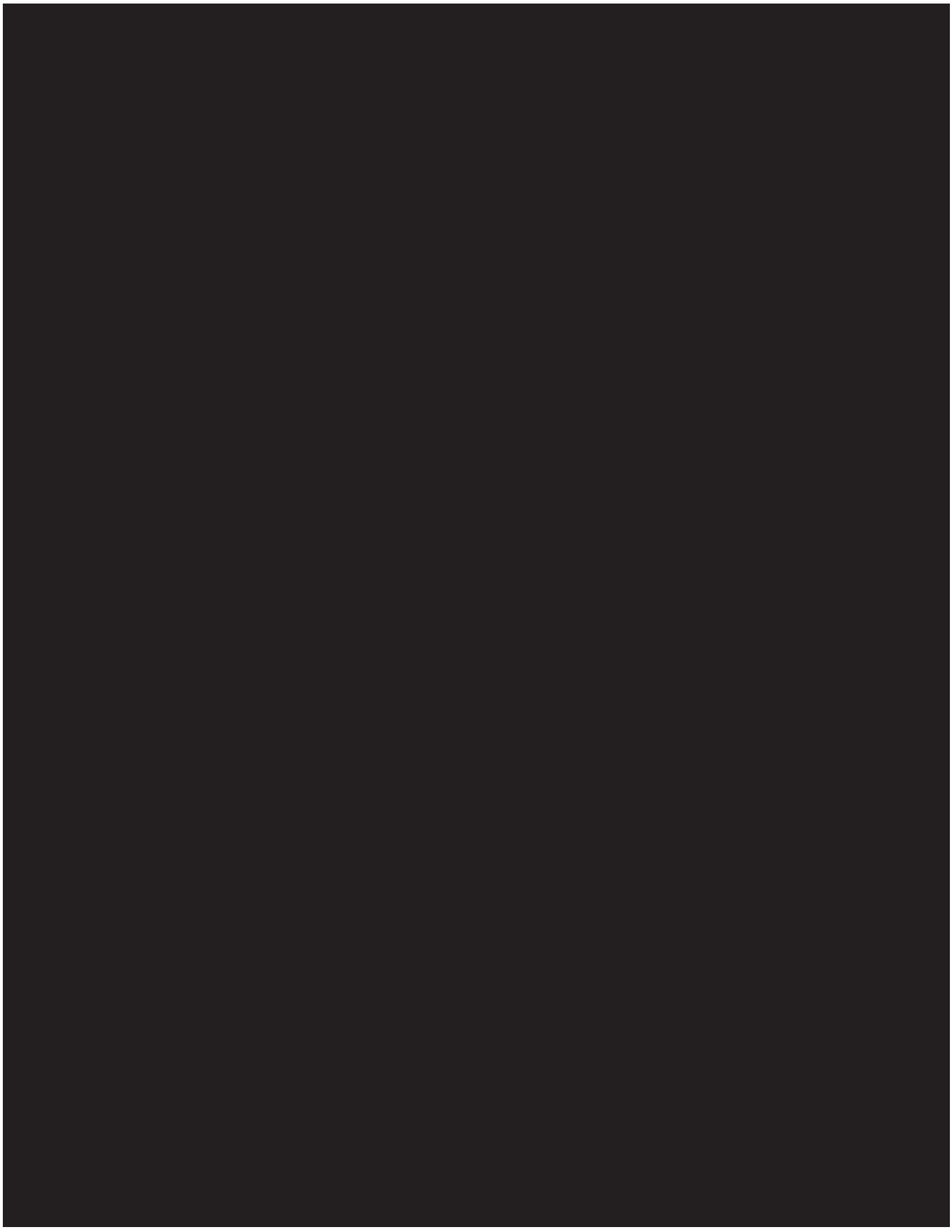
This study will consist of multiple cohorts/parts for different target populations with different treatment regimens and the sample size for each part has been provided as below.

10.1.1 mCRC 3rd line Participants: Part 1 Dose Optimization Cohorts

Sample size at each dose level depends on the observed toxicity and is not based on statistical considerations. Three to 6 participants will be evaluated at each dose level. Administration of treatment regimen to 6 participants at a dose level provides ~82% probability of observing at least one occurrence of any adverse event if there is a 25% incidence in the population from which the sample is drawn. Approximately 3 to 18 participants are estimated to be treated in these dose optimization cohorts. The total sample size for this part ranges from 3 to 18 participants.

10.1.2 mCRC 3rd line Plus Participants: Part 2 [redacted] Cohort

The purpose of Part 2 is to gather tolerability and preliminary efficacy, for nivolumab in combination with ipilimumab and trametinib or SOC (regorafenib) in pMMR/MSS 3L+ (no more than 4 prior lines of therapy) mCRC, including [redacted] for combination therapy with immune checkpoint inhibitor(s) and MEK inhibitor. Approximately 120 participants will be randomized in 2:1 ratio to receive nivolumab plus ipilimumab plus trametinib continuous dosing (Cohort 4), or SOC (regorafenib, Cohort 5).



[redacted]

10.1.3 mCRC 2nd line Participants: Part 1A Dose Optimization Cohorts

Sample size at each dose level depends on the observed toxicity and is not based on statistical considerations. Three to 6 participants will be evaluated at each dose level. Administration of treatment regimen to 6 participants at a dose level provides ~82% probability of observing at least one occurrence of any adverse event that would occur with a 25% incidence in the population from which the sample is drawn. Approximately 3 to12 participants are estimated to be treated for each of two dose optimization cohorts (nivolumab + ipilimumab + continuous trametinib dosing and nivolumab + ipilimumab + intermittent trametinib dosing). The total sample size for this part ranges from 6 to 24 participants.

10.1.4 mCRC 2nd line Participants: Part 1B [redacted] Cohorts

The safety and efficacy of the triplet combination regimen has been initially explored in the 2L setting. An additional [redacted] cohort will be initiated for the 2L participants to further optimize the patient selection strategy. Approximately 80 participants will be treated to establish expanded experience with the triplet regimen of nivolumab plus ipilimumab plus trametinib continuous dosing.

[redacted]

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined below. The population definition will apply to all cohorts unless specified otherwise:

Population	Description
Enrolled	All participants who sign informed consent and were registered into IRT.
Randomized	All participants who are randomized to any treatment in Part 2 (primary efficacy analysis population for Part 2 and outcome research assessment analysis population for Part 2).
Treated	All participants who take at least 1 dose of study medication.
Response-evaluable	All treated (randomized for Part 2) participants with measurable disease at baseline and at least one post-baseline tumor assessment.

[redacted]

Population	Description
[redacted]	

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before the first 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. Part 1A/1B, Part 1 and Part 2 will be analyzed independently. 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

The primary efficacy analyses will be performed on the treated population for all cohorts, except for Part 2 where the primary efficacy analyses will be performed on the randomized population. Efficacy in subgroups of interest will be evaluated in Part 2 and in Part 1B. [redacted] Other subgroups (e.g., the stratification factor of tumor sidedness, etc.) will be described in the Statistical Analysis Plan (SAP). Details on censoring scheme on time-to-event endpoints such as DOR, PFS, and OS and additional analyses will be described in the SAP. In Part 2, no crossover will be permitted between the two treatment arms upon discontinuation of study treatment.

Endpoint	Statistical Analysis Methods
Best Overall Response (BOR) for a participant will be assessed per RECIST 1.1 as applicable per investigator (primary endpoint). BOR is defined as the best response designation, recorded between the first dosing date (randomization date, for Part 2) 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. ORR is defined as the proportion of all treated (randomized, for Part 2) participants whose BOR is either confirmed complete response (CR) or confirmed partial response (PR). The disease control rate (DCR) is defined as the proportion of participants whose BOR is either confirmed CR or confirmed PR or stable disease (SD)	• Estimate of ORR/DCR and corresponding two-sided exact 95% CI using the Clopper-Pearson method by treatment
DOR and TTR (per investigator) DOR for a participant with a BOR of confirmed CR or PR, is defined as the time between the date of first confirmed response and the date of the first objectively documented tumor progression per RECIST 1.1 or death, whichever occurs first. The rules of censoring are the same as for PFS. Time to response (TTR) is defined for participants who had a confirmed CR or PR as the time from the first dosing date (randomization date, for Part 2) to the date of first documented CR or PR per RECIST 1.1.	• Estimate of median DOR/TTR using the Kaplan-Meier method and corresponding two sided 95% CI (using log-log transformation) by treatment
Progression Free Survival PFS (per investigator) and overall survival OS PFS for a participant is defined as the time from the first dosing date (randomization date for Part 2) to the date of first objectively documented disease progression per RECIST 1.1 (ie, radiologic) 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 tumor assessment. • Participants who did not have any on study tumor assessments and did not die will be censored on the first dosing date (randomization date, for Part2). • Participants who started any subsequent anti-cancer therapy without a prior reported progression or prior to death will be censored	• Estimate of median and rates at fixed time points by the Kaplan-Meier method and corresponding two sided 95% CI using log-log transformation (for median) and Greenwood formula (for rates) by treatment

Endpoint	Statistical Analysis Methods
at the last tumor assessment prior to initiation of the subsequent anticancer therapy. • Further explanation for various censoring scenarios for PFS will be specified in the SAP. OS for a participant is defined as the time from the first dosing date (randomization date for Part 2) to the date of death due to any cause. A participant who has not died will be censored at last known date alive.	
[redacted]	• [redacted]

10.3.2 Safety Analyses

All safety analyses will be performed on the Treated population.

Endpoint	Statistical Analysis Methods
Incidence of DLTs, AEs, SAEs, AEs leading to discontinuation, deaths AEs will be graded according to CTCAE (version 4.0).	DLT rate by dose level; Frequency distribution of treated participants with AE using the worst CTC grade. Participants will only be counted (1) once at the preferred term (PT) level, (2) once at the system organ class (SOC) level, and (3) once in the 'Total participant' row at their worst CTC grade, regardless of SOC or PT. Deaths will be summarized using frequency distribution
Laboratory abnormalities Laboratory values will be graded according to CTCAE (version 4.0)	Laboratory abnormalities will be summarized. Lab shift table using the worst CTC grade on treatment per participant.

[redacted]

[redacted]

10.3.6 Outcomes Research Analyses

[redacted]

[redacted]

10.3.6.3 Other Analyses

Not Applicable

10.3.7 Interim Analyses

Data were reviewed during the dose escalation/de-escalation evaluation phase (Part 1 and Part 1A) to determine the proposed combination regimens for Part 2 and Part 1B. Comprehensive analyses for Part 1 including safety, [redacted], and preliminary efficacy data were conducted to support dose selection for Part 2 (RP2D) as appropriate.

An interim analysis (IA) of Part 2 and Part1B cohorts will be conducted after an overall total of approximately 100 treated participants (including approximately 60 treated participants from Part 2) have a minimum of 4 months of follow-up after the first treatment (corresponding to at least 2 tumor assessments). The objectives of this IA will be a review of the safety data and to provide preliminary efficacy.

11 REFERENCES

1 Ohrling K, Edler D, Hallstrom M, et al: Mismatch repair protein expression is an independent prognostic factor in sporadic colorectal cancer. Acta Oncol. 2010;49.

2 Koopman M, Kortman G, Mekenkamp L, et al. Deficient mismatch repair system in patients with sporadic advanced colorectal cancer. Br J Cancer. 2009;100(2):266-73.

3 Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Eng J Med 2015. 372:2509-20.

4 Overman MJ, Kopetz S, McDermott RS, et al. Nivolumab ± ipilimumab in treatment (tx) of patients (pts) with metastatic colorectal cancer (mCRC) with and without high microsatellite instability (MSI-H): CheckMate-142 interim results. Poster presented at 2016 ASCO Annual Meeting. J Clin Oncol 34, 2016.

5 Curran MA, Montalvo W, Yagita H, Allison JP. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. Proceedings of the National Academy of Sciences. 2010; 107: 4275-80.

6 CA209012: Study of Nivolumab (BMS-936558) in Combination With Gemcitabine/Cisplatin, Pemetrexed/Cisplatin, Carboplatin/Paclitaxel, Bevacizumab Maintenance, Erlotinib, Ipilimumab or as Monotherapy in First-Line or in Switch Maintenance in Participants With Stage IIIB/IV Non-small Cell Lung Cancer (NSCLC) (CheckMate 012). NCT01454102.

7 CA209016: Nivolumab (BMS-936558; MDX-1106) in Combination With Sunitinib, Pazopanib, or Ipilimumab in Participants With Metastatic Renal Cell Carcinoma (RCC) (CheckMate016). NCT01472081.

8 Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med. 2015;372:2006-17.

9 CA209067: Phase 3 Study of Nivolumab or Nivolumab Plus Ipilimumab Versus Ipilimumab Alone in Previously Untreated Advanced Melanoma (CheckMate-067). NCT01844505.

10 Chen EX, Jonker DJ, Loree JM, et al. Effect of combined immune checkpoint inhibition vs. best supportive care alone in patients with advanced colorectal cancer, JAMA Oncol. 2020;6:831-8.

11 Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair–deficient/microsatellite instability–high metastatic colorectal cancer. Clin Oncol. 2018; 36:773-9.

12 Salmon H, Idoyaga J, Rahman A, et al: Expansion and Activation of CD103+ Dendritic Cell Progenitors at the Tumor Site Enhances Tumor Responses to Therapeutic PD-L1 and BRAF Inhibition. Immunity. 2010;44:924-38.

13 Ebert Peter JR, Cheung J, Yang Y, et al: MAP Kinase Inhibition Promotes T Cell and antitumor Activity in Combination with PD-L1 Checkpoint Blockade. Immunity. 2016;44:609-21.

[14] Hoeflich KP, Merchant M, Orr C, et al: Intermittent Administration of MEK Inhibitor GDC-73 plus PI3K Inhibitor GDC-0941 Triggers Robust Apoptosis and Tumor Growth Inhibition. Cancer Research. 012;72:210-9.

[15] Sumimoto H, Imabayashi F, Iwata T, et al: The BRAF–MAPK signaling pathway is essential for cancer-immune evasion in human melanoma cells. J Exper Med.2006;203:1651-6.

[16] Rinehart J, Adjei AA, LoRusso PM, et al: Multicenter Phase II Study of the Oral MEK Inhibitor, CI-1040, in Patients With Advanced Non-Small-Cell Lung, Breast, Colon, and Pancreatic Cancer. J Clin Oncol. 2004;22:4456-62.

[17] Infante JR, Fecher LA, Falchook GS, et al: Safety, pharmacokinetic, pharmacodynamic, and efficacy data for the oral MEK inhibitor trametinib: a phase 1 dose-escalation trial. Lancet Oncol. 2012; 13:773-81.

[18] Liu L, Mayes PA, Eastman S, et al: The BRAF and MEK Inhibitors Dabrafenib and Trametinib: Effects on Immune Function and in Combination with Immunomodulatory Antibodies Targeting PD-1, PD-L1, and CTLA-4. American Association for Cancer Research 21:1639-51, 2015.

[19] Eng C, Kim TW, Bendell J, et al. Atezolizumab with or without cobimetinib versus regorafenib in previously treated metastatic colorectal cnacer (IMblaze370): a multicentre, open-label, phase 3, randomised, controlled trial. Lancet Oncol 2019;20:849:61.

[20] Ferlay J, Shin HR, Bray F, et al. 2018 Globocan data base: Global Cancer Facts & Figures 4th Edition

[21] Siegel RL, Miller KD, Saurer AG, et al. Colorectal Cancer Statistics, 2020. CA Cancer J Clin. 2020;70:145-164.

[22] Cutsem, EV. Cervantes A, Nordlinger B. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014; 25 (sup 3); iii1-iii9.

[23] NCCN. http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf accessed on 13 Sept 2013.

[24] Tournigand C, André T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol. 2004 Jan 15;22(2):229-37.

[25] Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol. 2010 Nov 1;28(31):4706-13.

[26] Tabernero J, Van Cutsem E, Lakomy R, et al: Results from VELOUR, a phase 3 study of aflibercept versus placebo in combination with FOLFIRI for the treatment of patients with previously treated metastatic colorectal cancer. 2011 European Multidisciplinary Congress. Abstract 6LBA. Presented September 25, 2011.

[27] http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125085s267lbl.pdf accessed 13 Sept 2013.

[28] Tabernero J, Yoshino T, Cohn AL, et al: Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. The Lancet Oncology. 2015;16:499-508.

[29] http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125418s000lbl.pdf accessed 13 Sept 2013.

[30] http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125084s242nd Linebl.pdf accessed 13 Sept 2013.

[31] http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203085s001lbl.pdf accessed on 13 Sept 2013.

[32] Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, et al. Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer. N Engl J Med. 2015;372(20):1909-19.

[33] Schubbert S, Shannon K, Bollag G. Hyperactive Ras in developmental disorders and cancer. Nat Rev Cancer 2007; 7:295-308.

[34] Morris VK, Lucas FA, Overman MJ, et al. Clinicopathologic characteristics and gene expression analyses of non-KRAS 12/13, RAS-mutated metastatic colorectal cancer. Ann Oncol 2014; 25:2008-14.

[35] Bos JL, Fearon ER, Hamilton SR, et al. Prevalence of ras gene mutations in human colorectal cancers. Nature 1987; 327:293-7.

[36] Vaughn CP, Zobell SD, Furtado LV, Baker CL, Samowitz WS. Frequency of KRAS, BRAF, and NRAS mutations in colorectal cancer. Genes Chromosomes Cancer 2011; 50:307-12.

[37] Van Cutsem E, Cervantes A, Nordlinger B, Arnold D, ESMO Guidelines Working Group. Metastatic colorectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014; 25(suppl 3):iii1-9.

[38] Waring P, Tie J, Maru D et al. RAS mutations as predictive biomarkers in clinical management of metastatic colorectal cancer. Clinical Colorectal Cancer. 2015;15(2):95-103.

[39] Larki P, Gharib E, Yaghoob M. Coexistence of KRAS and BRAF Mutations in Colorectal Cancer: A Case Report Supporting the Concept of Tumor Heterogeneity. Cell Journal. 2017;19(1):113-117.

[40] Barras D. BRAF Mutation in Colorectal Cancer: An Update. Biomarkers in Cancer. 2015;7(S1): 9-12.

[41] Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in Combination with Oxaliplatin, Fluorouracil, and Leucovorin (FOLFOX4) for Previously Treated Metastatic Colorectal Cancer: Results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol. 2007; 25(12):1539-44.

[42] Bennouna J, Sastre J, Arnold D, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncol. 2013; 14(1):29-37.

[43] Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol, 2012; 30(28):3499-506.

[44] Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol. 2010; 28(31):4706-13.

[45] Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013; 381(9863):303-12.

[46] Aaltonen LA, Salovaara R, Kristo P, et al. Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. N Engl J Med 1998;338:1481-7.

[47] Popat S, Hubner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. J Clin Oncol 2005;23:609-18.

[48] NCCN current version March 2017.

[49] Pawlik TM, Paut CP, Rodriguez-Bigas MA. Colorectal carincogenesis: MSI-H versus MSI-L. Disease Markers. 2004;20:99-206.

[50] Gruber SB and Vilar E. Microsatellite instability in colorectal cancer-the stable evidence. Nat Rev Clin Oncol 2010;7:153-62.

[51] Rajagopalan H, Bardelli A, Lengauer C, et al. Tumorigenesis: RAF/RAS oncogenes and mismatch-repair status. Nature 2002;418:934.

