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Clinical Protocol CA209214

A Phase 3, Randomized, Open-Label Study of Nivolumab Combined with Ipilimumab Versus Sunitinib Monotherapy in Subjects with Previously Untreated, Advanced or Metastatic Renal Cell Carcinoma

(**CheckMate 214, CHECK**point pathway and nivolu**MA**b clinical Trial Evaluation 214)

Revised Protocol Number: 03
Incorporates amendment(s): 14 and Administrative Letter 01

[redacted]

24-hr Emergency Telephone Number
USA: 1-866-470-2267
International: +1-248-844-7390

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

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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 03	13-Nov-2017	Incorporates Amendment 14
Amendment 14	13-Nov-2017	Protocol amendment is being implemented to provide modifications to the protocol based on recommendations of the study's independent Data Monitoring Committee (DMC) after their review of the planned interim analysis of overall survival (OS), which met the pre-specified boundary for statistical significance for the co-primary endpoint of OS. As a result of the DMC assessment, this protocol amendment is being implemented to provide a mechanism for eligible subjects randomized to sunitinib treatment (Arm B) to receive nivolumab combined with ipilimumab therapy in a crossover extension phase. This amendment also provides the options for Arm A subjects to: 1) switch to a flat dose of nivolumab at 240 mg every 2 weeks if they are currently receiving nivolumab 3 mg/kg every 2 weeks and 2) discontinue treatment after 2 years even in the absence of disease progression or unacceptable toxicity. Protocol amendment also indicates that the interim analysis results should be considered the final primary analysis results of the protocol.
Administrative Letter 01	13-Feb-2017	Updated Medical Monitor and removed Study Director
Revised Protocol 02	04-Aug-2016	Incorporates Amendment 13
Amendment 13	04-Aug-2016	Added Objective Response Rate (ORR) as an additional co-Primary Endpoint. Included required updates based on Version 15 of the Nivolumab Investigator Brochure. Added language that allows for collection of additional survival data outside the original protocol specified visit windows. Added Study Director.
Revised Protocol 01	05-Nov-2014	Incorporates Amendment 04
Amendment 04	05-Nov-2014	Added an additional secondary objective related to incidence of AEs. Updated the IMDC prognostic factor for corrected calcium criteria. Added additional LFT testing for Arm A subjects. Incorporated minor changes to correct and/or maintain consistency throughout the protocol.
Original Protocol	17-Jul-2014	Not applicable

SYNOPSIS

Clinical Protocol CA209214

Protocol Title: A Phase 3, Randomized, Open-Label Study of Nivolumab Combined with Ipilimumab Versus Sunitinib Monotherapy in Subjects with Previously Untreated, Advanced or Metastatic Renal Cell Carcinoma

(CheckMate 214, CHECKpoint pathway and nivolu**MA**b clinical **T**rial **E**valuation 214**)**

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

- Nivolumab administered IV over 60 minutes at 3 mg/kg combined with ipilimumab administered IV over 30 minutes at 1 mg/kg every 3 weeks for 4 doses followed by nivolumab administered IV over 60 minutes at 3 mg/kg every 2 weeks or sunitinib 50 mg po Day 1 - 28 of each 42 day cycle until disease progression, unacceptable toxicity or other reasons specified in the protocol. Under Amendment 14, subjects receiving nivolumab at 3mg/kg every 2 weeks will have the option to switch to intravenous nivolumab dosing over 60 minutes at 240 mg every 2 weeks until disease progression, unacceptable toxicity or other discontinuation criteria specified in the protocol.

Study Phase: 3

Research Hypothesis: Treatment with nivolumab combined with ipilimumab will improve Objective Response Rate (ORR), Progression Free Survival (PFS), and Overall Survival (OS) compared to sunitinib monotherapy in subjects with previously untreated metastatic renal cell carcinoma (mRCC).

Objectives:

Primary Objectives

- To describe the ORR of nivolumab combined with ipilimumab and sunitinib monotherapy in intermediate and poor risk subjects with previously untreated mRCC based on IRRC assessments
- To compare the PFS of nivolumab combined with ipilimumab to sunitinib monotherapy in intermediate and poor-risk subjects with previously untreated mRCC, based on Independent Radiation Review Committee (IRRC) assessments
- To compare the OS of nivolumab combined with ipilimumab to sunitinib monotherapy in intermediate and poor-risk subjects with previously untreated mRCC

Key Secondary Objectives

- To compare the PFS of nivolumab combined with ipilimumab to sunitinib monotherapy in any-risk subjects with previously untreated mRCC, based on IRRC assessments
- To compare the OS of nivolumab combined with ipilimumab to sunitinib monotherapy in any-risk subjects with previously untreated mRCC
- To estimate the objective response rate (ORR) of nivolumab combined with ipilimumab and sunitinib monotherapy in subjects with previously untreated mRCC (any-risk), based on IRRC assessments
- To estimate the incidence of AEs of nivolumab combined with ipilimumab and sunitinib monotherapy in all treated subjects with previously untreated mRCC

Study Population:

Key Inclusion Criteria:

- Histological confirmation of RCC with a clear-cell component
- Advanced (not amenable to curative surgery or radiation therapy) or metastatic (AJCC Stage IV) RCC
- No prior systemic therapy for RCC with the following exception:
  a) One prior adjuvant or neoadjuvant therapy for completely resectable RCC if such therapy did not include an agent that targets VEGF or VEGF receptors and if recurrence occurred at least 6 months after the last dose of adjuvant or neoadjuvant therapy.
- Karnofsky Performance Status (KPS) of at least 70%
- Measurable disease as per RECIST 1.1
- Tumor tissue (formalin-fixed paraffin-embedded (FFPE) archival or recent acquisition) must be received by the central vendor (block or unstained slides) in order to randomize a subject to study treatment. (Note: Fine Needle Aspiration [FNA] and bone metastases samples are not acceptable for submission).
- Patients with favorable, intermediate and poor risk categories will be eligible for the study. Patients must be categorized according to favorable versus intermediate/poor risk status at registration.