[52] Oliveira C, Pinto M, Duval A, et al. BRAF mutations characterize colon but not gastric cancer with mismatch repair deficiency. Oncogene 2003;22:9192-6.

[53] Greenson JK, Bonner JD, Ben-Yzhak O, et al. Phenotype of microsatellite unstable colorectal carcinomas: Well-differentiated and focally mucinous tumors and the absence of dirty necrosis correlate with microsatellite instability. Am J Surg Pathol 2003;27:563-70.

[54] Dolcetti R, Viel A, Doglioni C, et al. High prevalence of activated intraepithelial cytotoxic T lymphocytes and increased neoplastic cell apoptosis in colorectal carcinomas with microsatellite instability. Am J Pathol 1999;154:1805–13.

[55] Guidoboni M, Gafa` R, Viel A, et al. Microsatellite instability and high content of activated cytotoxic lymphocytes identify colon cancer patients with a favorable prognosis. Am J Pathol 2001;159: 297–304.

[56] Duval A, Rolland S, Compoint A, et al. Evolution of instability at coding and non-coding repeat sequences in human MSI-H colorectal cancers. Hum Mol Genet 2001;10:513–8.

[57] Kammertoens T, Blankenstein T. Making and circumventing tolerance to cancer. Eur J Immunol 2009;39:2345–53.

[58] Schwitalle Y, Kloor M, Eiermann S, et al. Immune response against frameshift-induced neopeptides in HNPCC patients and healthy HNPCC mutation carriers. Gastroenterology 2008;134:988–97.

[59] Saeterdal I, Bjørheim J, Lislerud K, et al. Frameshift mutation-derived peptides as tumor specific antigens in inherited and spontaneous colorectal cancer. Proc Nat Acad Sci USA 2001;98:13255–60.

[60] Alexander J, Watanabe T, Wu TT, et al. Histopathological identification of colon cancer with microsatellite instability. Am J Pathol 2001;158:527–35.

[61] Banerjea A, Ahmed S, Hands RE, et al. Colorectal cancers with microsatellite instability display mRNA expression signatures characteristic of increased immunogenicity. Mol Cancer 2004;3:21.

[62] Brahmer JR, Drake CG, Wollner, I, et al. Phase I Study of Single-Agent Anti–Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates. J Clin Oncol 2010;28:3167-75.

[63] Guinney, J., Dienstmann, R., Wang, X. et al. The consensus molecular subtypes of colorectal cancer. Nat Med 2015;21:1350-6.

[64] Piskol R, Huw L, Sergin I, et al. Clinically applicable gene expression classifier reveals intrinsic and extrinsic contributions to consensus molecular subtypes in primary and metastatic colon cancer. Clinical Cancer Research 2019;25:4431-42.

[65] Eide, P.W., Bruun, J., Lothe, R.A. et al. CMScaller: an R package for consensus molecular subtyping of colorectal cancer pre-clinical models. Sci Rep 2017;25:4431-42.7

[66] Teufel M, Schwenke S, Seidel H, et al. Molecular subtypes and outcomes in regorafenib-treated patients with metastatic colorectal cancer (mCRC) enrolled in the CORRECT trial. J Clin Oncol 2015;33(Suppl 15):3558.

[67] Lenz HJ, Ou FS, Venook AP, et al. Impact of Consensus Molecular Subtype on Survival in Patients With Metastatic Colorectal Cancer: Results From CALGB/SWOG 80405 (Alliance). J Clin Oncol 2019;37:1876-1885.

[68] Stintzing S, Wirapati P, Lenz HJ, et al. Consensus molecular subgroups (CMS) of colorectal cancer (CRC) and first-line efficacy of FOLFIRIs cetuximab or bevacizumab in the FIRE3 (AIO KRK-0306) trial. Ann Oncol 2019;30:1796-1803.

[69] Johnson B, Thomas JV, Dasari A, et al. A phase II study of durvalumab (MEDI4736) (anti-PD-L1) and trametinib (MEKi) in microsatellite stable (MSS) metastatic colorectal cancer (mCRC). J Clin Oncol 2020;38, 152.

[70] Lee MS, Selitsky SR, Parker, JS, et al. Association of consensus molecular subtypes (CMS) with time to progression (TTP), progression free survival (PFS), and overall survival (OS) with second-line FOLFIRI ± regorafenib in metastatic colorectal cancer (mCRC). J Clin Oncol 2019;37(Suppl 4):597.

[71] Pardoll D. Does the immune system see tumors as foreign or self? Annu Rev Immunol. 2003;21:807-39.

[72] Zitvogel L, Tesniere A, Kroemer G. Cancer despite immunosurveillance: immunoselection and immunosubversion. Nat Rev Immunol. 2006;6:715-27.

[73] Dunn GP, Bruce AT, Ikeda H, et al. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol. 2002;3:991-8.

[74] Greenwald RJ, Freeman GH, Sharpe AH. The B7 family revisited. Annu Rev Immunol. 2004;23:515-48.

[75] Freeman FJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 2000; 192(7): 1027-34.

[76] Sharpe AH, Wherry EJ, Ahmed R, et al. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. Nature Immunol. 2007;8:237-45.

[77] Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009;15:7412-20.

[78] Nivolumab Clinical Study Report: CA209-016 December 2016.

[79] BMS Clinical Study Report CA209004, December 2014.

[80] Wolchok JD, Kluger H, Callahan MK et al. Nivolumab plus Ipilimumab in Advanced Melanoma. N Engl J Med 2013;369:122-33.

[81] Nivolumab Investigator Brochure.

[82] Andre T, Lonardi S, Wong MK-Y et al. Combination of nivolumab (NIVO) + ipilimumab (IPI) in the treatment of patients (pts) with deficient DNA mismatch repair (dMMR)/high microsatellite instability (MSI-H) metastatic colorectal cancer (mCRC): CheckMate 142 Study. Poster presented at the 2017 ASCO Annual Meeting; June 2-6, 2017; Chicago, IL USA.

[83] Chen, et al. CD38 as a novel immune checkpoint and a mechanism of resistance to the blockade of the PD-1/PD-L1 axis. J Clin Oncol 2017; 35: suppl 7S, abstract 79.

[84] Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al: Updated results from a phase III trial of nivolumab (NIVO) combined with ipilimumab (IPI) in treatment-naive patients (pts) with advanced melanoma (MEL) (CheckMate 067). ASCO Meeting Abstracts 34:9505, 2016.

[85] Tosolini M, Kirilovsky A, Mlecnik B, et al. Clinical Impact of Different Classes of Infiltrating T Cytotoxic and Helper Cells (Th1, Th2, Treg, Th17) in Patients with Colorectal Cancer; Cancer Res February 15 2011;(71)(4):1263-71.

[86] Deaglio S, Mehta K, Malavasi F. Human CD38: a (r)evolutionary story of enzymes and receptors. Leuk.Res. 2001;25:1-12.

[87] Vaisitti T, Aydin S, Rossi D et al. CD38 increases CXCL12-mediated signals and homing of chronic lymphocytic leukemia cells. Leukemia 2010;24:958-69.

[88] Malavasi F, Deaglio S, Damle R et al. CD38 and chronic lymphocytic leukemia: a decade later. Blood. 2011;118:3470-8.

[89] Hellmann MD, Gettinger SN, Goldman JW, et al. CheckMate 012: Safety and efficacy of first-line (1L) nivolumab (nivo; N) and ipilimumab (ipi; I) in advanced (adv) NSCLC. ASCO Meeting Abstracts 34:3001, 2016.

[90] Ipilimumab Investigator Brochure.

[91] Trametinib Investigator Brochure.

[92] Schadendorf D, Larkin J, Chiarion-Sileni V, et al. Efficacy and quality of life outcomes in patients with advanced melanoma (MEL) who discontinued treatment with nivolumab (NIVO) plus ipilimumab (IPI) due to toxicity in a phase III trial (CheckMate 067). 2016 Annual Meeting of the European Association of Dermato-Oncology; 2016 August 31-September 3; Vienna, Austria.

[93] Schadendorf D, Hodi FS, Robert C, et al. Pooled Analysis of Long-Term Survival Data from Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. J Clin Oncol 2015; 33: 1889-94.

[94] Brahmer J, Horn L, Jackman D, et al. Five-year follow-up from the CA209-003 study of nivolumab in previously treated advanced non-small cell lung cancer: clinical characteristics of long-term survivors. Oral presentation presented at: American Association for Cancer Research (AACR) Annual Meeting. 2017 April 1-5; Washington, DC, USA.

[95] Felip E, Gettinger SN, Burgio MA, et al. Three-year follow-up from Checkmate 017/057: Nivolumab versus docetaxel in patients with previously treated advanced non-small lung cancer (NSCLC). Poster discussion presentation at the European Society of Medical Oncology Annual Meeting. 2017 Sep 8-12; Madrid, Spain. Poster 1301PD.

[96] Spigel DR, McLeod M, Hussein MA, et al. Randomized results of continuous vs 1-year fixed duration in patients with advanced non-small cell lung cancer. Oral presentation at the European Society of Medical Oncology Annual Meeting. 2017 Sep 8-12; Madrid, Spain.

[97] Mayer RJ, Van Cutsem E, Falcone A et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med 2015; 372:1909-19.

[98] Shitara K, Arita S, Shirakawa T, et al. REVERCE: randomized phase II study of regorafenib followed by cetuximab versus the reverse sequence for metastatic colorectal cancer patients previously treated with fluoropyrimidine, oxaliplatin, and irinotecan. J Clin Oncol 2019; 36:557.

[99] Arita S, Shirakawa T, Matsushita Y, et al. Efficacy and safety of TAS-102 in clinical practice of salvage chemotherapy for metastatic colorectal cancer. Anti-cancer Res 2016; 36:1959-66.

[100] Bekaii-Saab T, Kim R, Kim TW, et al. Third- or later-line therapy for metastatic colorectal cancer: reviewing best practice. Clin Colorectal Cancer 2019;18:e117-e129.

[101] Petrelli F, Tomasello G, Borgonovo K, et al. Prognostic survival associated with left-sided vs. right-sided colon cancer: a systematic review and meta-analysis. JAMA Oncol. 2017;3(2)-211-9.

[102] Arnold D, Lueza B, Douillard J.Y. et al. Prognostic and predictive value of primary tumor side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Ann Onocol 2017;28:1713-29.

[103] Desai J, Hong YS, Kim J, et al. Efficacy and Safety of Cobimetinib and Atezolizumab in an Expanded Phase 1b Study of Microsatellite-Stable (MSS) Metastatic Colorectal Cancer (mCRC). Eur Soc Med Oncol 2016;Poster 470P.

[104] Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. Nature 2002; 417:949-54.

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
1L	first line
2L	second line
3L	third line
3L+	third line plus
5-FU	5-fluorouracil
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
AST	aspartate aminotransferase
AT	aminotransaminases
[redacted]	[redacted]
BICR	blinded independent central review
[redacted]	[redacted]
BMS	Bristol-Myers Squibb
BOR	best overall response
BP	blood pressure
BSA	body surface area
BSC	best supportive care
BUN	blood urea nitrogen
C	Celsius
C1	chloride
Ca	calcium
CBC	complete blood count
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
cHL	classical Hodgkin's lymphoma
CI	confidence interval
[redacted]	[redacted]
[redacted]	[redacted]

Term	Definition
CMS	consensus molecular subtype
CNS	central nervous system
COVID-19	Coronavirus Disease 2019
CR	complete response
CRC	colorectal cancer
CRF	Case Report Form, paper or electronic
CSR	Central Serous Retinopathy
DCR	disease control rate
dL	deciliter
DLT	dose limiting toxicity
dMMR	deficient mismatch repair
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)
FDA	Food and Drug Administration
[redacted]	[redacted]
FSH	follicle stimulating hormone
g	gram
GCP	Good Clinical Practice
[redacted]	[redacted]
h	Hour
H&N	head and neck
HBsAg	hepatitis B surface antigen
HCG	human chorionic gonadotrophin
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy

Term	Definition
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IL	interleukin
[redacted]	[redacted]
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
I-O	Immuno-oncology
IP	investigational product
IRB	Institutional Review Board
irPR	immune-related partial response
irSD	immune-related stable disease
IRT	interactive response technology
IU	International Unit
IV	intravenous
K	potassium
kg	kilogram
L	Liter
LDH	lactate dehydrogenase
LFT	Liver function tests
LLN	lower limit of normal
LPFT	last patient first treatment
LPLV	last patient last visit
LVEF	left ventricular ejection fraction
MAPK	mitogen activated protein kinase
mCRC	metastatic colorectal cancer
MEK	mitogen-activated protein kinase enzymes
mg	milligram
µg	microgram
Mg	magnesium
min	minute

Term	Definition
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 stable
MST	medical surveillance team
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
N	number of subjects or observations
Na	sodium
NCCN	national comprehensive cancer network
ng	nanogram
NSCLC	nonsmall cell lung cancer
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic
PD-L1	program cell death ligand 1
PE	physical examination
PFS	progression-free survival
[redacted]	[redacted]
pMMR	proficient mismatch repair
PPES	Palmar-planta erythrodysesthesia
PO	per os (by mouth route of administration)
[redacted]	[redacted]
PR	partial response
QD, qd	quaque die, once daily
RCC	renal cell carcinoma
RP2D	Recommended Phase 2 dose

Term	Definition
[redacted]	[redacted]
RVO	retinal vein occlusion
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOP	Standard Operating Procedures
STAT3	Signal transducer and activator of transcription 3
TBD	to be decided
TEAE	treatment-emergent adverse event
Treg	T-regulatory cell
TSH	thyroid stimulating hormone
TTR	time to response
UC	urothelial carcinoma
ULN	upper limit of normal
US	United States
[redacted]	[redacted]
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

- 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 serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

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

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

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

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

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

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

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

BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS

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

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

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

DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY

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

BMS protects Personal Information with adequate and appropriate security controls as indicated under the data protection laws. To align with the recommended security standards, BMS has adopted internal security standards and policies to protect personal data at every stage of its processing.

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

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 drug integrity in accordance with

If	Then
	requirements applicable under law and the SOPs/standards of the sourcing pharmacy.

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

CASE REPORT FORMS

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

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

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

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

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

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

MONITORING

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and

requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

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

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

RETURN OF STUDY TREATMENT

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

If..	Then
Study treatments supplied by BMS (including its vendors	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (e.g., cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.

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

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

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

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

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

STUDY AND SITE CLOSURE

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

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

DISSEMINATION OF CLINICAL STUDY DATA

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

CLINICAL STUDY REPORT AND PUBLICATIONS

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

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

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Involvement in trial design and data interpretation
- Regional representation (e.g., among top quartile of enrollers from a specified region or country)

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.

Scientific publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any

Principal Investigator, sub-investigator, or any other member of the study staff without the prior written consent of the Sponsor.

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

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

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

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

ADVERSE EVENTS

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

SERIOUS ADVERSE EVENTS

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

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

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

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

EVALUATING AES AND SAES

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

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

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 treatment assignment.

All SAEs must be followed to resolution or stabilization.

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

Every adverse event must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's case report form.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Appendix 4 provides general information and definitions related to women of childbearing potential and methods of contraception that can be applied to most clinical trials. For information specific to this study regarding acceptable contraception requirements for female and male participants, refer to Section 6.1 of the protocol. Only the contraception methods as described in Section 6.1 are acceptable for this study.

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

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

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

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

End of Relevant Systemic Exposure

End of relevant systemic exposure is the timepoint where the Investigational Medicinal Product (IMP) or any active major metabolites have decreased to a concentration that is no longer considered to be relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed-adverse-effect level or the time required for 5 half-lives of the IMP to pass.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

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

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal • Combined (estrogen- and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion

• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence • Periodic abstinence (including, but not limited to, calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception for this study
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 4 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 4 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 4 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 4 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 Appendix 3 for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting.

APPENDIX 5 NIVOLUMAB MANAGEMENT ALGORITHMS FOR STUDIES UNDER CTCAE VERSION 4.0

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.

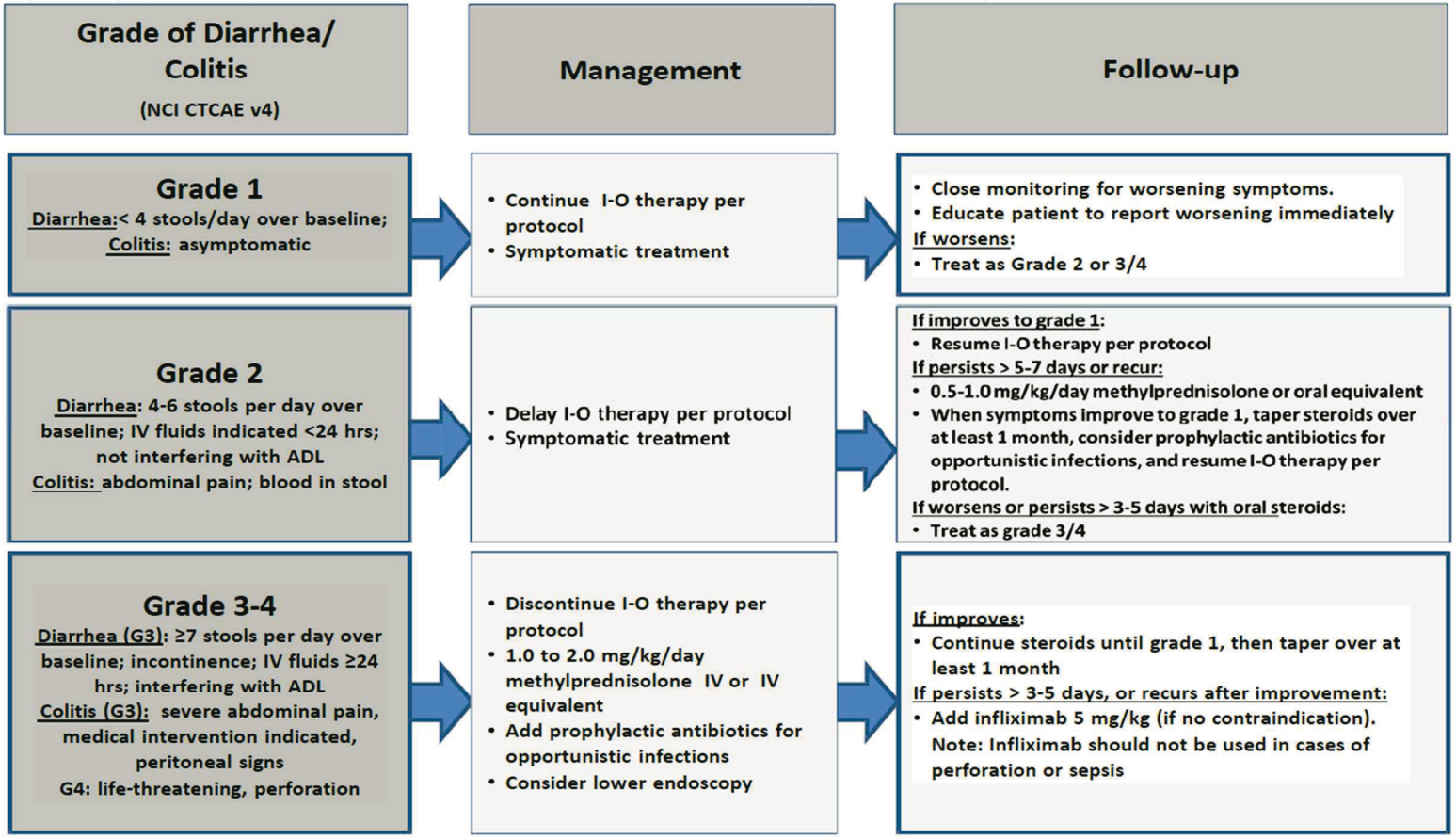
Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

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

For adverse events that may be related to both nivolumab and/or ipilimumab and trametinib, both Management Algorithms for Nivolumab and Ipilimumab (Appendix 5) AND Trametinib Dose Modification guideline (Appendix 6) need to be carefully reviewed and followed. Where toxicity management guidelines differ between the two, the most stringent/conservative guideline should be followed.

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.

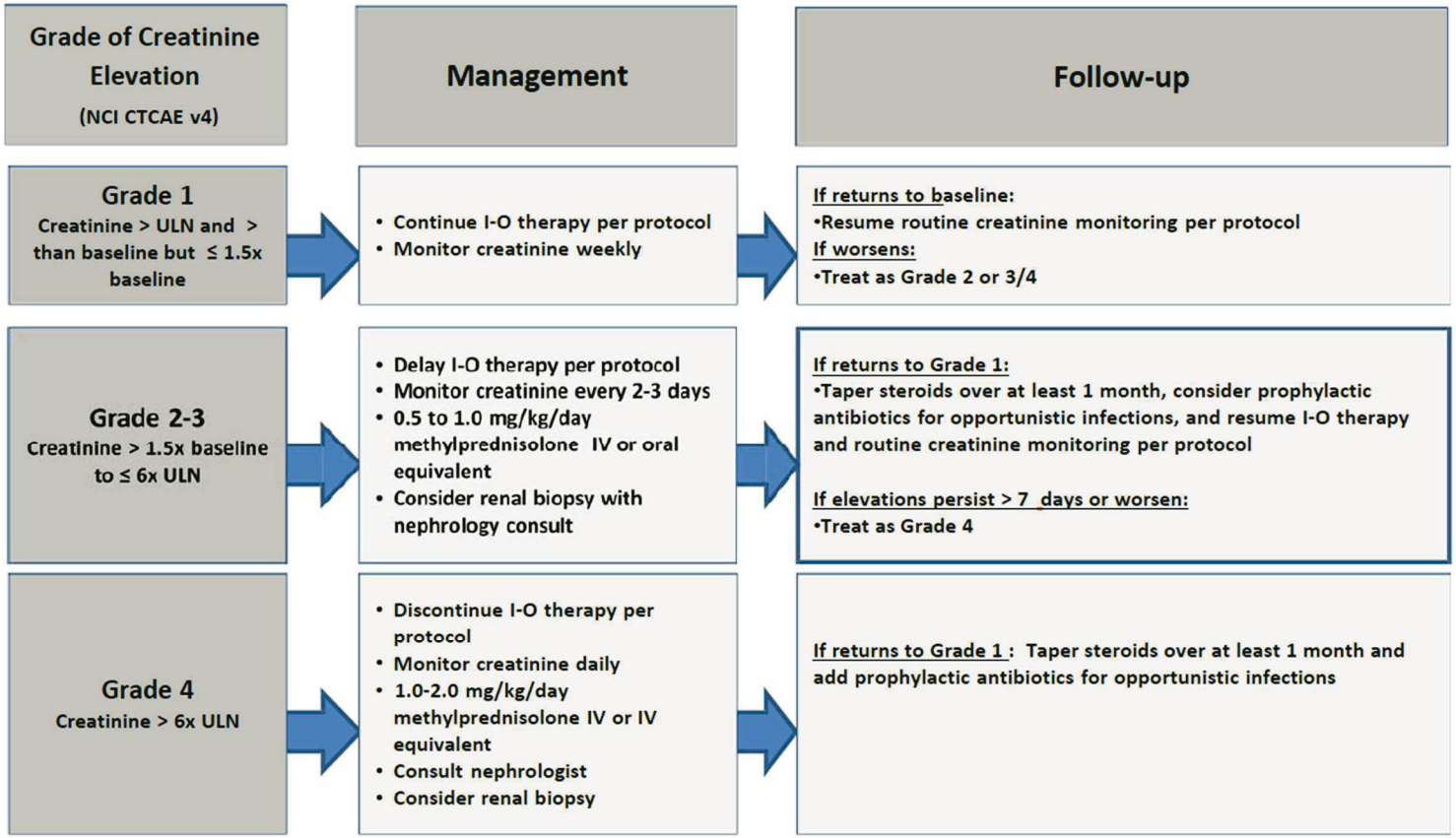


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Renal Adverse Event Management Algorithm

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

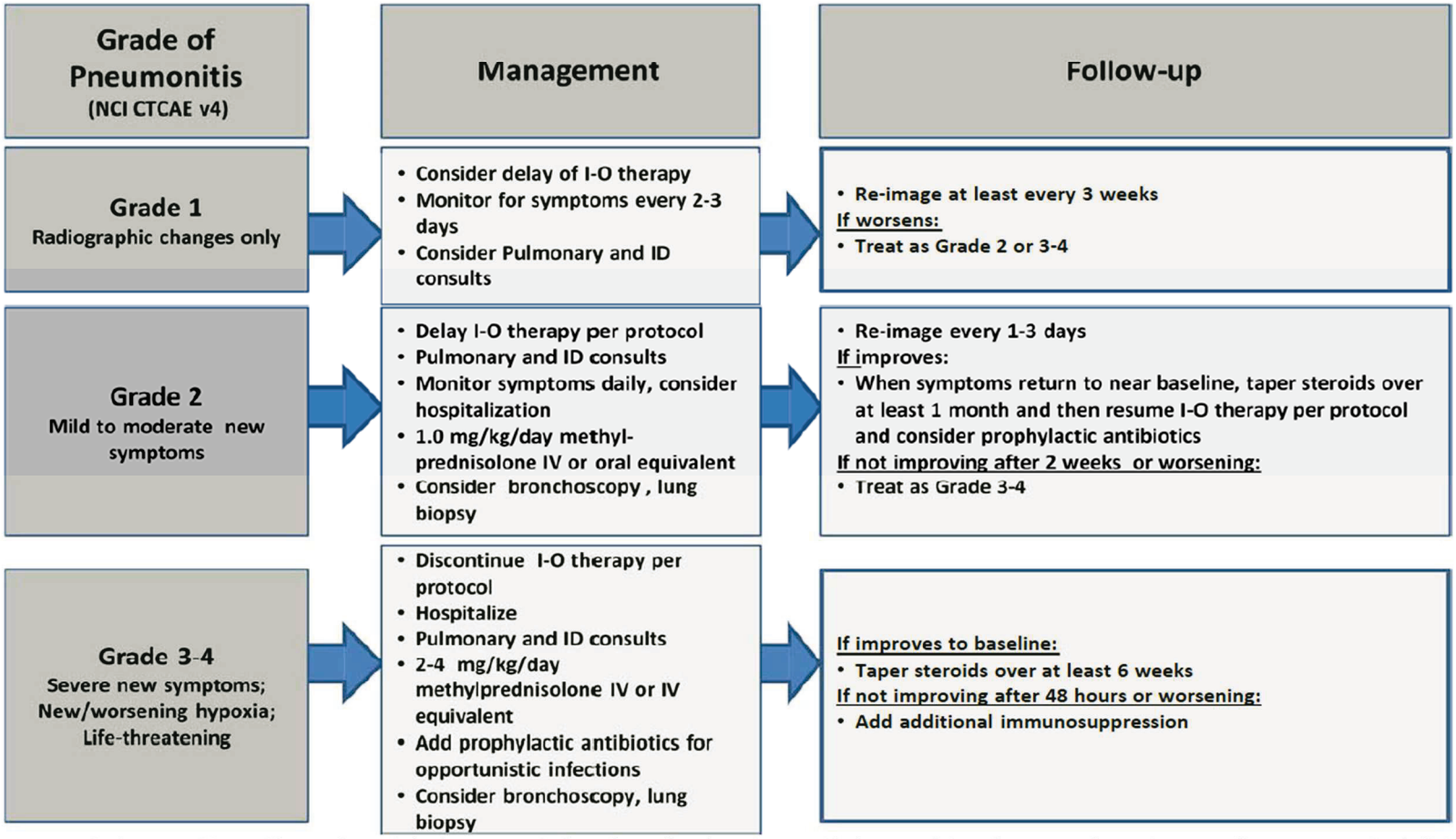


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

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.

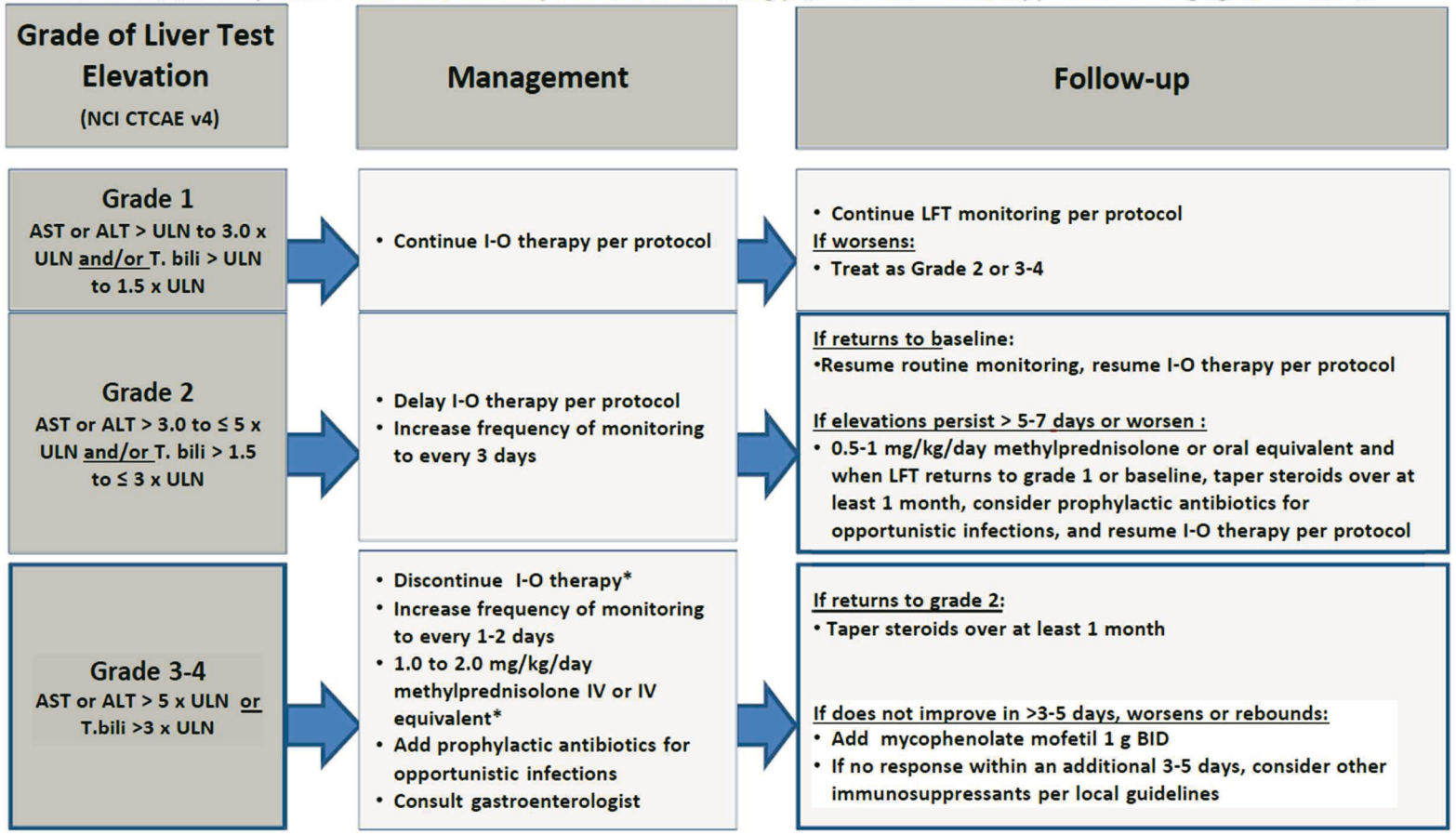


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

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.



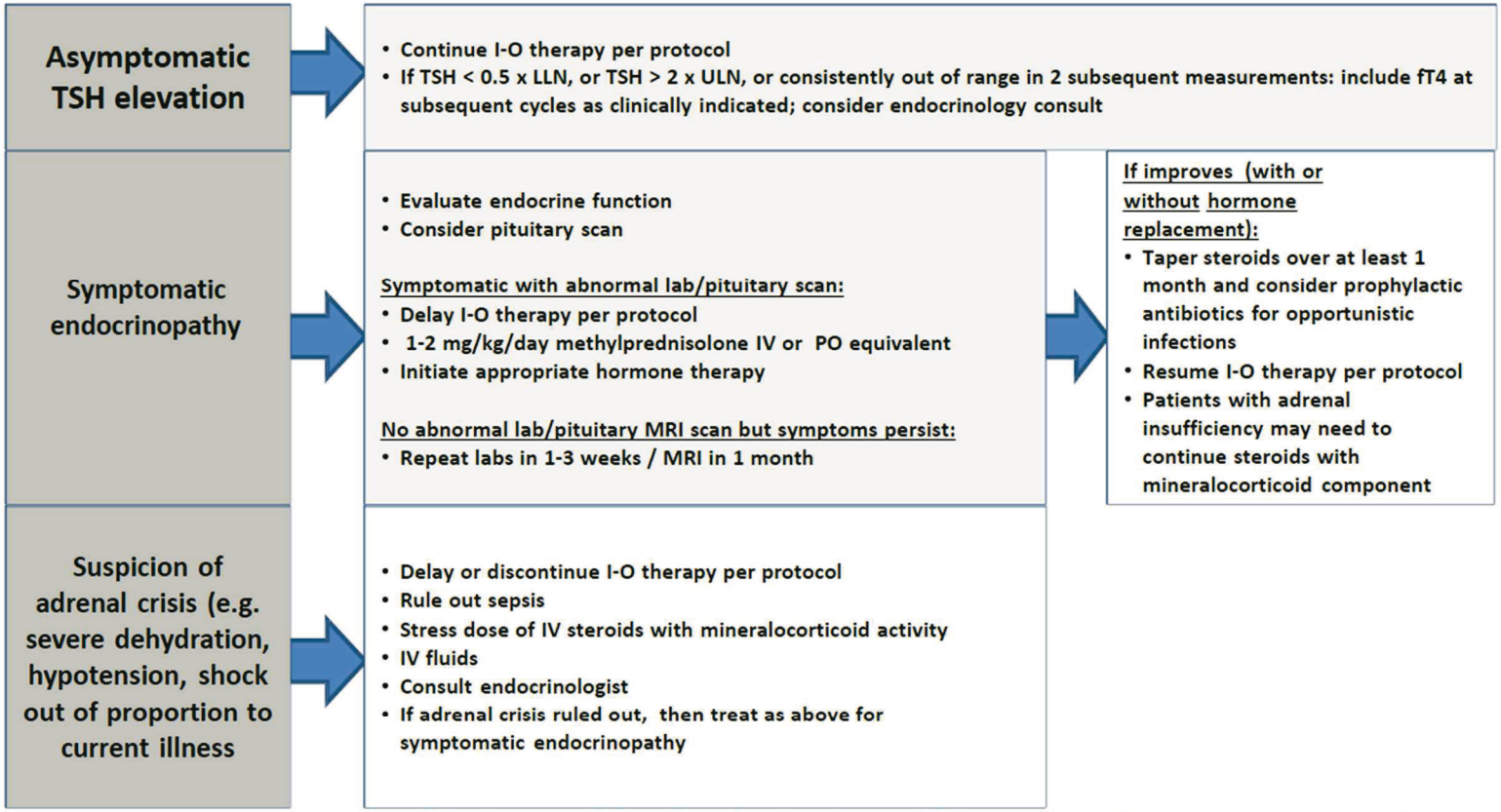
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

28-Sep-2020

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.

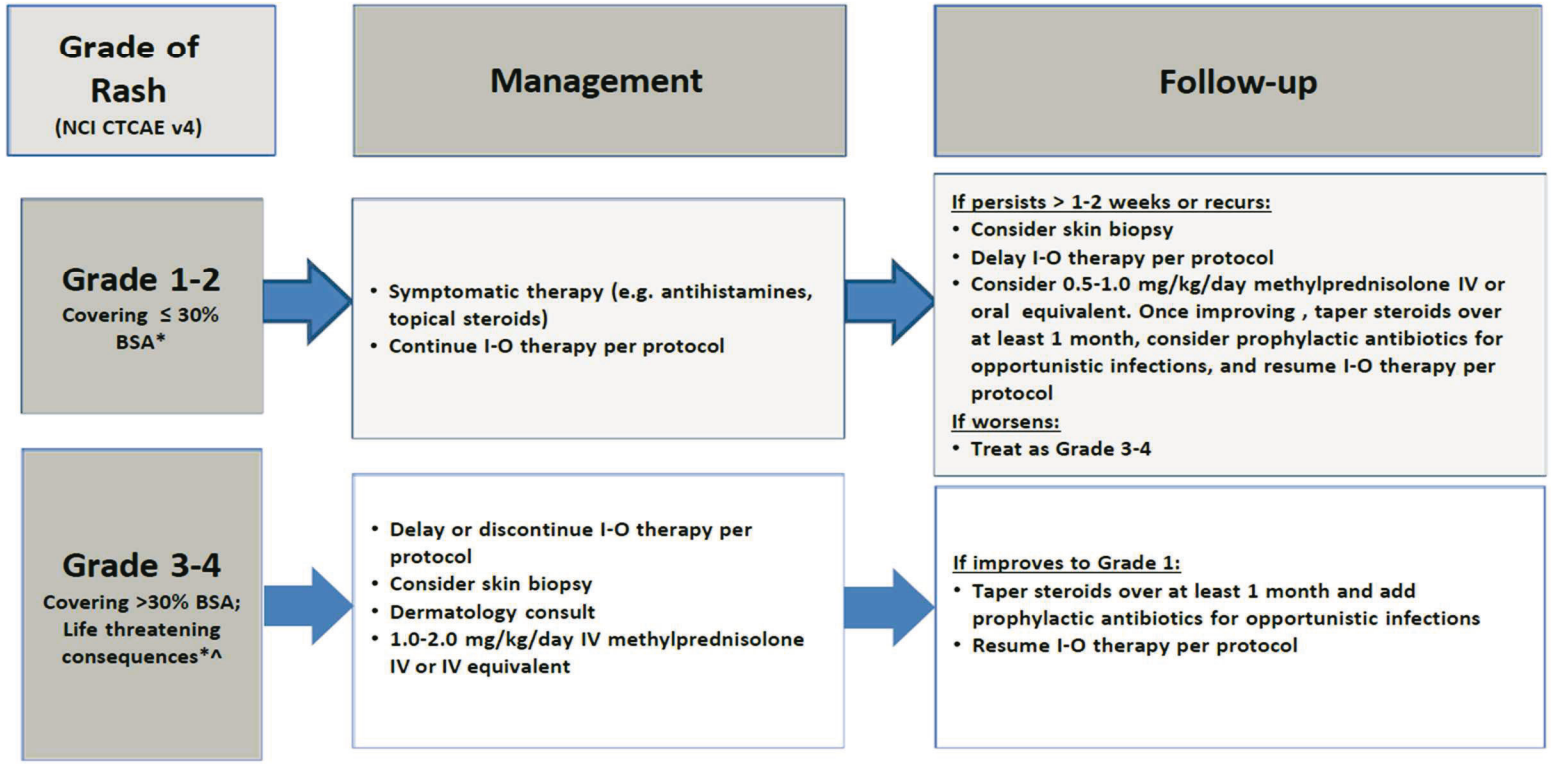


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

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.