  To be eligible for the Intermediate and Poor-Risk cohort, at least one of the following prognostic factors as per International Metastatic RCC Database Consortium (IMDC) must be present:

  a) KPS equal to 70
  b) Less than 1 year from diagnosis to randomization
  c) Hemoglobin less than the LLN
  d) Corrected calcium concentration greater than 10 mg/dL
  e) Absolute neutrophil count greater than the ULN
  f) Platelet count greater than the ULN

  If none of the above factors are present, subjects are only eligible for the favorable-risk cohort. The favorable-risk cohort may close to enrollment earlier than the intermediate- or poor-risk cohort.

Key Exclusion Criteria:

- Any history of or current CNS metastases. Baseline imaging of the brain is required within 28 days prior to randomization.
- Prior systemic treatment with VEGF or VEGF receptor targeted therapy (including, but not limited to, sunitinib, pazopanib, axitinib, tivozanib, and bevacizumab).
- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.
- Any active or recent history of a known or suspected autoimmune disease or recent history of a syndrome that required systemic corticosteroids (> 10 mg daily prednisone equivalent) or immunosuppressive medications except for syndromes which would not be expected to recur in the absence of an external trigger. Subjects with vitiligo or type I diabetes mellitus or residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement are permitted to enroll.
- Any condition requiring systemic treatment with corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days prior to first dose of study drug. Inhaled steroids and adrenal replacement steroid doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
- Uncontrolled adrenal insufficiency.
- Ongoing symptomatic cardiac dysrhythmias, uncontrolled atrial fibrillation, or prolongation of the Fridericia corrected QT (QTcF) interval defined as > 450 msec for males and > 470 msec for females, where $QTcF = QT / \sqrt[3]{RR}$
- Poorly controlled hypertension (defined as systolic blood pressure (SBP) of ≥ 150 mmHg or diastolic blood pressure (DBP) of ≥ 90 mmHg), despite antihypertensive therapy
- History of any of the following cardiovascular conditions within 12 months of enrollment: cardiac angioplasty or stenting, myocardial infarction, unstable angina, coronary artery by-pass graft surgery, symptomatic peripheral vascular disease, class III or IV congestive heart failure, as defined by the New York Heart Association
- History of cerebrovascular accident including transient ischemic attack within the past 12 months
- History of deep vein thrombosis (DVT) unless adequately treated with low molecular weight heparin.
- History of pulmonary embolism within the past 6 months unless stable, asymptomatic, and treated with low molecular weight heparin for at least 6 weeks.
- History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within the past 6 months.
- Serious, non-healing wound or ulcer.
- Evidence of active bleeding or bleeding susceptibility; or medically significant hemorrhage within prior 30 days.
- Any requirement for anti-coagulation, except for low molecular weight heparin.
- 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.
- Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).
- Any positive test for hepatitis B or hepatitis C virus indicating acute or chronic infection.
- Known medical condition (eg, a condition associated with diarrhea or acute diverticulitis) that, in the investigator's opinion, would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results.
- Major surgery (eg, nephrectomy) less than 28 days prior to the first dose of study drug.
- Anti-cancer therapy less than 28 days prior to the first dose of study drug or palliative, focal radiation therapy less than 14 days prior to the first dose of study drug.

- Presence of any toxicities attributed to prior anti-cancer therapy, other than alopecia, that have not resolved to Grade 1 (NCI CTCAE v4) or baseline before administration of study drug.
- Receiving concomitant CYP3A4 inducers or strong CYP3A4 inhibitors (See Appendix 4).
- Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of sunitinib (eg, malabsorptive disorder, ulcerative disease, uncontrolled nausea, vomiting, diarrhea, or small bowel resection).
- Left ventricular ejection fraction (LVEF) less than the LLN as assessed by echocardiography or multigated acquisition (MUGA) scan.
- Any of the following laboratory test findings:
  a) WBC < 2,000/mm^3
  b) Neutrophils < 1,500/mm^3
  c) Platelets < 100,000/mm^3
  d) AST or ALT > 3 x ULN (> 5 x ULN if liver metastases are present)
  e) Total Bilirubin > 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)
  f) Serum creatinine > 1.5 x upper limit of normal (ULN) or creatinine clearance < 40 mL/min (measured or calculated by Cockroft-Gault formula)

Amendment 14 Update:

Specific eligibility criteria for subjects in the poor or intermediate cohorts originally randomized to the sunitinib Arm B and now entering the nivolumab combined with ipilimumab crossover extension phase are included in the protocol in Section 3.1.1.

Study Drug: includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

Study Drug for CA209214		
Medication	**Potency**	**IP/Non-IP**
Nivolumab	3 mg/kg	IP
Ipilimumab	1 mg/kg	IP
Sunitinib	50 mg	IP

Study Assessments: Objective Response Rate, Overall Survival, and Progression Free Survival are the co-primary endpoints of the study. Subjects will be assessed for response by CT or MRI beginning at 12 weeks (± 1 week) after randomization and continuing every 6 weeks (± 1 week) for the first 13 months and then every 12 weeks (± 1 week) until progression or treatment discontinuation, whichever occurs later. Overall survival is defined as the time from randomization to the date of death.

Amendment 14 Update:

The schedule of assessments for subjects in the poor or intermediate cohorts originally randomized to the sunitinib Arm B and now entering the nivolumab combined with ipilimumab crossover extension phase are included in the protocol in Section 5.1.

Statistical Considerations:

Sample Size: The sample size of the study accounts for the three co-primary efficacy endpoints: ORR, based on IRRC assessments, PFS, based on IRRC assessments and OS, evaluated in intermediate and poor-risk subjects with previously untreated mRCC. The overall alpha for this study is 0.05, which is split with 0.001 to evaluate ORR, 0.009 to evaluate PFS and 0.04 to evaluate OS.

ORR will be analyzed initially on a descriptive basis and will occupy an administrative adjustment of alpha of 0.001. PFS will be evaluated for treatment effect at an alpha of 0.009 (two-sided, penalized 0.001 from a 0.01 allocation) with at least 90% power; no interim analysis of PFS is planned. OS will be evaluated for treatment effect at an alpha level of 0.04 (two-sided) with 90% power, accounting for two formal interim analyses to assess efficacy.

It is estimated that approximately 1070 previously untreated mRCC subjects will be randomized in a 1:1 ratio. Among them, approximately 820 subjects (76.6%) with intermediate/poor risk subjects and approximately 250 (23.4%) subjects with favorable risk as per IMDC (IMDC prognostic score = 0) will be randomized. Assuming a fixed accrual rate of 57 subjects per month (40 intermediate/poor risk subjects per month), it will take approximately 20.5 months to randomize 1070 subjects (820 intermediate/poor risk subjects).

[redacted]

Endpoints:

Co-Primary Endpoints

Objective Response Rate, Progression-free Survival and Overall Survival are the co-primary endpoints.

Objective Response Rate

Objective response rate is defined as the proportion of randomized subjects who achieve a best response of complete response (CR) or partial response (PR) using the RECIST1.1 criteria based on IRRC assessment. BOR is defined as the best response designation, as determined by the IRC, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. As described in Section 5.4, confirmation of response is required. Duration of response (DOR) is defined as the time between the date of first documented response (CR or PR) to the date of the first documented progression as determined by the IRC (per RECIST 1.1), or death due to any cause, whichever occurs first. For subjects who neither progress nor die, the duration of objective response will be censored at the same time they will be censored for the primary definition of PFS (Section 8.3.1.2). Time to Objective Response (TTR) is defined as the time from randomization to the date of the first confirmed documented response (CR or PR), as assessed by the IRC. DOR and TTR will be evaluated for responders (confirmed CR or PR) only.

Primary Definition of Progression-free Survival

The primary definition PFS is specified as the time between the date of randomization and the first date of documented progression, based on IRRC assessments (as per RECIST 1.1 criteria), or death due to any cause, whichever occurs first. Subjects who die without a reported progression will be considered to have progressed on the date of their death. The following censoring rules will be applied for the primary definition of PFS.

- Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment.
- Subjects who did not have any on study tumor assessments and did not die will be censored on their date of randomization.
- Subjects who receive subsequent systemic anti-cancer therapy prior to documented progression will be censored at the date of the last tumor assessment prior to the initiation of the new therapy.

Secondary Definition of Progression-free Survival

The secondary definition of PFS is defined as the time between the date of randomization and the first date of documented progression, based on IRRC assessments (as per RECIST 1.1 criteria), or death due to any cause,

whichever occurs first. Subjects who die without a reported progression will be considered to have progressed on the date of their death. The following censoring rules will be applied for the secondary definition of PFS.

- Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment.
- Subjects who did not have any on study tumor assessments and did not die will be censored on their date of randomization.

Finally, PFS based on investigator assessments will also be analyzed applying both the primary and the secondary definitions.

More detail on PFS will be provided in a separate Statistical Analysis Plan.

Overall Survival

Overall survival is defined as the time from randomization to the date of death from any cause. For subjects that are alive, their survival time will be censored at the date of last contact ("last known alive date"). Overall survival will be censored for subjects at the date of randomization if they were randomized but had no follow-up.

Secondary Endpoints

AE Incidence Rate

Adverse events incident rate is defined as the proportion subjects with any grade adverse events among subjects treated in each treatment arm. Events reported from the first dose and up to and including 100 days following the last dose of study treatment could be included in estimating this incidence rate.

Analyses: One of the primary objectives of the study is to describe the objective response rate per IRRC in the two treatment arms among intermediate and poor risk subjects. The ORR analysis will occupy a 0.001 administrative allocation of alpha.

The number and percentage of subjects in each category of best overall response per IRRC (complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD], or unable to determine [UD]) according to the IRRC will be presented, by treatment group. An estimate of the response rate and an associated exact two-sided 95% CI (Clopper and Pearson[36]) will be presented, by treatment group.

Sensitivity analysis based on investigator-determined ORR may also be performed. DOR and TTR will also be evaluated. Descriptive analysis of the response in the investigator's choice group (ie, subjects treated with investigator's choice among ORR population) will also be provided.

At the time of the formal ORR analysis, no PFS or OS analysis will be conducted because of the immaturity of those specific endpoints. A reduced analysis will be defined in the data presentation plan.

One of the primary objectives of the study is to compare the progression-free survival (based on IRRC assessments) of nivolumab combined with ipilimumab to sunitinib monotherapy in intermediate and poor-risk subjects with previously untreated mRCC. A two-sided stratified 0.009 log-rank test will be used to do a formal comparison of PFS.