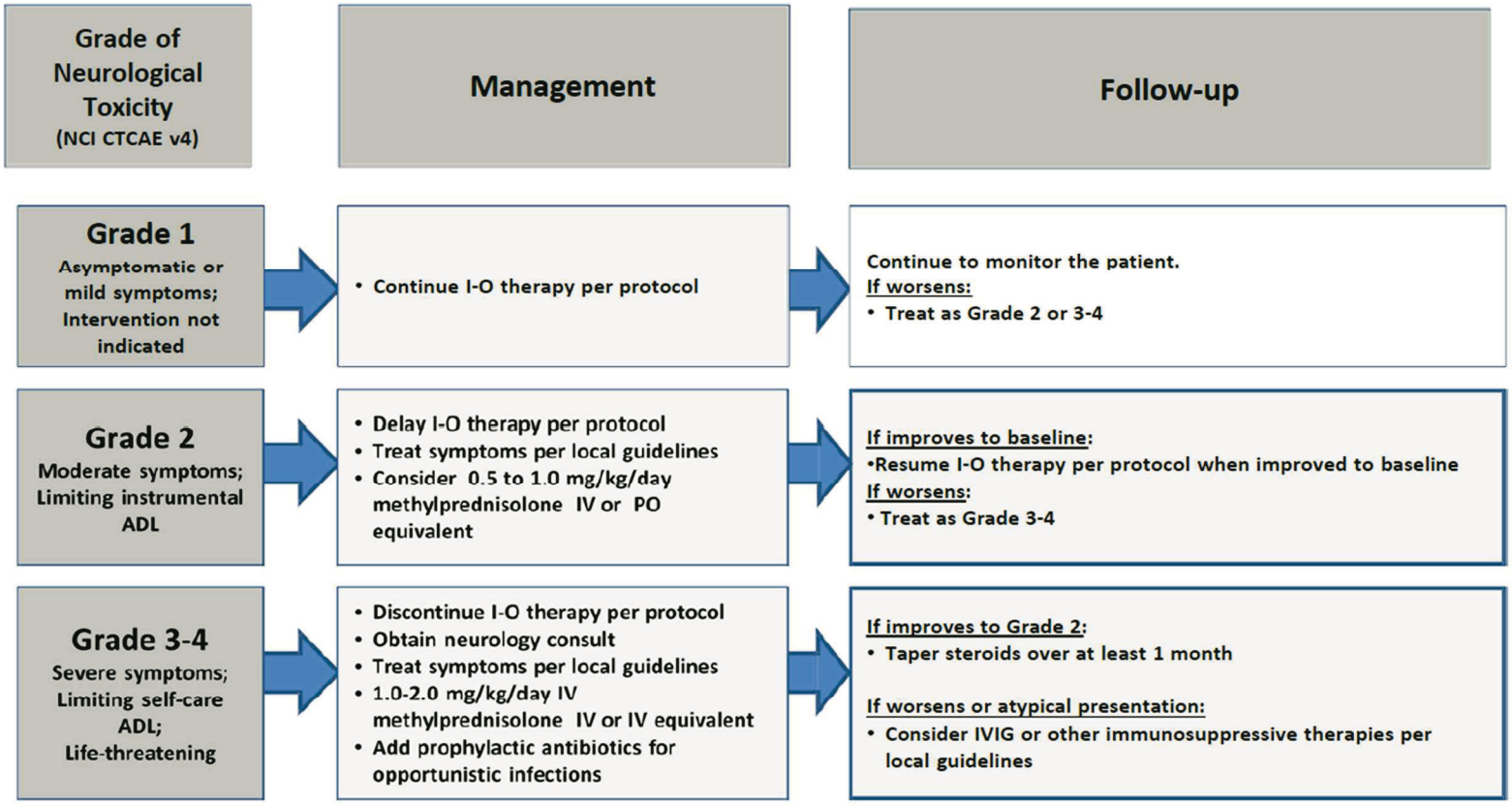
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^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.

28-Sep-2020

Neurological Adverse Event Management Algorithm

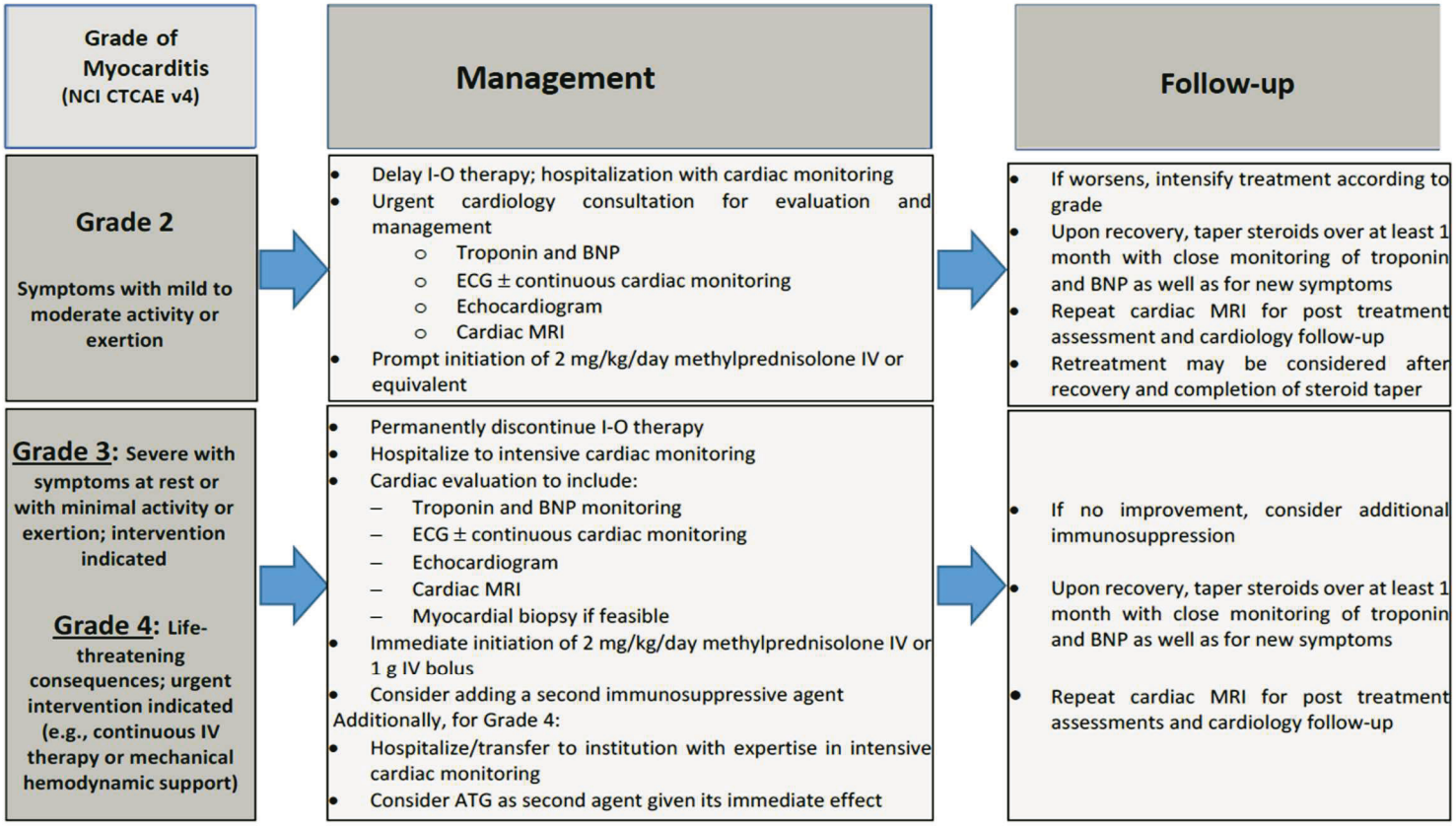
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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.

28-Sep-2020

Myocarditis Adverse Event Management Algorithm

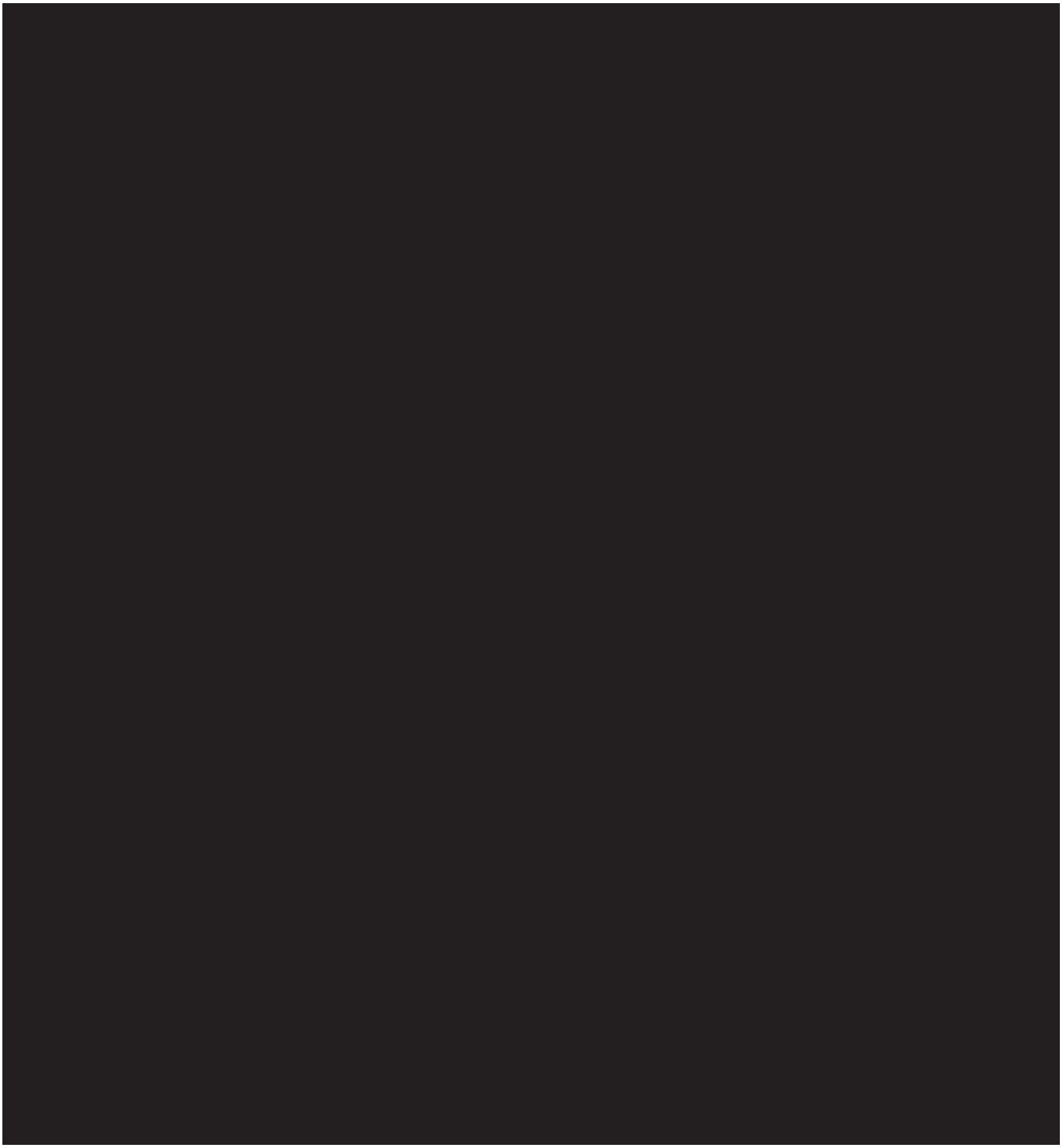


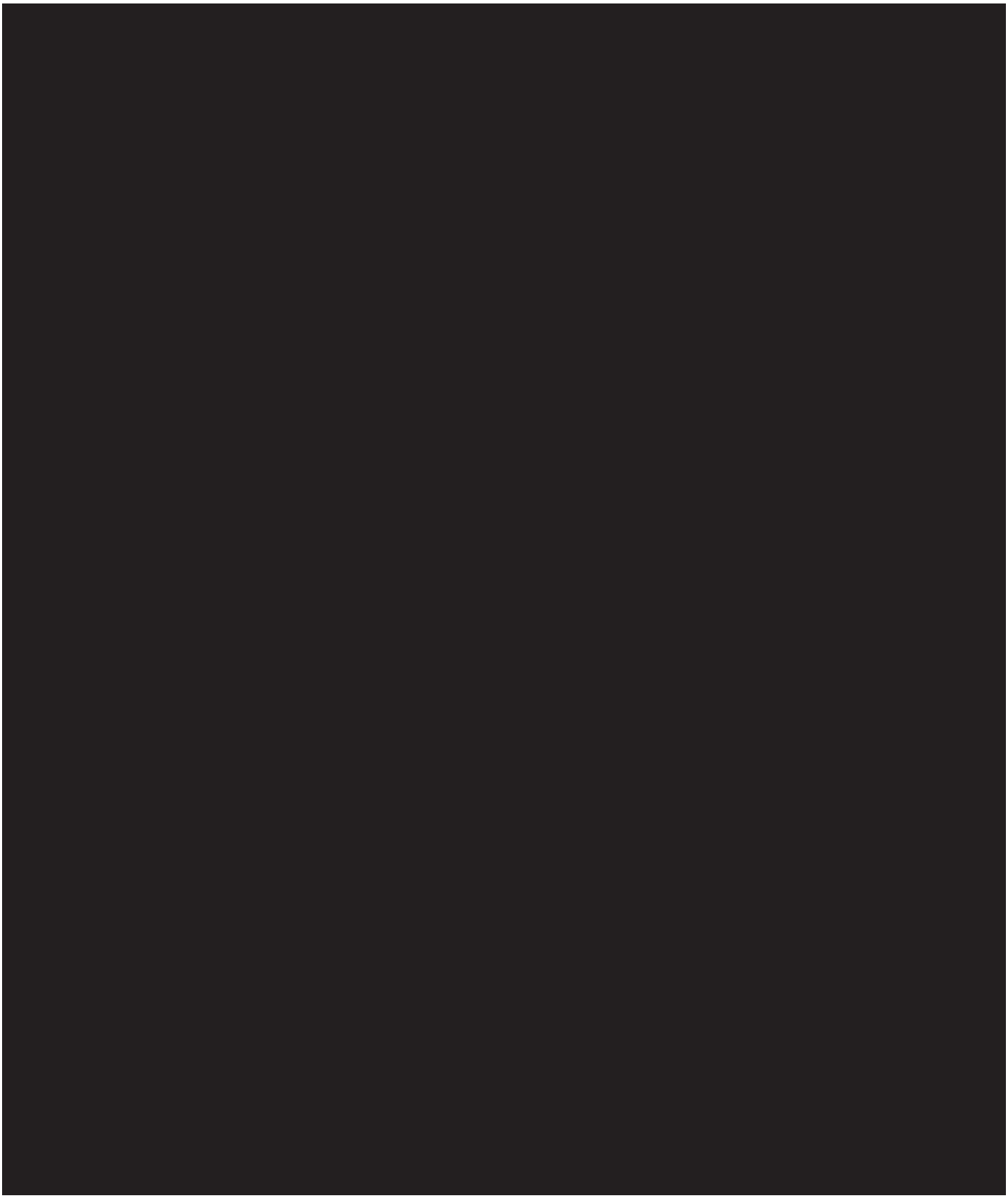
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