A stratified log-rank test will be used to compare the PFS of subjects randomized to nivolumab combined with ipilimumab to that of subjects randomized to sunitinib. Median PFS will be estimated via the Kaplan-Meier product limit method. Two-sided 99.1% CI for the median PFS will be computed for each randomized arm. Kaplan-Meier plots of PFS will be presented. Hazard ratios (HR) and corresponding two-sided (1-adjusted α)% confidence intervals (CI) will be estimated using a Cox proportional hazards model, with treatment arm as a single covariate, stratified by the stratification factors, corresponding to each comparison of PFS.

The totality of PFS results will be presented in a single graphical display that includes Kaplan-Meier curves for the two treatment arms, the log-rank p-values for the formal comparison, the HRs and corresponding CIs, and the two median estimates and corresponding CIs.

OS will be compared between the treatment arms using a two sided, $\alpha = 0.04$ level log-rank test (adjusted for interim analyses), stratified using the same factor as in PFS. A similar analysis as in PFS will be conducted for OS.

Hazard ratios (HR) and corresponding two-sided 96% confidence intervals (CI) will be estimated using a Cox proportional hazards model, with treatment arm as a single covariate, stratified by the stratification factors, corresponding to the comparison of OS.

Amendment 14 Update:

Optional Switch to Nivolumab 240mg Flat Dosing and Optional Discontinuation after 2 Years of Study Treatment (Arm A)

[redacted]

Arm A subjects who have completed at least 2 years of treatment have the option to discontinue study treatment at

[redacted]

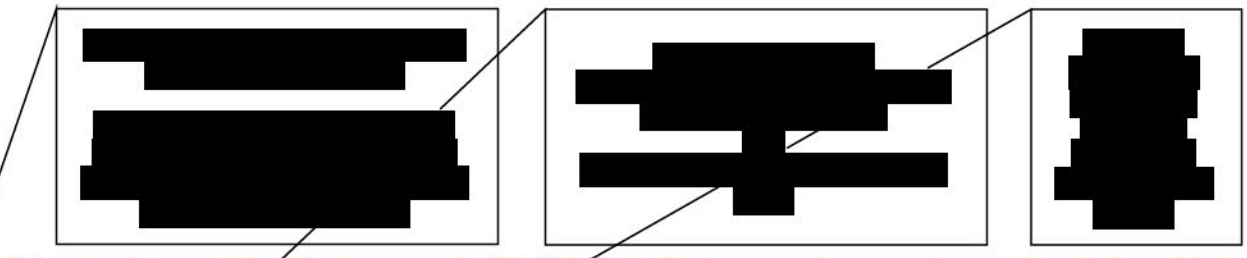
Nivolumab combined with Ipilimumab Crossover Extension Phase (Arm B)

With this amendment, all subjects in the poor or intermediate cohorts randomized to the sunitinib treatment (Arm B) who meet eligibility criteria may enter the nivolumab combined with ipilimumab crossover extension phase, according to the schema below. These subjects will be eligible to enter the crossover arm and receive BMS supplied study drug for a maximum of 2 years but no longer than up to 12 months after the approval of investigational product by the responsible health authority or until the investigational product becomes commercially available within the country, whichever occurs sooner. BMS reserves the right to terminate access to study drug if any of the following occur: a) the marketing application is rejected by the responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market. These subjects will follow the assessment schedules outlined in Tables 5.1-5 and 5.1-6 of the protocol.

Subjects treated with sunitinib who have ended study treatment will be able to receive treatment with nivolumab combined with ipilimumab via the crossover extension phase of the study, assuming eligibility criteria are met (including a 14-day washout period for prior systemic anti-cancer therapy). Details are provided in Section 3.1.1.

Subjects currently receiving treatment with sunitinib may continue to be treated and monitored as specified in the protocol as long as they are continuing to derive benefit from sunitinib in the judgment of the investigator. These subjects may receive nivolumab combined with ipilimumab once they are discontinued from sunitinib therapy, assuming basic eligibility criteria are met (including a 14-day washout period from the last dose of sunitinib).

[redacted]



*Treatment beyond investigator-assessed RECIST 1.1-defined progression may be considered for subjects meeting criteria according to Section 4.5.7. Treatment beyond progression for subjects in the nivolumab combined with ipilimumab crossover extension phase should be discussed with the BMS Medical Monitor prior to subjects receiving additional study drug. Criteria for discontinuation of treatment beyond progression are described in Section 4.5.7. Subjects who discontinue study therapy for reasons other than progression should continue to be scanned until disease progression is documented.

1 INTRODUCTION AND STUDY RATIONALE

[redacted]

1.2 Research Hypothesis

Treatment with nivolumab combined with ipilimumab will improve ORR, PFS, or OS, compared to sunitinib monotherapy in subjects with previously untreated mRCC.

1.3 Objectives(s)

1.3.1 Primary Objectives

- To describe the ORR of nivolumab combined with ipilimumab and sunitinib monotherapy in intermediate and poor-risk subjects with previously untreated mRCC, based on IRRC assessments
- To compare the PFS of nivolumab combined with ipilimumab to sunitinib monotherapy in intermediate and poor-risk subjects with previously untreated mRCC, based on IRRC assessments
- To compare the OS of nivolumab combined with ipilimumab to sunitinib monotherapy in intermediate and poor-risk subjects with previously untreated mRCC

1.3.2 Secondary Objectives

- To compare the PFS of nivolumab combined with ipilimumab to sunitinib monotherapy in any-risk subjects with previously untreated mRCC, based on IRRC assessments
- To compare the OS of nivolumab combined with ipilimumab to sunitinib monotherapy in any-risk subjects with previously untreated mRCC
- To estimate the objective response rate (ORR) of nivolumab combined with ipilimumab and sunitinib monotherapy in subjects with previously untreated mRCC (any-risk), based on IRRC assessments

- To estimate the incidence of AEs of nivolumab combined with ipilimumab and sunitinib monotherapy in all treated subjects with previously untreated mRCC

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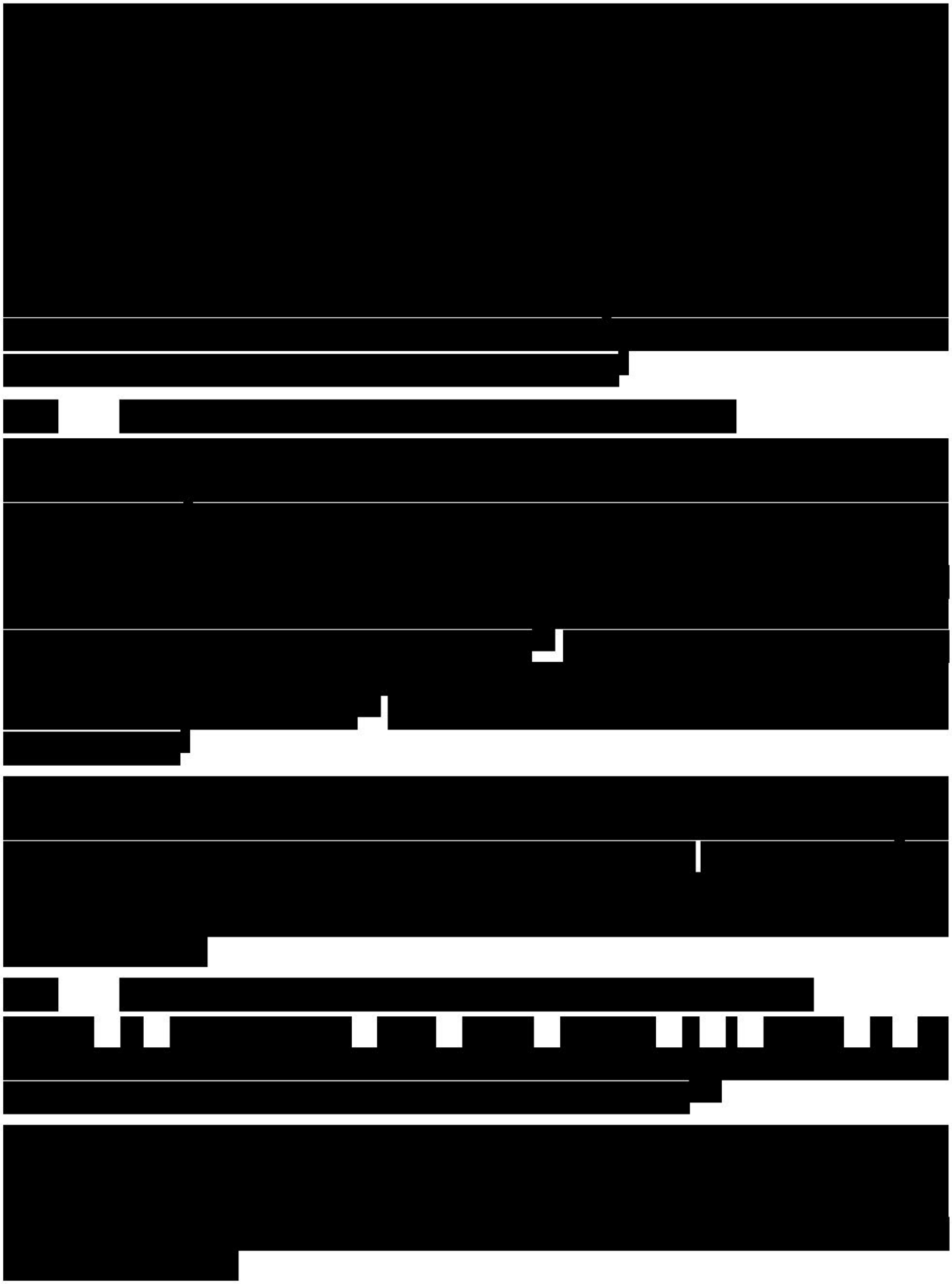