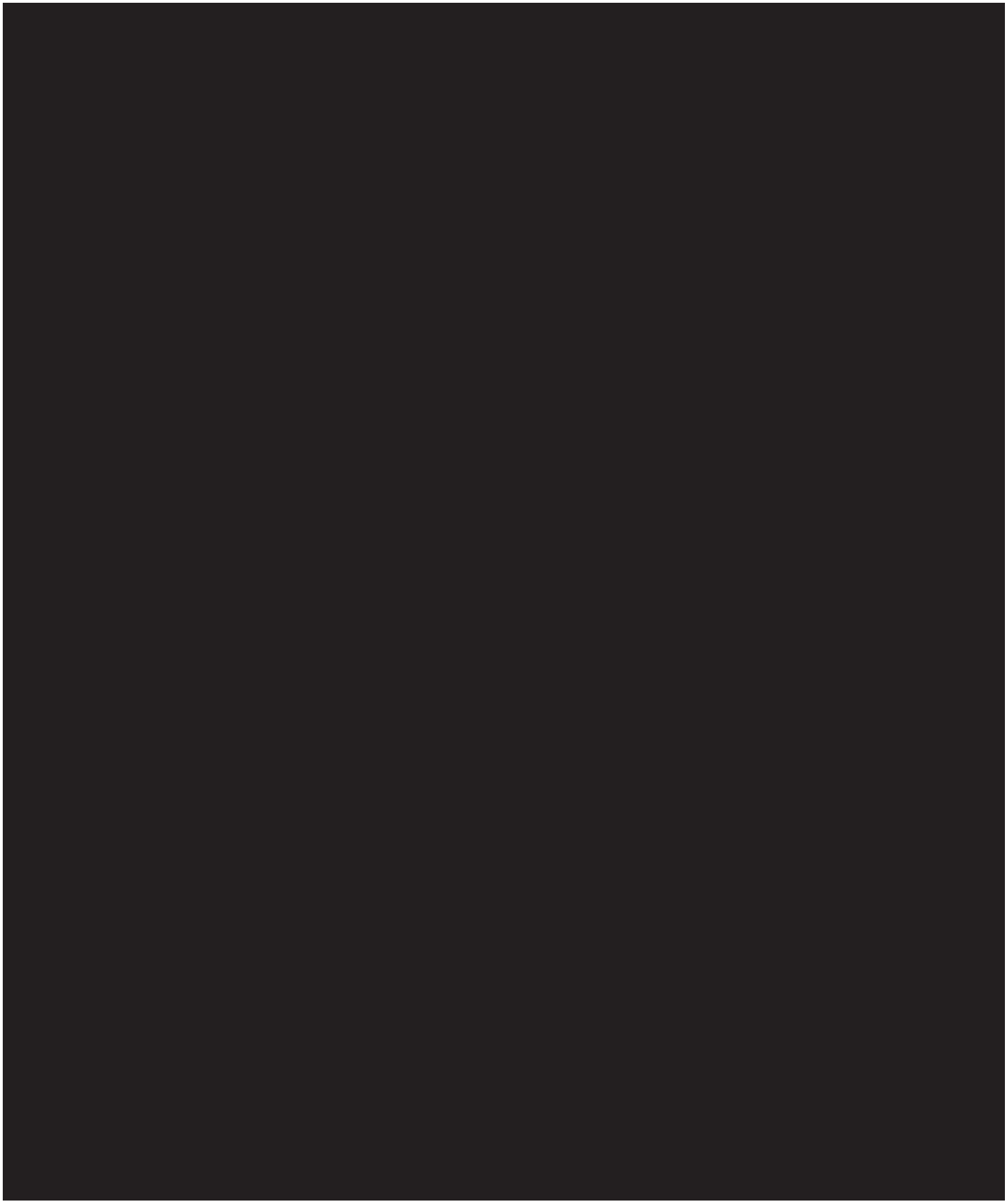
28-Sep-2020

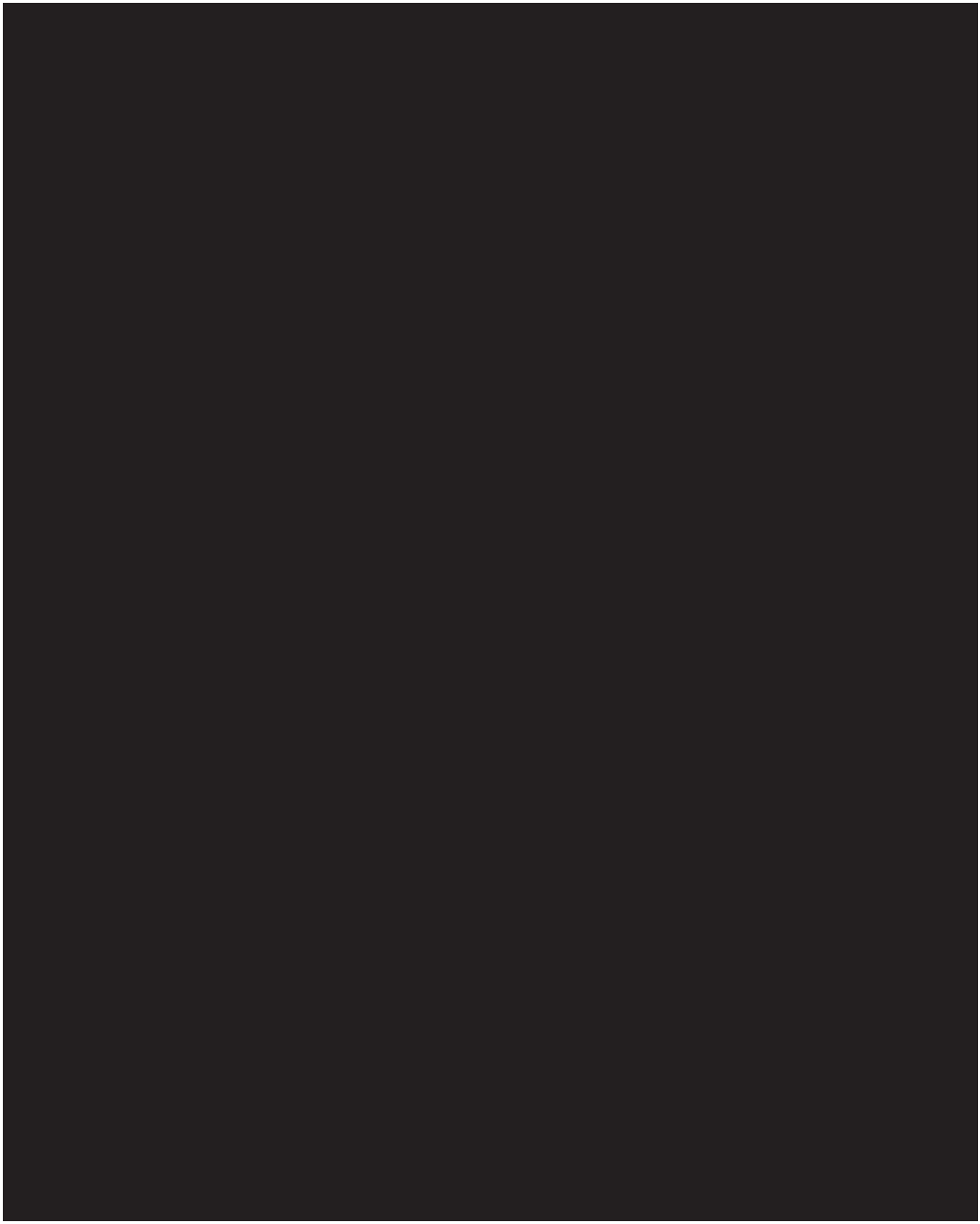
APPENDIX 6 TRAMETINIB DOSE MODIFICATION GUIDELINES

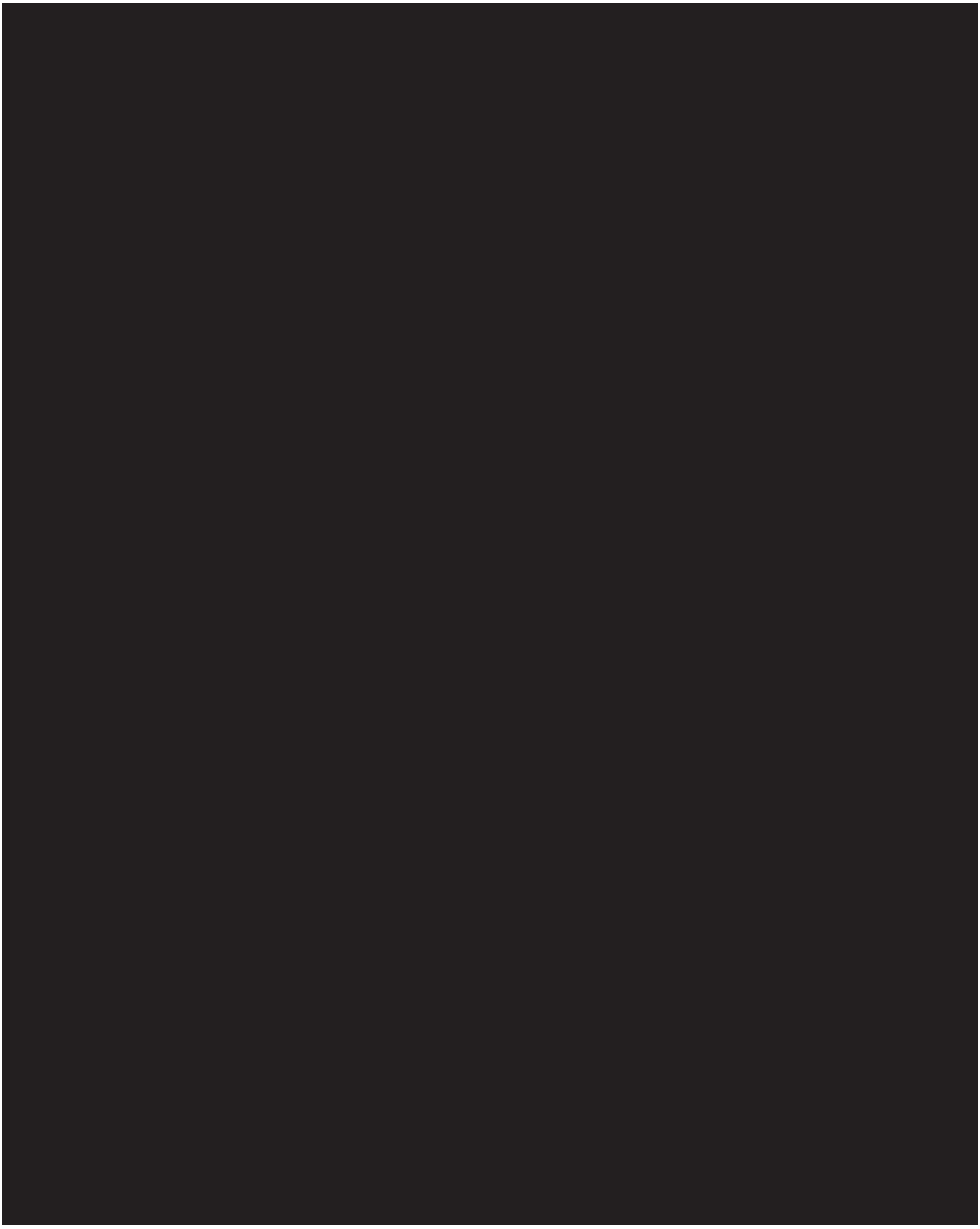
For adverse events that may be related to both nivolumab and/or ipilimumab and trametinib, both Management Algorithms for Nivolumab and Ipilimumab (Appendix 5) AND Trametinib Dose Modification guideline (Appendix 6) need to be carefully reviewed and followed. Where toxicity management guidelines differ between the two, the most stringent/conservative guideline should be followed.

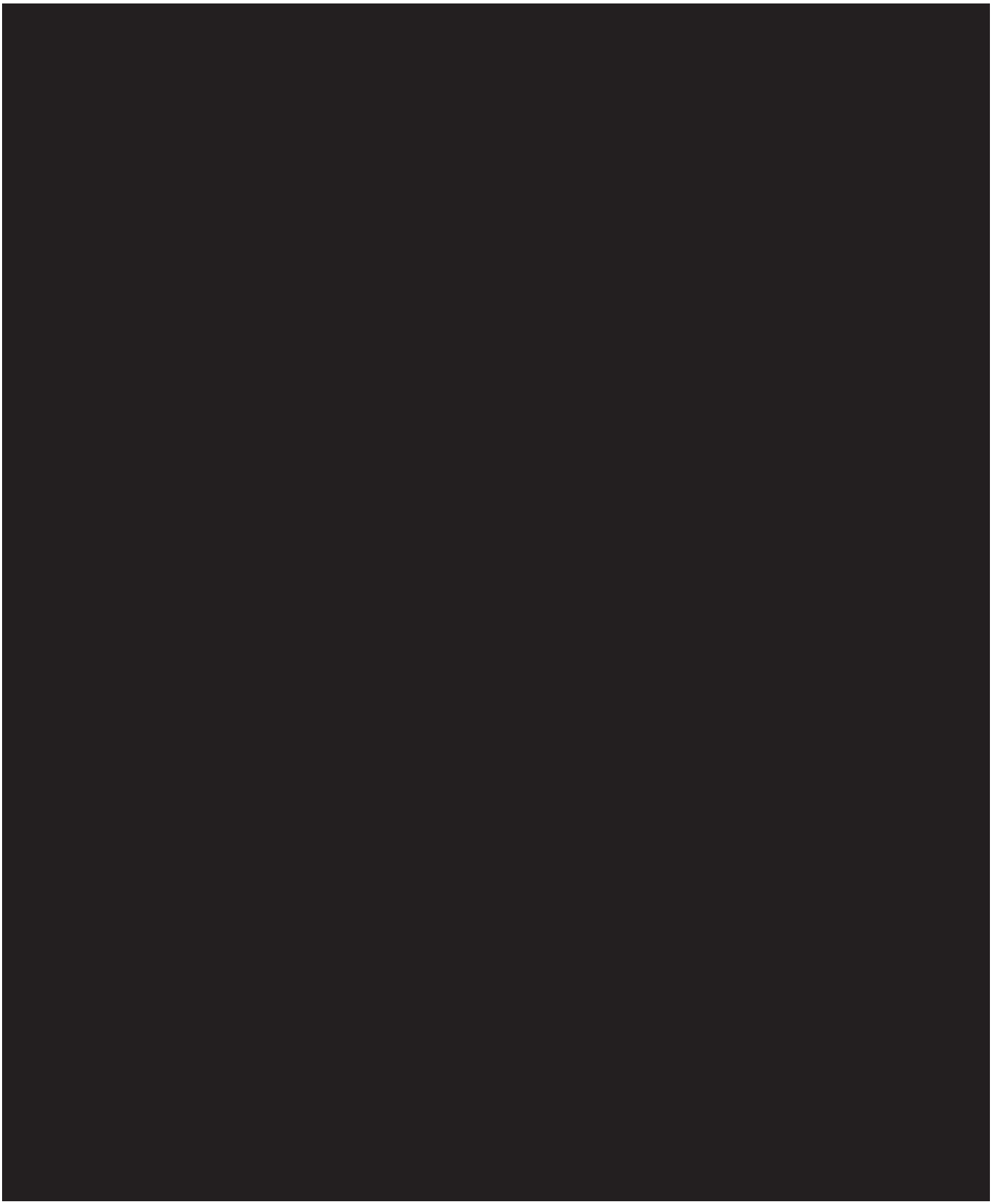


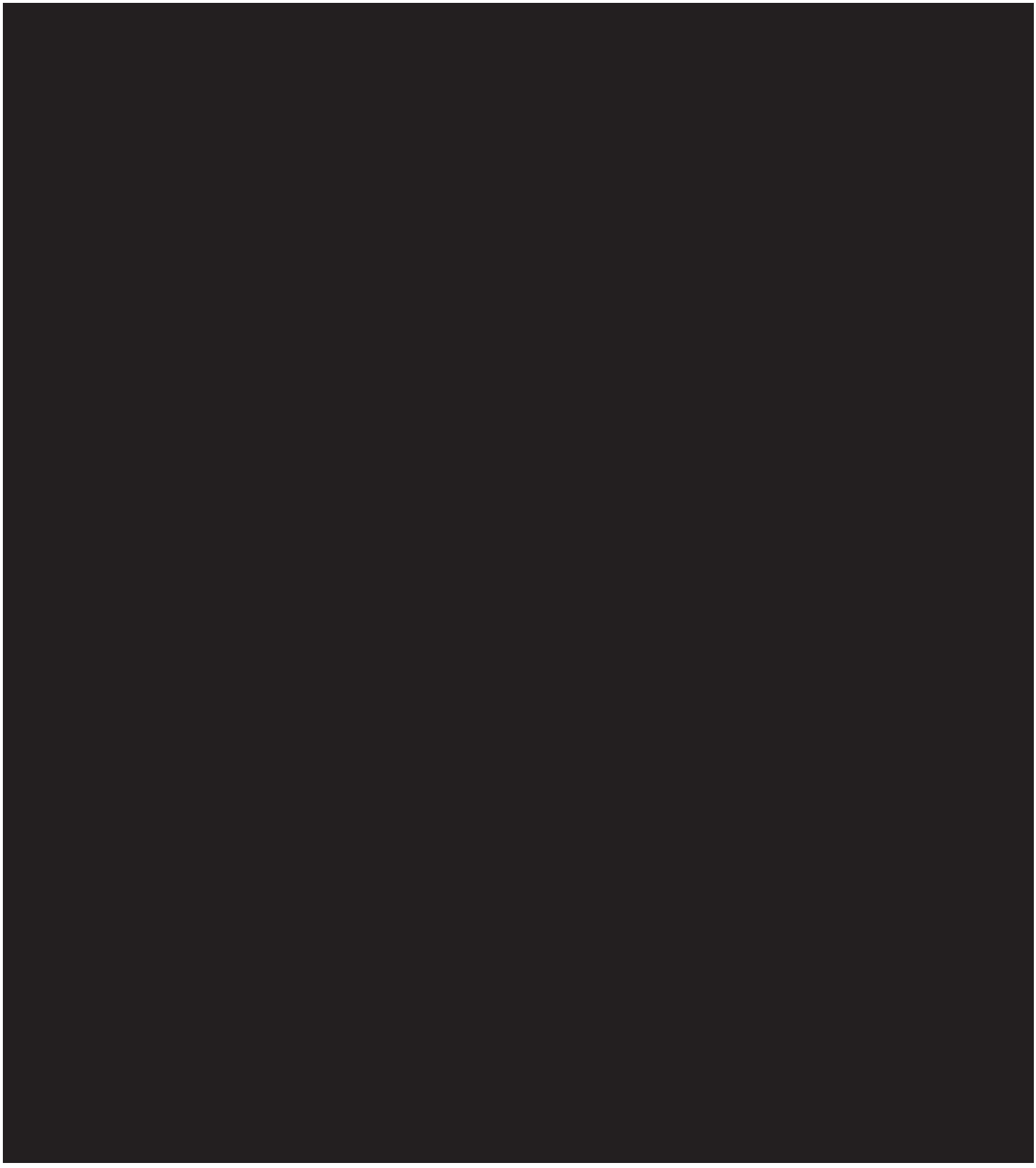


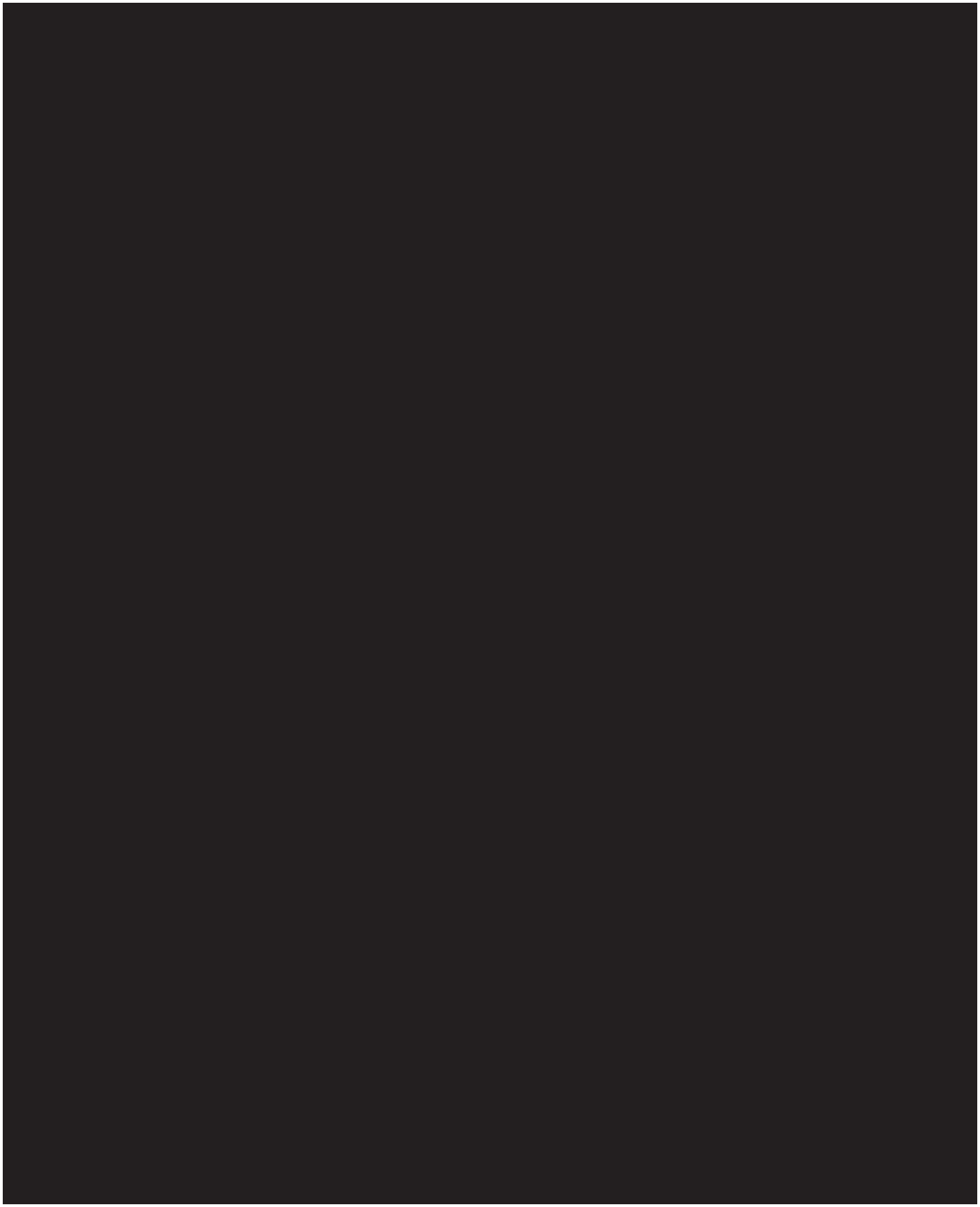


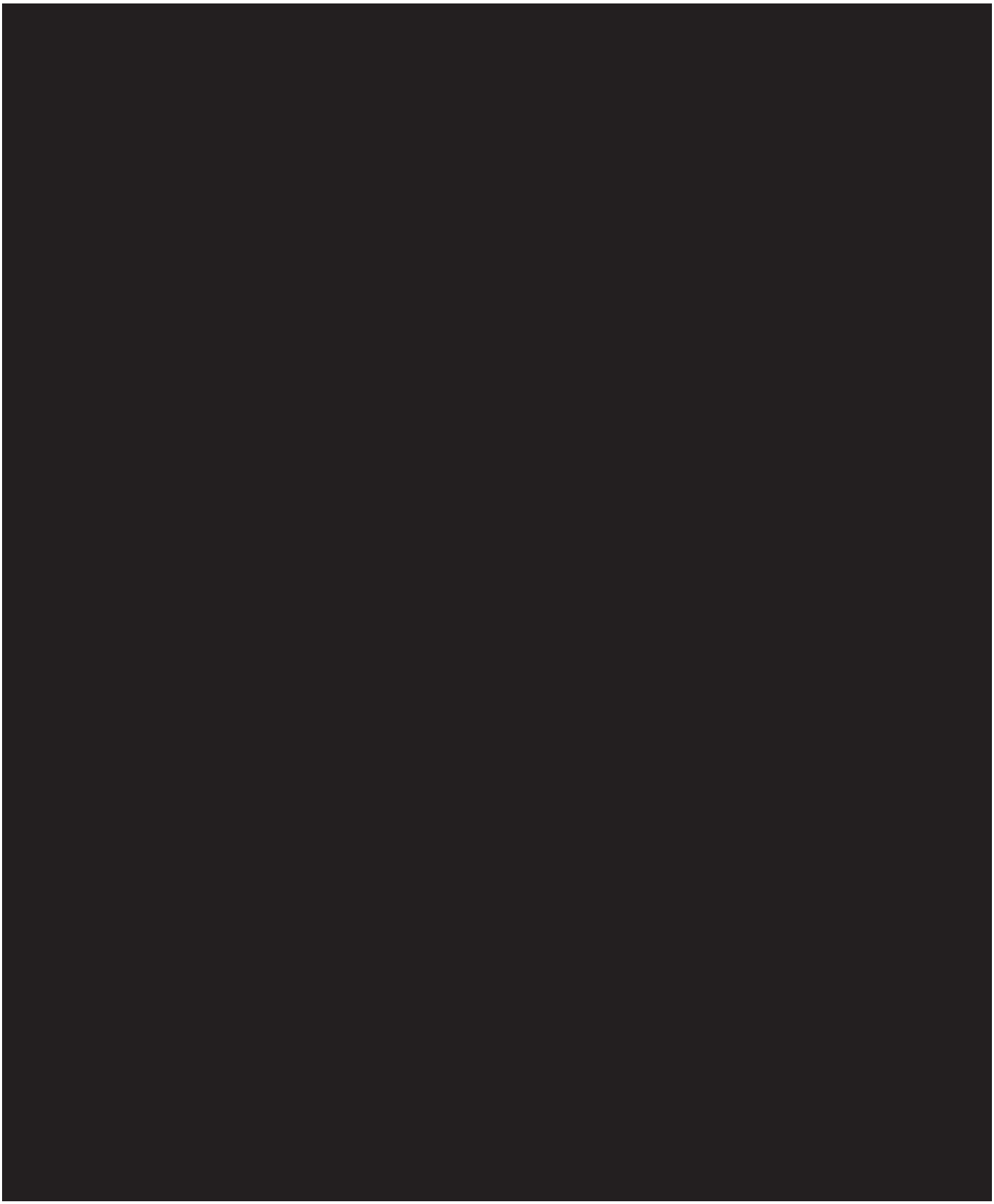


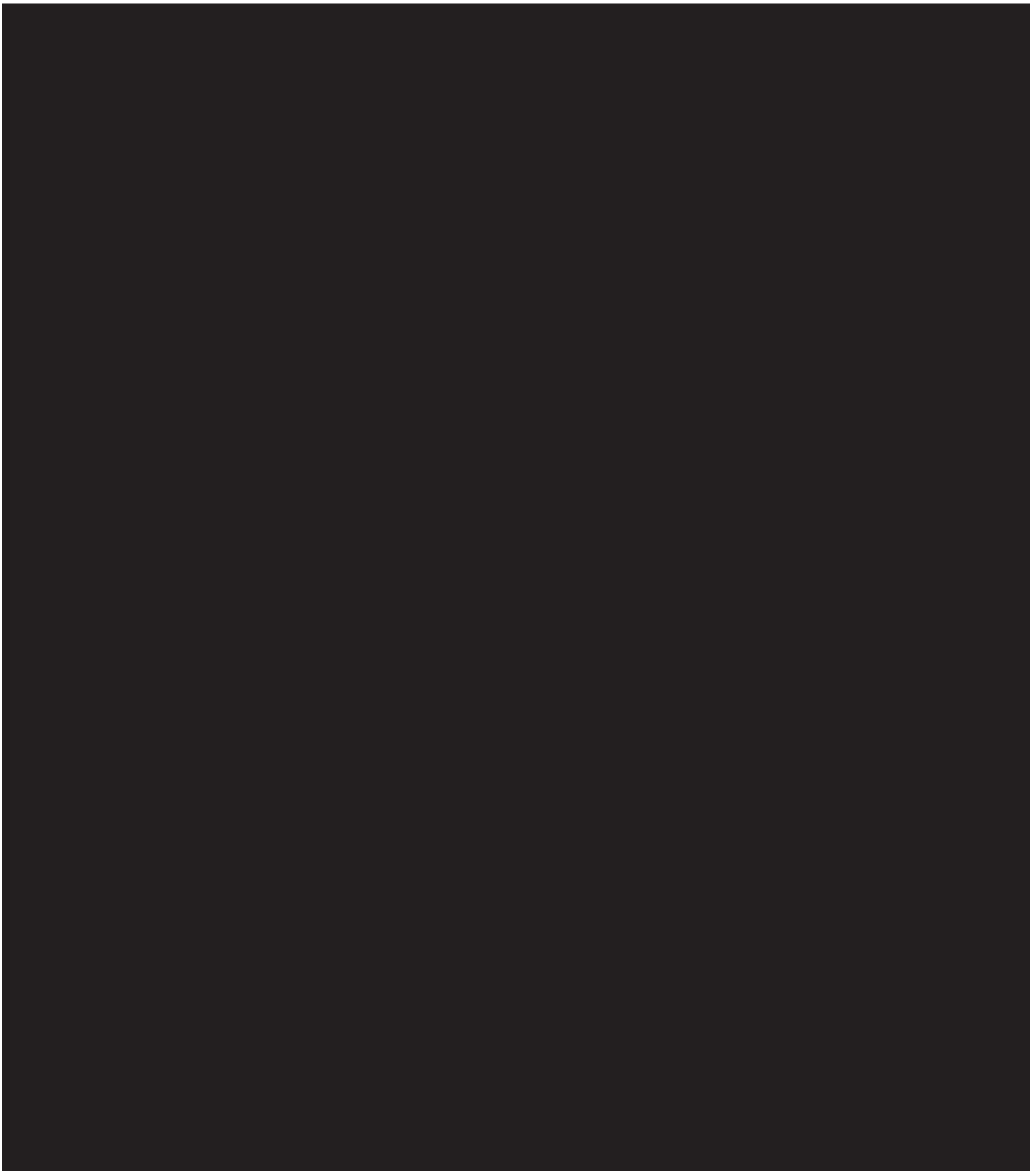


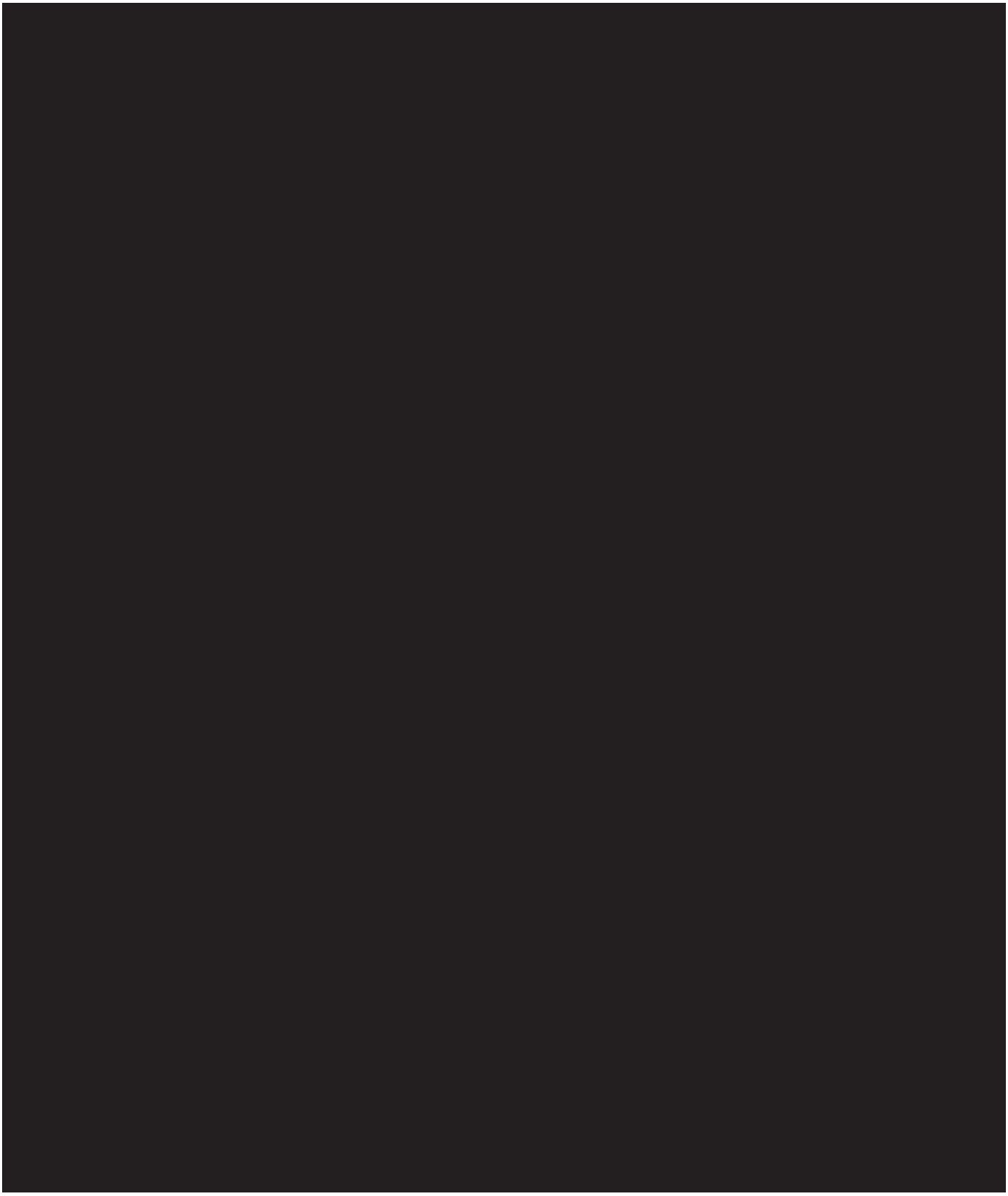




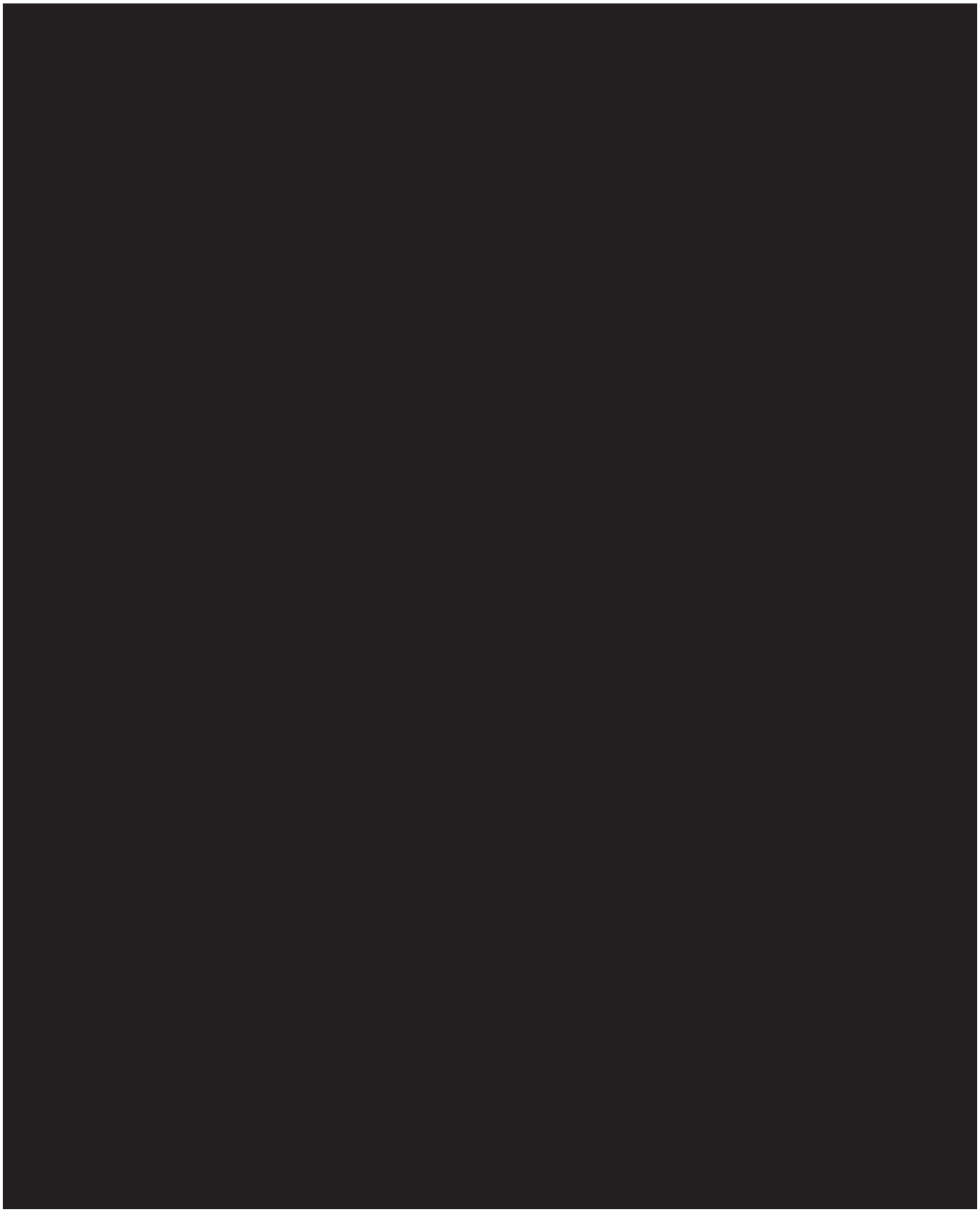








[redacted]



APPENDIX 7 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**

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

How to contact ECOG:

Revised: July 27, 2006

APPENDIX 8 RECIST 1.1 GUIDELINES (WITH BMS MODIFICATIONS)

1 EVALUATION OF LESIONS

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

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

2 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.

3 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.

4 SPECIAL considerations REGARDING LESION MEASURABILITY

4.1.1 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.

5 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').

6 RESPONSE CRITERIA

6.1 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.

6.1.1 Special Notes on the Assessment of Target Lesions

6.1.1.1 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.

6.1.1.2 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.

6.1.1.3 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'.

6.2 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.

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

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

6.2.1.1 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.

6.2.1.2 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.

6.2.2 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.

6.3 Response Assessment

6.3.1 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.

6.3.2 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.

6.3.3 Best Overall Response

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

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

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

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD

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	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
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.

6.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive or subsequent repeat assessments that should be performed no less than 28 days after the criteria for response are first met. Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE or PR (eg, CR NE CR or CR PR CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (eg, PR NE PR or PR SD PR). However, only one (1) intervening time point will be allowed between PR/CRs for confirmation.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered to not have progressive disease.

REFERENCES

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

APPENDIX 9 MSI/MSS STATUS TESTING

TESTING PANEL DESCRIPTIONS (PCR AND IHC)

FDA or other health authority approved testing should be used. If not, documentation demonstrating validation of the test performance (preferable under CLIA or equivalent ex-US) is required to be submitted for sponsor or representative to review.

1. Bethesda method (PCR) Panel Description and Classification of MSI Status

- Reference panel:
  - BAT25 (mononucleotide)
  - BAT26 (mononucleotide)
  - NR-21 (mononucleotide)
  - NR-24 (mononucleotide)
  - MONO-27 (mononucleotide)
  - D5S346 (dinucleotide)
  - D2S123 (dinucleotide)
  - D17S250 (dinucleotide)
- Alternative loci:
  - BAT40
  - BAT34C4
  - NR-22
  - TGF-β-RII
  - ACTC (635/636)
- Classification:
  - **If 5 loci tested (reference panel):**
    - **MSI-H:** ≥ 2 markers with instability
    - **MSI-L:** 1 marker with instability
    - **MSS or MSI-L:** 0 markers with instability
  - **If > 5 loci tested (reference panel plus alternative loci):**
    - **MSI-H:** ≥ 30-40% markers with instability
    - **MSI-L:** < 30-40% markers with instability
    - **MSS or MSI-L:** 0 markers with instability
  - **In the case of 1 PCR amplification failure:**
    - If ≥ 3 markers of 4 → **MSI-H**
    - If 1 marker of 4 → **re-amplify**

2. Promega MSI Multiplex system version 1.1

- 5 mononucleotide markers:
  - BAT-25

  - BAT-26
  - NR-21F
  - NR-24
  - MONO-27
- Two polymorphic pentanucleotide markers
  - Penta C
  - Penta D
- Data interpretation:
  - MSS: no instability at any of the loci
  - MSI-Low: instability at a single mononucleotide locus
  - MSI-H: instability at ≥ 2 mononucleotide loci

Reference: Murphy KM et al., "Comparison of the Microsatellite Instability analysis system and the Bethesda Panel for the Determination of Microsatellite Instability in Colorectal Cancers" Journal of Molecular Diagnostics Vol 8, 2006, p305

3. IHC method - Panel Description and Classification of MSI Status

Panel

- hMSH2
- hMLH1
- hMSH6
- hPMS2

Classification:

- **MSI-H:** ≥ 1 markers with instability
- **MSS:** 0 markers with instability
- **MSI-L:** not evaluable with this technique

APPENDIX 10 KRAS/NRAS AND BRAF MUTATIONAL TESTING

FDA or other health authority approved testing should be used for local testing. If not, documentation demonstrating validation of the test performance (preferable under CLIA or equivalent ex-US) is required to be submitted for sponsor or representative to review.

For RAS:

DNA sequencing to identify RAS (KRAS and NRAS) mutations in codons 12 and 13 (exon 2), 59 and 61 (exon 3), and 117 and 146 (exons 4).