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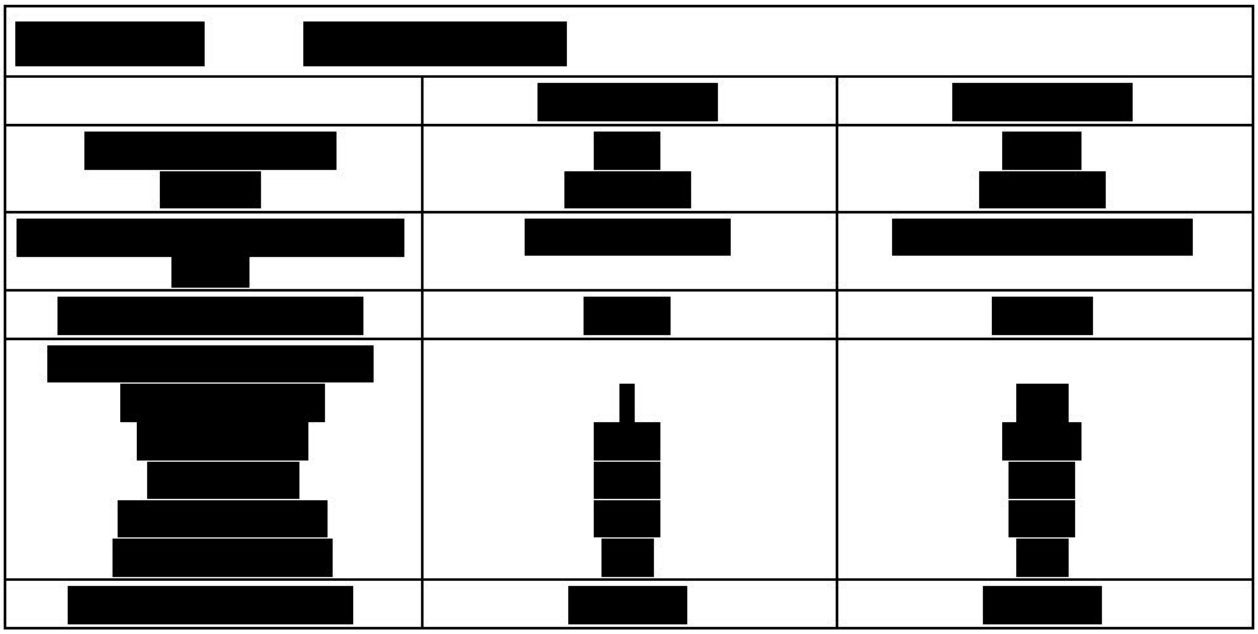

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1.5 Overall Risk/Benefit Assessment

Patients with mRCC have multiple treatment options available to them, but none of the 7 available targeted agents have been able to demonstrate a significant improvement in overall survival when compared to each other. Median overall survival remains less than 4 years for treatment-naive patients with the most favorable prognosis, and is substantially shorter for patients who possess adverse prognostic factors. Therefore, new therapeutic options with the potential to provide greater survival across risk groups are needed. Nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg has demonstrated substantial clinical activity, as measured by ORR, while still exhibiting an acceptable safety profile. These immunotherapy-induced responses are expected to be more durable than those induced by VEGF receptor therapy, and are therefore likely to translate into improvements in PFS and OS vs sunitinib.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS 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 (eg, loss of medical licensure, debarment).

2.2 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, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

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

2.3 Informed Consent

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 subject volunteers to participate.

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

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) 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.
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the

subject'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 subject records.

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

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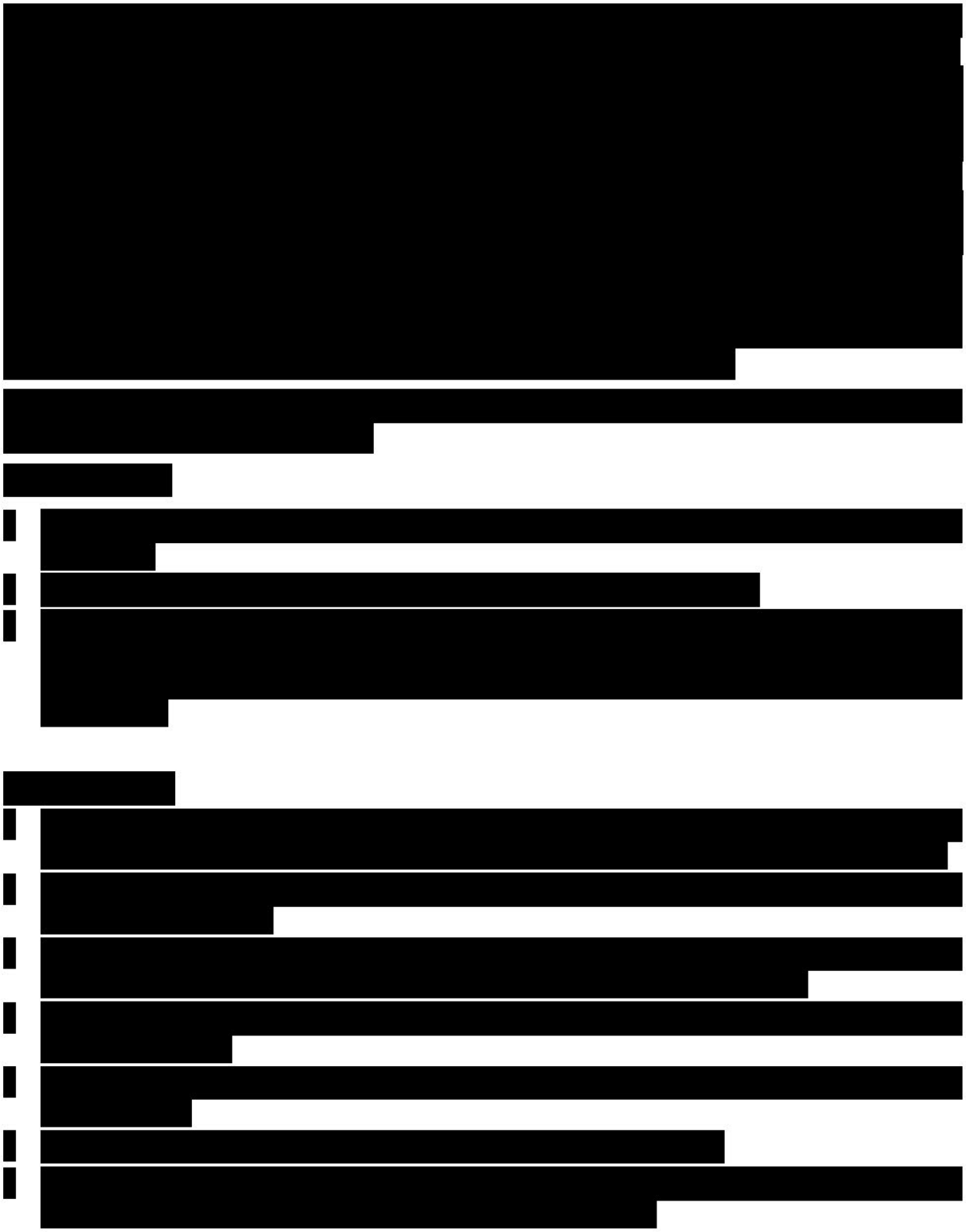