Note: for participants who had received anti-EGFR agents in prior line(s) of therapy, RAS mutation testing may be repeated after completing such therapy per local institutional guidelines. Participant enrollment will be based on initial testing results [redacted]. For Part 2, stratification of RAS mutation status is based on initial local testing results.

For BRAF:

DNA sequencing to identify BRAF mutation, including but not limited to V600.

BRAF mutation status is required for participants for eligibility and stratification purposes.

References:

Misale S, Yaeger R, Hobor S, et al. Emergence of KRAS mutations and acquired resistance to anti-EGFR therapy in colorectal cancer. Nature. 2012 June; 486:532-536.

Knickelbein K and Zhang L. Mutant KRAS as a critical determinant of the therapeutic response of colorectal cancer. Genes Dis. 2015 March; 2(1): 4–12.

APPENDIX 11 NYHA FUNCTIONAL CLASSIFICATION

NYHA Class	Patients with Cardiac Disease (Description of HF Related Symptoms)
Class I (Mild)	Patients with cardiac disease but without resulting in limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation (rapid or pounding heart beat), dyspnea (shortness of breath), or anginal pain (chest pain).
Class II (Mild)	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain
Class III (Moderate)	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV (Severe)	Patients with cardiac disease resulting in the inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Reference: The Criteria Committee of the New York Heart Association. *Nomenclature and Criteria for Diagnosis of the Heart and Great Vessels*. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

APPENDIX 12 COUNTRY SPECIFIC APPENDIX

Criteria for exclusion of HIV-positive subjects in Argentina, Czech Republic, Germany, and Any Other Countries Where Exclusion of HIV Positive Participants Is Locally Mandated

Section 6.2 Exclusion Criteria, Exclusion criterion 3.1	"Known history of testing positive 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

Pregnancy added as a reason for permanent discontinuation from study treatment in Czech Republic and any Other Countries Where Locally Mandated

Section Number & Title	Country-specific language
Section 8.1 Discontinuation from Study Treatment	"In the case of pregnancy, the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the BMS Medical Monitor/designee of this event. In all cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Refer to Section 9.2.5 Pregnancy."
Section 9.2.5 Pregnancy	The following language is not applicable for the Czech Republic: "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."

APPENDIX 13 GUIDANCE TO SITES ON TUMOR LOCATION AND SIDEDNESS

Please adhere to the following guidance when assigning tumor sidedness in eCRF and IRT transactions for participants enrolled to CA209-9N9:

Right Sided

- Cecum
- Ascending Colon
- Hepatic Flexure
- Transverse Colon
- Unknown OR Both-Sided locations

Left Sided

- Splenic Flexure
- Descending Colon
- Sigmoid Colon

Please note that the location of the primary tumor (not a metastatic site) should be used to define the sidedness.

APPENDIX 14 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for the Protocol amendment 03; 17-Dec-2021

The main reasons for Protocol Amendment 03 for CA2099N9 are to expand the eligibility criteria of Part 2 to include participants who have received at least 2 (no more than 4) prior lines of therapy, [redacted]; [redacted] Additional updates include removal of the 40 mg (10 mg/mL) potency of nivolumab solution for use moving forward, [redacted] clarification of nivolumab intravenous (IV) administration procedure, and clarification of treatment discontinuation requirements. Administrative Letters 04 and 05 are also incorporated.

Summary of Key Changes of Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated staff/contact information for the Clinical Trial Physician.	Provided current study contact information.
Synopsis: Rationale Study Population Objectives and Endpoints: Parts 1B and 2 Study Schematic [redacted] (Part 2) phase Section 3.1: Study Rationale Table 4-2: Objectives and Endpoints: Parts 1B and 2 Section 5.1: Overall Design Section 5.1.3: Part 2: [redacted] for the Triplet Regimen and Standard of Care Arm Section 5.4.2: Rationale for Choice of Standard of Care Treatment in Part 2 Section 5.4.3: Rationale for Stratification in Part 2	Updated to include participants in Part 2 who have received at least 2 (no more than 4) prior lines of therapy.	Expanded the eligibility criteria to be more representative of the later line microsattelite stable (MSS) metastaic colorectal cancer (mCRC) patient population.

Summary of Key Changes of Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.1: Inclusion Criteria	Criterion 2) b) i) was noted as "Not applicable per Protocol Amendment 03" and a new criterion 2) b) iii) was added to include 3L+. Criterion 2) d) i) was noted as "Not applicable per Protocol Amendment 03" and a new criterion 2) d) x) was added to include 3L+. Criterion 2) d) v) was noted as "Not applicable per Protocol Amendment 03" and a new criterion 2) d) xi) was added to include 3L+. Criterion 2) d) viii) was noted as "Not applicable per Protocol Amendment 03" and a new criterion 2) d) xii) was added to include 3L+. Criterion 2) d) ix) was noted as "Not applicable per Protocol Amendment 03" and a new criterion 2) d) xiii) was added to include 3L+.	
Section 8.1: Discontinuation from Study Treatment	Updated to state 3L+ mCRC participants in Cohorts 4 and 6 were permitted to receive treatment beyond progression.	
Section 10.1.2: mCRC 3rd line Plus Participants: Part 2 [redacted] Cohort	Updated to include participants in Part 2 who have received 2 (no more than 4) prior lines of therapy.	
[redacted]		
Synopsis: Study Drug for CA2099N9 Table 7-1: Study treatments for CA2099N9	Removed the 40 mg (10 mg/mL) potency of nivolumab solution for injection for use moving forward.	Removed to be in accord with nivolumab updated guidance.

Summary of Key Changes of Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		

Summary of Key Changes of Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Table 2-1: Screening Procedural Outline (CA2099N9)	Updated the timing of the following assessments from within 14 days prior to first dose to within 28 days prior to first dose: • ECOG status • Safety assessment of signs and symptoms • Echocardiogram or MUGA • ECG • Local laboratory tests	Updated to assist with sites ability to effectively pre-screen participants.
Table 2-3: On-Treatment Assessments (Part 2 mCRC 3rd line, Triplet, [redacted] CA2099N9 Cohort 4)	[redacted]	Incorporated Administrative Letter 04.
Section 3.2.5: Nivolumab Mechanism of Action	Added two additional paragraphs at the end of the section.	Updated to reflect the latest available medical data and literature.
Section 3.2.6: Ipilimumab Mechanism of Action	Replaced text with updated information.	Updated to reflect the latest available medical data and literature.
Section 3.2.7: Nivolumab Combined with Ipilimumab Clinical Activity	Added a summary paragraph at the beginning of the section.	Added to be in accord with nivolumab and ipilimumab updated BMS guidance.
Section 3.2.8: Trametinib Mechanism of Action and Clinical Activity	Removed “monotherapy” from the following:	A comparable safety profile has been observed for trametinib in combination studies.

Summary of Key Changes of Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	"Across all completed monotherapy studies for trametinib at the recommended dose of 2 mg daily, the most common AEs were rash, diarrhea, fatigue, edema peripheral, nausea, dermatitis acneiform, vomiting, constipation, anemia, pruritus, alopecia, hypertension, decreased appetite, dyspnea and dry skin."	
Section 5.4.1: Rationale for 2 year treatment duration for Immunotherapy (Nivolumab + Ipilimumab)	Deleted text that referred to Keynote-010 and Keynote-006 data.	The text was updated to align with BMS guidance as pembrolizumab analyses suggested higher progression rates after completing 2 years of treatment; however, overall, published data are supportive of a 2-year treatment duration.
Section 5.4.2: Rationale for Choice of Standard of Care Treatment in Part 2	Updated text on regorafenib to confirm that the drug may provide benefit in the 3L+ setting, and that prior TAS-102 is allowed.	Updated based on more recent available information.
Section 6.1: Inclusion Criteria	Criterion 2) a) was updated from version 4.0 to Edition 7.0 for the American Joint Committee on Cancer.	Updated to reflect the latest available version of the American Joint Committee on Cancer.
Section 6.1: Inclusion Criteria Appendix 4: Women of Childbearing Potential Definitions and Methods of Contraception	Noted Criterion 3) e) as "Not applicable per Protocol Amendment 03" and a new criterion was added, 3) g). Updated contraception requirements for male participants with partner(s) of childbearing potential to specify that contraception was required for 4 months after the last dose of study treatment.	As the use of contraception by male participants treated with nivolumab is no longer applicable, the period for contraception use after the last dose of study treatment was updated from 7 months to 4 months, which is approximately 5 half-lives for trametinib.
Section 6.2: Exclusion Criteria	Noted Criterion 2) b) as "Not applicable per Protocol Amendment 03" and a new criterion was added, 2) o).	Updated exclusion of participants with prior malignancy active within the previous 3 years to within the previous 2 years per United States Food and Drug Administration (FDA) guidance "Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies Guidance for Industry" issued July 2020. This is to allow for participants with prior cancers whose natural history or treatment does not have the potential to interfere with the safety or efficacy

Summary of Key Changes of Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
		assessment of nivolumab/ipilimumab or study drugs.
Section 7.1.4.1: Cohort 4 Triplet Regimen Section 7.1.5: Part 1A Completed (Triplet Regimen, Cohort 2 Group and Cohort 3 Group: Closed for Enrollment) Section 7.1.6: Part 1B (Triplet Regimen, Cohort 6)	Updated text to clarify: • Nivolumab IV infusion is approximately 30 minutes • The line can be flushed to ensure the complete nivolumab dose is administered over the approximately 30-minute infusion • When nivolumab and ipilimumab are administered on the same day, nivolumab is to be administered first followed promptly by a flush of diluent to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be ipilimumab treatment and will start after the infusion line has been flushed, filters changed, and the participant has been observed to ensure no infusion reaction has occurred	Updated to reflect the most recent guidance from BMS.
Table 7.4.4.1-1: Dose Delay and Modification for Events Considered Related to Trametinib (excluding pyrexia) Section 7.4.4.2: Guidelines for Specific Trametinib-related Toxicities Appendix 6: Trametinib Dose Modification Guidelines	Updated the table title to clarify that dose delay and modification guidelines for events considered to be related to trametinib did not apply to pyrexia. Added the following note to the table: "In participants who experience retinal vein occlusion, trametinib treatment should be permanently discontinued." Added pyrexia to the list of toxicities that may be related to trametinib and included the event in the dose modification guidelines in Appendix 6.	Updated to align with the latest trametinib Investigator's Brochure and safety information.
Section 7.7.1: Prohibited and/or Restricted Treatments	Added the following text: "Non-live Coronavirus Disease 2019 (COVID-19) vaccination is considered a simple concomitant medication within the study. However, the safety and efficacy of non-live vaccines (including non-live COVID-19 vaccines) in	Added to be in accord with nivolumab and ipilimumab updated BMS guidance.

Summary of Key Changes of Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	participants receiving nivolumab, ipilimumab, or trametinib are unknown."	
Section 8.1: Discontinuation from Study Treatment Section 8.1.2: Nivolumab and Ipilimumab Dose Discontinuation Section 8.1.3: Trametinib Dose Discontinuation	Added the following text: "Any criteria leading to the discontinuation of nivolumab, ipilimumab, or trametinib as part of the triplet investigative regimen in Parts 1B and 2 will require discontinuation of the entire regimen."	Added to clarify treatment discontinuation requirements.
Section 9.4.3: Ophthalmic Examination	Added note for ophthalmic examination at screening that 7-day window does not apply at Cycle 1 Day 1.	Added to clarify timing of ophthalmic examinatin at screening.

[redacted]

Summary of Key Changes of Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 2: Study Governance Considerations	The following modifications were made: • Updated first paragraph of Monitoring section to further describe that details on monitoring can be found in the monitoring plan. • Added section for Dissemination of Clinical Study Data.	These changes were made to: • Clarify expectations for monitoring. • Provide details on how clinical study information will be made available.
Appendix 4: Women of Childbearing Potential Definitions and Methods of Contraception	Updated to include: • An introductory paragraph • Guidance for females treated with hormone replacement therapy • Description of end of relevant systemic exposure • Combined (estrogen- and progestogen-containing) hormonal contraception and progesterone-only hormonal contraception as highly effective methods that are user dependent • Clarification that periodic sexual abstinence, withdrawal, spermicides only, and lactational amenorrhea method are not acceptable methods	Updated to reflect the most recent BMS guidance.
Appendix 5: Nivolumab Management Algorithms for Studies Under CTCAE Version 4.0	Updated the appendix title to clarify that the management algorithms were specific to CTCAE version 4.0 and updated the guidance for each of the algorithms to the latest version.	Updated to reflect the most recent management algorithms for CTCAE version 4.0.
All	Minor formatting and typographical corrections.	These changes are minor and, therefore, have not been summarized.

Overall Rationale for the Revised Protocol 02, 06-Oct-2020

CA2099N9 has been revised to further optimize patient selection for the triplet combination therapy with immune checkpoint blockage (nivolumab with ipilimumab) and mitogen-activated protein kinase enzymes (MEK) inhibitor (trametinib) in MSS mCRC. Protocol Revision 01 was finalized in March 2018; however, it was not implemented due to emerging data from Phase 3 IMblaze 370 released at ESMO World GI in June 2018. As IMblaze370 did not demonstrate enhanced efficacy with the doublet combination therapy (program cell death ligand 1 [PD-L1] blockage and MEK inhibitor), CA2099N9 has been revised to enroll patients only to the triplet regimen in the 2L and 3L setting (Parts 1B and 2, respectively). The sample size was increased to approximately 120 patients (2:1 randomization to triplet regimen or regorafenib) in Part 2 and

approximately 80 patients to be treated in Part 1B (triplet regimen) to allow for further assessment of clinical safety, efficacy, and [redacted] in MSS mCRC.

In addition, Administrative Letters 02 and 03, described in the document history, have been incorporated.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated Information for the Clinical Trial Physician and Clinical Scientist.	Alignment with current BMS protocol study team structure.
Throughout the protocol	The dose optimization part of the study (Part 1 and Part 1A) has completed. Enrollment is closed in Part 1 and Part 1A cohorts. Throughout the protocol, text has been added to indicate tables, sections, and text with procedures now completed or cohorts where enrollment has closed.	Part 1 and Part 1A text and tables remain in the protocol to reflect the dose optimization phase of the protocol, which has now completed.
	Per Revised Protocol 02, regorafenib is the SOC option in the study (Part 2 [Cohort 5]) as described in Section 5.4.2. All information connected to TAS-102 as a SOC treatment in this study has been deleted (text, tables, and appendices).	Align protocol with revised study design.
	NCI-CTCAE version 4.0 has been specified as the correct NCI-CTCAE version to be used in this study.	Clarification.
• Synopsis, Study Rationale • Section 3.1, Study Rationale • Section 3.1.1, Research Hypothesis	Text added or changed to specify the following: • 2L and 3L pMMR/MSS patients will be enrolled in Part 1B and Part 2, respectively. • Triplet regimen dose, determined in the dose optimization phase of the study, is nivolumab 6 mg/kg Q4W + ipilimumab 1 mg/kg Q8W + trametinib 1.5 mg continuous QD. • Goal of study: further assessment of clinical safety, efficacy, and [redacted] in MSS mCRC.	Align with revised study design.
• Synopsis, Number of Participants • Section 5.2 Number of Participants	Specification for participant enrollment in Parts 1B and 2. Approximately 200 participants will be enrolled in Parts 2 and 1B.	Aligned with new study design.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
• Synopsis, Objectives and Endpoints • Section 4, Objectives and Endpoints, Table 4-2, Objectives and Endpoints Parts 1B and 2	• All objectives updated to align with change in study design for Parts 1B and Part 2. • Primary endpoint is ORR: changed from OS (Part 2) and safety (Part 1B). • Best Overall Response (BOR), and Overall Survival included in list of secondary endpoints. • Additional secondary objective and endpoint added to evaluate efficacy in Consensus Molecular Subtypes (CMS). • [redacted]. • Footnote added to specify RECIST v1.1 for response criteria	Objectives and endpoints revised to align with new study design.
• Synopsis, Overall Design and Figure 1-1 • Section 5.1, Overall Design and Figure 5.1-1	Part 1B and Part 2 will enroll 2L and 3L pMMR/MSS mCRC patients, respectively, to treatment with triplet regimen or standard of care (Part 2 only). The recommended Phase 2 dose for Parts 2 and 1B triplet regimen, determined in the dose optimization phase of the study, is nivolumab 6 mg/kg Q4W + ipilimumab 1 mg/kg Q8W + trametinib 1.5 mg continuous QD.	Data from IMblaze370 did not demonstrate enhanced efficacy with the doublet combination therapy (PD-L1 blockage and MEK inhibitor), CA2099N9 has been revised to enroll patients only to the triplet regimen in the 2L and 3L setting (Parts 1B and 2, respectively).
	The proportion of participants with RAS mutations enrolled into Part 1B and Part 2 cohorts will be monitored on an ongoing basis. The target will be approximately 65% mutant, 35% wild type. If accrual diverges significantly from this goal, accrual in a cohort may be paused after discussion between the sponsor and the investigators.	This cap will be to ensure that sufficient numbers of RAS wild-type patients as well as RAS mutant patients are enrolled to allow appropriate interpretation of results.
Synopsis, Number of Participants	Specification for enrollment goal in Parts 1B and 2.	Alignment with revision to study design.
Section 2.0, Schedule of Activities	Procedures with notable revisions include:	Schedule of Activities Tables aligned with updated study design and revised to include clarifications for the study sites.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-1, Screening Procedural Outline ()(CA2099N9)	• Medical History: Appendix 13 has been added as reference for tumor sidedness. • BRAF Mutation Status: BRAF V600 mutant participants are not eligible for this study. • [redacted]. • Participant Registration and Treatment Assignment: Refer to Section 7.2 for stratification factors now included.	[redacted]
• Section 2.0, Schedule of Activities: Table 2-3 On-Treatment Assessments (Part 2 mCRC 3rd line, Triplet [redacted] CA2099N9) Cohort 4 • Section 2.0, Schedule of Activities: Table 2-6 On-Treatment Assessments (Part 1B mCRC 2nd line, Triplet [redacted], CA2099N9 [Cohort 6])	Table titles and column headers updated to reflect change in study design, which includes updated regimen, assessment days, and cohort numbers. Procedures with notable revisions include: • Laboratory Tests: Schedule of assessments revised (including CEA) and instruction on creatinine clearance and TSH revised for clarity. • [redacted] • [redacted] • Body Imaging: Note includes instructions on scans to vendor. • Outcomes Research Assessment: Notes rewritten for clarity and with corrected naming of assessment tool. • Clinical Drug Supply: Added line for administration of ipilimumab (Table 2-3 only) and notes revised for each part of triplet regimen. • Table footnotes updated.	Schedule of Activities Tables aligned with updated study design and revised to include clarifications for the study sites. [redacted]
Section 2.0, Schedule of Activities: Table 2-4 On-Treatment Assessments (Part 2 mCRC 3rd line, Regorafenib, [redacted]	Table title and column header updated to include updated regimen, assessment schedule, and cohort number. Procedures with notable revisions include:	Schedule of Activities Tables aligned with updated study design and revised to include clarifications for the study sites.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted] CA2099N9) Cohort 5	• Laboratory Tests: Schedule of assessments revised (including CEA) and instruction on creatinine clearance and TSH revised for clarity. • [redacted] • Body Imaging; Note includes instructions on scans to vendor. • Outcomes Research Assessment: Notes rewritten for clarity and with corrected naming of assessment tool. • Clinical Drug Supply: Regorafenib note revised. • Table footnotes updated.	[redacted]
Section 2.0 Schedule of Activities: Table 2-7: Follow-Up Period (All treatment cohorts) (CA2099N9)	Procedures with notable revisions include: • Review of Subsequent Cancer Therapies: Note includes instructions on information to be collected for subsequent therapies. • Laboratory Tests: instruction on creatinine clearance and TSH revised. • Body Imaging; Note includes instructions on scans to vendor. • Outcomes Research Assessment: Notes rewritten for clarity and with corrected naming of assessment tool. • Footnote c has been updated to reflect a 14 day window rather than 7 days for Survival Follow-Up Visits.	Schedule of Activities Tables aligned with updated study design and revised to include clarifications for the study sites. Change in window for follow-up reflects alignment with study treatment standard.
Section 3.1.2, Rationale for the Combination of Nivolumab and Ipilimumab with Trametinib in MSS CRC Population Section 3.1.3, Rationale for Adding Ipilimumab to Nivolumab and Trametinib	Section 3.1.3 was revised to include updated clinical data to support triplet regimen in light of lack of clinical efficacy of the doublet treatment regimen of PD-(L)1 inhibition in combination with MEK inhibition as reported in the recent IMblaze370 Phase 3 trial. Revisions to this section addressed content in Section 3.1.3, which was previously deleted.	Updated to reflect most recently reported clinical data.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.2.4, Consensus Molecular Structure	New section to provide background on CMS subtypes and to support study objective to evaluate efficacy in CMS subtypes. Includes Table 3.2.4-1: 2l+ Clinical Data in Consensus Molecular Subtypes (CMS) of mCRC	Updated to provide context for CMS subtyping [redacted]
Section 3.3, Overall Benefit Risk	New paragraph added to address addition of Parts 1B and 2 to study design.	Included to further detail potential benefit of the triplet regimen.
Section 3.3.1, Summary of Safety and Efficacy in Relevant Clinical Trials: Table 3.3.1-1	Table updated with summary of clinical data regarding 3L + mCRC.	Updated to reflect most recently reported clinical data.
• Section 3.3.2 Safety Monitoring on Study Treatment • Section 5.1.4 Data Monitoring Committee and Other External Committee • Section 5.1.4.2, Data Monitoring Committee	Data monitoring committee will not be utilized for this Phase1/2 study as indicated in Section 5.1.4. Section 5.1.4.2 was removed.	Safety was established in Part 1 and Part 1A cohorts.
• Section 5.1.2, Part 1B: [redacted] for Triplet Regimen • Section 5.1.3, Part 2: [redacted] for Triplet Regimen and Standard of Care • Arm	These sections describe Part 1B and Part 2.	Aligns with new study design.
Section 5.1.4.1, Blinded Independent Central Review	[redacted]	[redacted]
Section 5.4.2, Rationale for Choice of Standard of Care (SOC) Treatment in Part 2	Regorafenib addressed as standard of care choice.	Regorafenib is the standard of care option for this study: Cohort 5 (Part 1B).
Section 5.4.3, Rationale for Stratification in Part 2	Two stratification factors, primary tumor location (right vs left sided tumor) and extended RAS status (wild-type vs mutant) were chosen to compare for the evaluation of the triplet regimen.	Clinical data support primary tumor location as having significant prognostic impact. Extended RAS (KRAS and NRAS) testing is standard practice in guiding treatment decisions in mCRC.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.5.1.1, Rationale for Nivolumab Dosing	New paragraph to address nivolumab dose in this revision.	Text added to support Phase 2 nivolumab dose for Parts 1B and 2.
Section 5.5.2, Rationale for the Dose of Trametinib	Updated to include rationale for dose of trametinib to be used in Parts 1B and 2.	The recommended Phase 2 dose of trametinib in the triplet regimen for Parts 2 and 1B will be 1.5 mg continuous QD, which is based on the initial safety, efficacy, [redacted] data observed from Parts 1 and 1A.
Section 5.5.4, Rationale for Dose Selection of Regorafenib in 3rd line MSS/mCRC	Section updated to address choice of regorafenib as standard of care option.	Dose of regorafenib is based on approved labels across various regions.
Section 6.1, Inclusion Criteria	2) b) i): Addition of Part 2 (third line setting) to inclusion for MSS status 2) b) ii) Criterion is no longer applicable: ie, eligibility of participants with pMMR/MSS and dMMR/MSI-H mCRC 2) c) i) Note that in Part 2 and Part 1B proportion of participants with RAS mutation and wild type will be monitored. 2) d) i) added Part 2 to inclusion criteria specifying number of lines of prior therapy 2) d) v) Participants who received FOLFOXIRI (or equivalent) in the first-line setting may now be considered for enrollment in the 3L setting (Part 1 or Part 2) but not the 2L setting (Part 1A or Part 1B 2) d) vii) Per revised protocol 02, criterion no longer applies. [redacted]. 3)d) and 3)e) contraception requirement for participants randomized to standard of care arm now addressed.	Alignment with updates to study design and on study population to be enrolled in Part 1B and Part 2.
Section 6.2, Exclusion Criteria	1) a) All parts of the study require verification of BRAF mutation status; therefore reference to study parts was removed. 2) m) vii: exclusion criterion is noted to apply to both potential participants in Part 1B and Part 2.	Clarification for mutation testing and alignment with current standards for study treatments.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	2(n) Participants who have received a live/attenuated vaccine within 30 days of randomization are now excluded. 5)a) Added qualifier that in countries where permitted prisoners or participants are involuntarily incarcerated may be eligible.	
Section 7 Treatment, Table 7-1 Study treatments for CA2099N9	50 mg added to Ipilimumab Solution for Injection.	Alignment to reflect updated availability in ipilimumab vial sizes.
• Section 7.1.4, Part 2 (Triplet Regimen, Cohort 4 and Standard of Care Arm (Cohort 5) including Table 7.1.4.1, Dose Schedule of Nivolumab + Ipilimumab and Trametinib in Part 2 (Cohort 4) • Section 7.1.4.1 Cohort 4 Triplet regimen • Section 7.1.4.2, Cohort 5 Regorafenib including Table 7.1.4.2-1, Recommended Dose of Regorafenib Part 2 (Cohort 5) • Section 7.1.6, Part 1B (Triplet Regimen, Cohort 6) including Table 7.1.6-1, Dose Schedule of Nivolumab, Ipilimumab, and Trametinib in Part 1B (Cohort 6)	These sections have been revised to reflect changes in Part 2 and Part 1B Cohorts per Revised Protocol 02, including dose schedules for the triplet regimen and treatment with regorafenib. Weight-based dosing information added.	Updated to align with revisions for Part 2 and Part 1B cohorts.
Section 7.2, Method of Treatment Assignment including Table 7.2-1 Unique Cohort Numbers in Parts 1, 1A, 1B, and 2.	Updated to include cohort numbering and dosing for Parts 1B and 2. Test added to support stratification.	Align with changes in the study design.
Section 7.3, Blinding	As Part 2 is randomized/open label, access to treatment codes is restricted from all BMS personnel prior to database lock.	Aligned with current protocol standard.
Section 7.4.1, Nivolumab/Ipilimumab Dose Delay	Myocarditis added to list of management algorithms.	Alignment with current standard for treatment with immuno-oncology agents.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
• Section 7.4.4.2, Guidelines for Specific Trametinib Related Toxicities • Appendix 6, Trametinib Dosing Modifications	QTc prolongation removed as toxicity related to trametinib.	QTc prolongation is no longer considered as trametinib related toxicity.
• Section 7.4.4.3, Dose Modification for Trametinib Table 7.4.4.3-1: Potential Trametinib Dose Levels in Part 1B and Part 2 • Section 8.1.3, Trametinib Dose Discontinuation	Text and table changes for dose modifications and discontinuation for trametinib.	Adjusted for study population.
Section 7.7.1, Prohibited and/or Restricted Treatments Section 7.7.3, Permitted Therapies	Text added to Section 7.7.1: Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) within 100 days post last dose of nivolumab without or with ipilimumab. Similar information deleted from Section 7.7.1.	Alignment with standard language for participants enrolled in studies with immuno-oncology treatment.
Section 8.1, Discontinuation from Study Treatment	Treatment beyond progression is allowed for participants in Cohort 4 and Cohort 6. Language regarding notification of pregnancy updated.	Revised for study population and to align with current standard for reporting pregnancy.
• Section 8.1.1, Nivolumab Dose Discontinuation (Part 1) • Section 8.1.2, Nivolumab and Ipilimumab Dose Discontinuation •	Section titles changed. The following note was removed from both sections: **Consideration can be given to participants with abnormal baseline AST or ALT or abnormal baseline bilirubin values. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.	Titles were changed to reflect revised study design. Paragraph was removed as sufficient guidance is provided within the section.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 8.1.5, Treatment Beyond Progression	Language in this section has been updated to align with standard for clinical trials with immuno-oncology agents and to specify that treatment beyond progression is permitted in Cohorts 4 and 6.	Alignment with current standard imaging language and particulars for this study.
Section 8.1.6, Post Study Treatment Study Follow-up	Text added to address sponsor request for survival language outside of protocol-defined window.	Aligned with current standard protocol language.
Section 9.1.1.2, Imaging Schedule and Assessment	Language added to specify imaging schedule for participants treated beyond progression.	Section aligned with revised study design.
Section 9.1.1.3, Tumor Assessment by Investigator Sites	Language updated to imaging standard for sending of scans to the vendor. Instructions to site for Part 1B and Part 2 included. Language added for BOR of stable disease (SD) requiring minimum of 49 days from first dose to date of first imaging assessment.	Clarification and alignment with current protocol standard.
[redacted]		
Section 9.2, Adverse Events	Change in Trametinib Adverse Events of Special Interest: Deletion: Diarrhea, Edema Addition: Venous Thromboembolism	Revised per current Investigator Brochure (IB) for trametinib.
Section 9.2.1, Time Period and Frequency for Collecting AE and SAE Information	Language not relevant to this study was deleted. Text added for reporting of SAEs for participants assigned to treatment but not treated.	Correction and updated to current protocol standard.
Section 9.2.2, Method of Detecting AEs and SAEs.	Section updates to align with current standard language for immuno-oncology treatments.	Alignment with program-wide standard.
Section 9.2.4, Regulatory Reporting Requirements for SAEs	Redundant text removed.	Alignment with current protocol standard.
Section 9.4.3, Ophthalmic Examination	Ophthalmic examination during treatment and Follow-Up periods is not required for Cohort 5 participants, unless clinically indicated.	Ophthalmic examination is required for all participants treated with trametinib.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 9.9, Health Economics OR Medical Resource Utilization and Health Economics	Updated to specify that data will be collected for participants in Part 1B and Part 2.	Aligned with addition of [redacted] cohorts.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.1.2, mCRC 3rd line Participants: Part 2 [redacted] Cohort, [redacted]	[redacted]	Aligns with revised study design and study objectives.
Section 10.1.4, mCRC 2nd line Participants: Part 1B [redacted] Cohorts	[redacted]	
Section 10.2, Populations for Analyses	Revised definitions to include randomized cohorts from Part 2.	
Section 10.3.1, Efficacy Analyses	Updated to support study design revisions including efficacy in subgroups of interest, which are specified. Detailed revision for efficacy endpoints (eg, to include randomized cohorts from Part 2 or new endpoints) and statistical methods.	
Section 10.3.2, Safety Analyses	Minor revisions.	
[redacted]		
Section 10.3.7, Interim Analyses	An interim analysis of Part 2 and Part 1B cohorts has been defined and the section has been updated.	
Section 11, References	Updated to include references to support new text in background sections.	
Appendix 5, Nivolumab Management Algorithms	Updated to current management algorithms, which includes algorithm for myocarditis.	Aligned with current Management Algorithms for all immuno-oncology agents.
Appendix 10, KRAS/NRAS and BRAF Mutational Testing	Participant enrollment will be based on initial testing results [redacted]	Confirmation of enrollment status.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	[redacted]	
Appendix 12, Country Specific Appendix	France, Spain, and Italy have been deleted from the countries that require criteria for exclusion of HIV-positive subjects. Pregnancy added as a reason for permanent discontinuation from study treatment in Czech Republic and any Other Countries Where Locally Mandated.	Correction of regulatory requirements for the Czech Republic, France, Spain, and Italy.
Appendix 13, Guidance to Sites on Tumor Location and Sidedness	Replaces previous Appendix 13 with new on Specifications for Tumor Sidedness.	Specifications for stratification factor (tumor sidedness) for participants in Part 2.
Appendix 14, Revised Protocol Summary of Change History	The summay of key changes for Revised Protocol 01 is included as Appendix 14. Of note, Revised Protocol 01 was approved but was not implemented.	This appendix is in alignment with standard for revised protocols.
Throughout the protocol	Minor editorial and format changes.	Revised for clarity.

Overall Rationale for the Revised Protocol 01, 01-Mar-2018

The protocol has been amended to include a randomized comparator arm (Cohort 7) for Part 2 consisting of standard-of-care regimens (regorafenib or TAS-102) per investigator's choice for ≥ 3rd line metastatic colorectal cancer (mCRC). The rationale is to allow a direct comparison of safety and efficacy between study treatment and standard of care treatment in a randomized controlled trial design (Part 2). In addition, primary endpoint for Part 2 has been changed to Overall Survival (OS), which is the standard endpoint for efficacy assessment in oncology trials. The demonstration of clinically meaningful improvements in survival compared to current therapies in the treatment of later line mCRC as well as manageable safety, provides an opportunity to support registration.

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2. Schedule of Activities	New table (Table 2-4) added.	New table added to detail schedule of activities for Cohort 7.
Section 5.1. Overall Design	Section 5.1 amended to include details relating to the comparator arm.	The study design has been amended to include the details relating to the addition of the comparator arm in Cohort 7.

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1.4.2. Data Monitoring Committee for Part 2	New Section (Section 5.1.4.2) added.	A Data Monitoring Committee has been introduced to ensure participant safety and monitor evaluable data for efficacy during Part 2 of the study design.
Section 5.2. Number of Participants	Number of participants for the randomized Part 2 has been detailed.	The number of participants to be studied in Part 2 (based on the sample size justification presented in Section 10.1) has been amended to allow for the 2:1 randomization between Cohorts 4 and 7.
Section 5.4.1 Rationale for Treatment Duration	Rationale updated. No change to study conduct.	Most updated rationale added supporting maximum treatment duration of 2 years from first dose.
Section 5.4.2. Rationale for Choice of Comparator Treatments in Part 2	New Section (Section 5.4.2) added.	Section added to detail the rationale for the choice of standard-of-care chemotherapy regimens included for comparator purposes in Cohort 7.
Section 5.4.3. Rationale for Stratification in Part 2	New Section (Section 5.4.3) added.	Section added to detail the rationale for the stratification factors (right versus left sided tumors and RAS/BRAF double wild-type versus mutant [RAS or BRAF, or both]) adopted as part of the randomization for Part 2 of the study.
Section 5.5.4. Rationale for Dose Selection of TAS-102 in ≥ 3rd line mCRC	New Section (Section 5.5.4) added.	Section added to detail the rationale for the dose selection for TAS-102 to be used in Part 2, Cohort 7.
Section 5.5.5. Rationale for Dose Selection of Regorafenib in ≥ 3rd Line mCRC	New Section (Section 5.5.5) added.	Section added to detail the rationale for the dose selection for regorafenib to be used in Part 2, Cohort 7.
Section 6.1. Inclusion Criteria	Prior lines of therapy clarified.	Section 6.1, 2) d) revised to clarify the relevant prior lines of therapy for Parts 1 and 2.
Section 6.2. Exclusion Criteria	3) Additional contraindications with respect to medical history and concurrent diseases added. 4) Botanical washout period changed from 4- to 2 weeks prior to first dose. Note referring to 7.7.1 added.	5) Section 6.2 revised to include contra-indications for treatment with regorafenib and TAS-102. 6) Correction of washout duration to 2 weeks prior to first dose. Clarification regarding marijuana use added to Section 7.7.1.
Section 7. Treatment	Table 7-1 amended.	Table 7-1 amended to include details pertaining to regorafenib and TAS-102.
Section 7.1.1 Nivolumab and Ipilimumab Infusion	Change “saline” to “diluent” for line flushing between infusions.	Change clarifies that the post-nivolumab infusion may be done with diluent not only saline.

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.1.4.2. Cohort 7 Regorafenib or TAS-102, Section 7.1.4.3. Regorafenib Dosing in Part 2, and Section 7.1.4.4. TAS-102 Dosing in Part 2	New Sections (Sections 7.1.4.2, 7.1.4.3, and 7.1.4.4) added.	Sections added to detail the treatments assigned and starting doses in Cohort 7.
Section 7.2. Method of Treatment Assignment	Table 7.2-1 modified to include Cohort Number in 7.	Table 7.2-1 modified to include details for Cohort 7.
Section 7.2. Method of Treatment Assignment	Section 7.2 revised to include stratification details relating to treatment assignment for Cohorts 4 and 7.	Section revised to detail the stratification factors (right versus left sided tumors and RAS/BRAF double wild-type versus mutant [RAS, or BRAF, or both]) adopted as part of the randomization for Part 2 of the study.
Section 7.4. Dosage Modification	Section 7.4 revised to include details regarding dose modifications for regorafenib (Section 7.4.6) and TAS-102 (Section 7.4.7).	Section revised to provide initial guidance on dose modifications for the additional study treatments introduced with this protocol amendment.
Section 7.7.1 Prohibited and/or Restricted Treatments	Clarification added regarding marijuana.	Marijuana may not be prohibited if medically prescribed or locally legal.
Section 7.7.3. Permitted Therapies	Section amended to include reference to supportive care.	As supportive care is routine for regorafenib and TAS-102, suitable reference to this has been included.
Sections 8.1.1 Nivolumab Dose Discontinuation and 8.1.2 Nivolumab and Ipilimumab Dose Discontinuation	Myocarditis added to the list of events that require discontinuation.	Addition aligns discontinuation with SmPC and USPI.
Section 8.1.4. TAS-102 Dose Discontinuation	New Section (Section 8.1.4) added.	Section added to detail instances requiring discontinuation of TAS-102.
Section 8.1.5. Regorafenib Dose Discontinuation	New Section (Section 8.1.5) added.	Section added to detail instances requiring discontinuation of regorafenib.
Section 8.1.6 Treatment Beyond Progression	Added that treatment beyond progression may continue to a maximum of 2 years from first dose.	Clarification of maximum duration of treatment.
Section 9.9. Health Economics OR Medical Resource	Details regarding healthcare resource utilization data capture included.	Healthcare resource utilization data will be collected for Part 2.

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Utilization and Health Economics		
Section 10.1.2. mCRC ≥ 3rd line Participants: Part 2 Dose Expansion Cohort	New Section (Section 10.1.2) added.	Section added to detail the sample size determination for Part 2, based on the primary efficacy of OS, and to detail the plans for interim analyses in this part of the study.
Section 10.3.1. Efficacy Analyses	Details regarding OS added to Endpoints and Statistical Methods	Details regarding OS (primary efficacy endpoint for Part 2) included.
Section 10.3.7. Interim Analyses	New Section (Section 10.3.7) added.	Interim analyses prospectively detailed for the efficacy comparison in Part 2 between Nivolumab + Trametinib and Regorafenib/TAS-102.