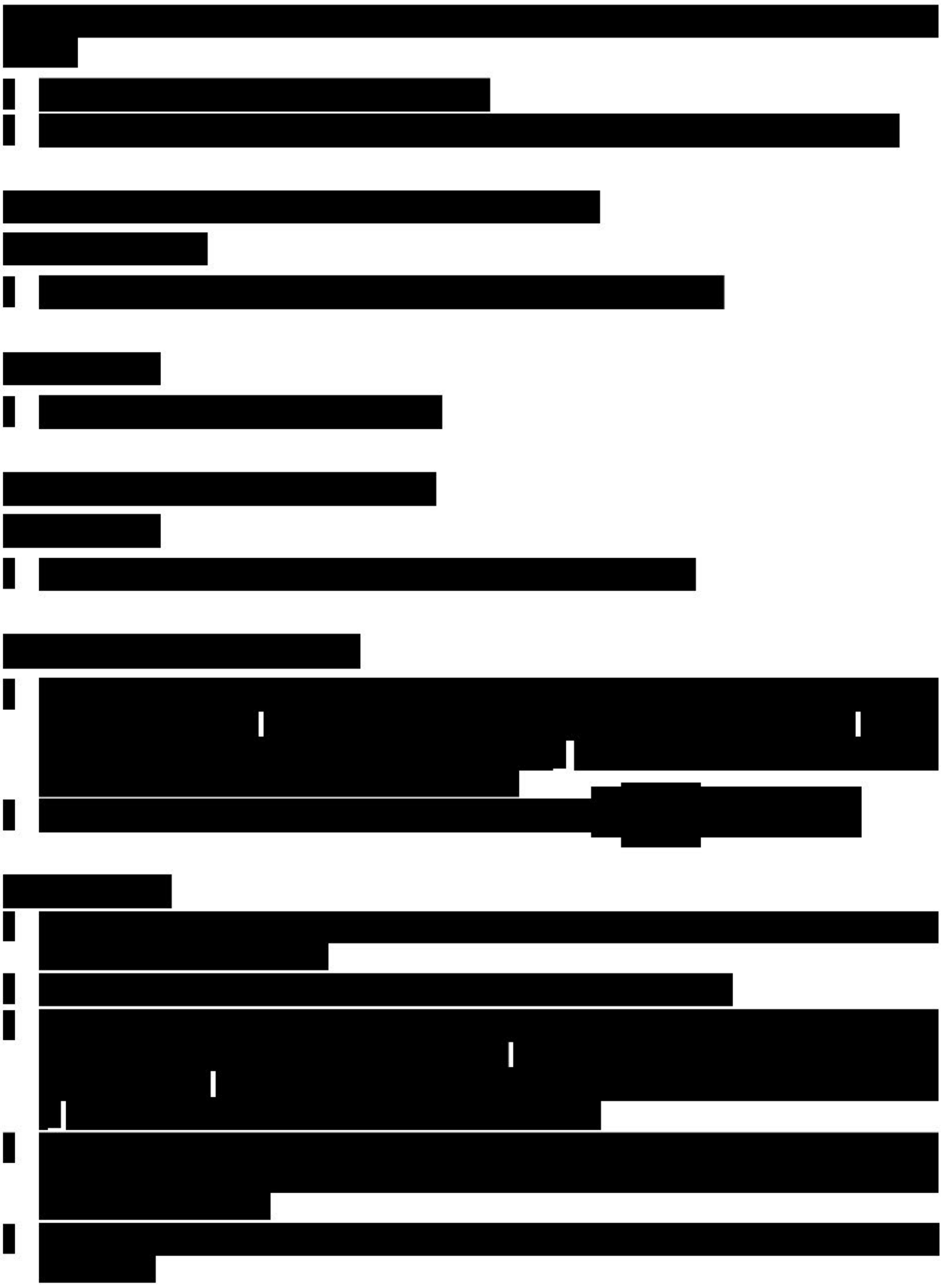

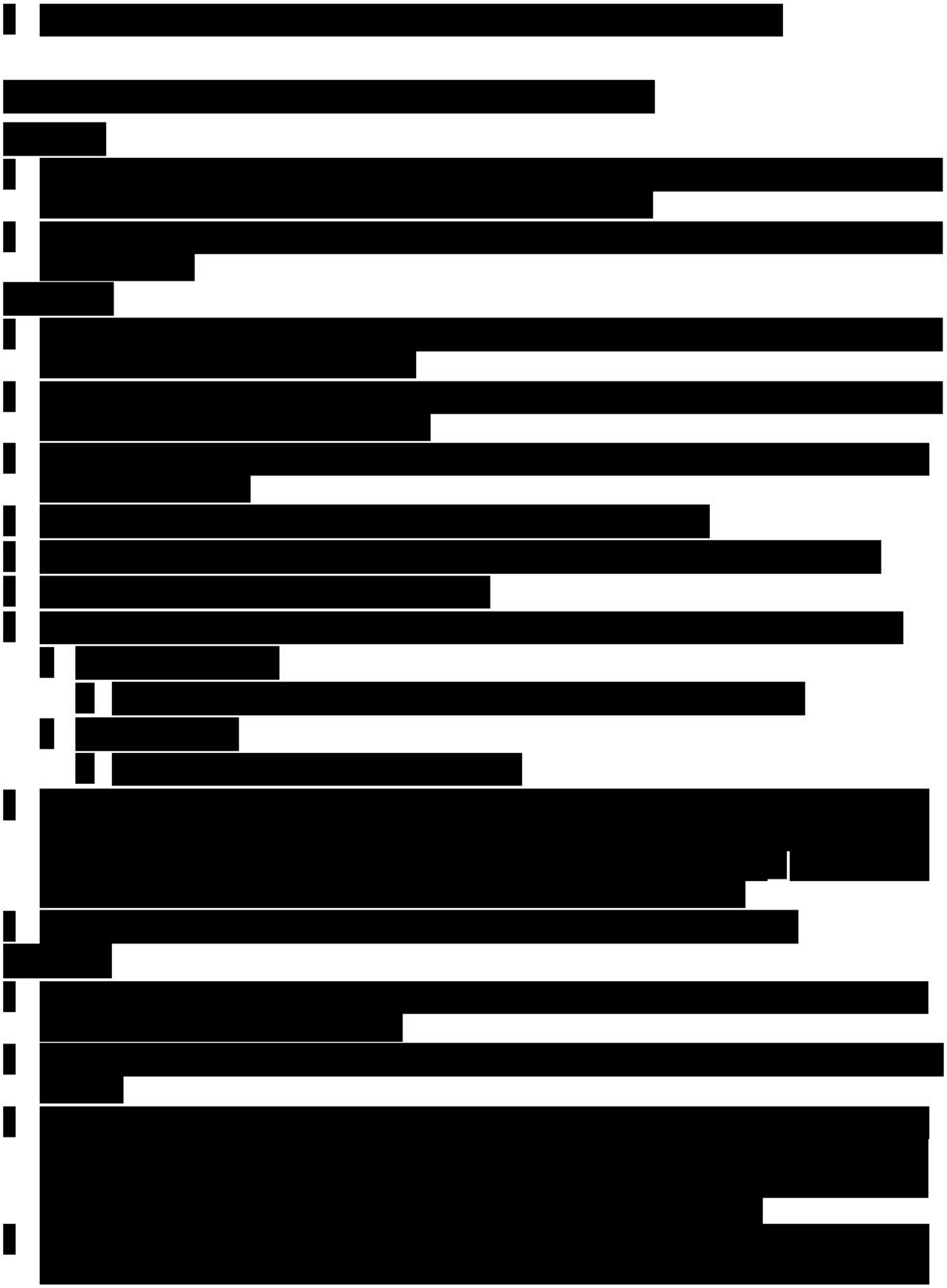

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3.1.1 *Nivolumab combined with Ipilimumab Crossover Extension Phase (Only for Subjects Originally Randomized to Arm B)*

Inclusion Criteria for the Crossover Extension Phase

1) Signed Written Informed Consent

a) Subjects 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 subject care.

b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the study.

2) Target Population

a) Subjects previously randomized to sunitinib treatment (Arm B) who were classified as either intermediate or poor risk per IMDC prognostic score prior to randomization.

b) Prior anti-cancer therapy, including sunitinib and palliative radiotherapy, must have been completed at least 14 days prior to first dose of nivolumab combined with ipilimumab.

c) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 or baseline prior to first dose of nivolumab combined with ipilimumab.

d) KPS of at least 70% (See Appendix 2)

e) Laboratory values must meet the following criteria and should be obtained within 14 days prior to first dose of nivolumab combined with ipilimumab:

i) WBC $\geq$ 2000/μL

ii) Neutrophils $\geq$ 1500/μL

iii) Platelets $\geq 100 \times 10^3$/μL

iv) Hemoglobin $\geq$ 9.0 g/dL

v) Serum creatinine $\leq$1.5 x ULN or creatinine clearance (CrCl) $\geq$40 mL/minute

(using Cockcroft/Gault formula):

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

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

vi) AST/ALT ≤ 3.0 x ULN (≤5 x ULN for subjects with liver metastases)
vii) Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL.

Exclusion Criteria for the Crossover Extension Phase

1) Medical History and Concurrent Diseases

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

b) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days prior to the first dose of nivolumab combined with ipilimumab. Corticosteroids with minimal systemic absorption (for example, topical, inhalational, or as specified in Section 3.4.3) and adrenal replacement steroid doses > 10 mg daily prednisone or equivalent are permitted in the absence of active autoimmune disease.

c) Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 28 days prior to the first dose of nivolumab combined with ipilimumab.

d) For Arm B subjects receiving sunitinib treatment or in the follow-up phase who have not received any subsequent systemic therapy at the time of Amendment 14: treatment with any subsequent systemic anticancer therapy.

e) For Arm B subjects in the follow-up phase who are receiving or have received any subsequent systemic anticancer therapy at the time of Amendment 14: treatment with any additional line of subsequent systemic anticancer therapy beyond the one being given or last received at the time of Amendment 14

f) Prior treatment with an anti-PD-1,anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

g) Uncontrolled adrenal insufficiency.

2) Physical and Laboratory Test Findings

a) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

b) Known positive test for Hepatitis B virus or Hepatitis C virus indicating acute or chronic infection.

3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit and subjects who have no exceeded 2 years of study treatment in the crossover extension phase will be eligible to receive BMS supplied study drug. Study drug 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 drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.3 Study Population

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

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Subjects 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 subject care.

b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study.

2. Target Population

a) Histological confirmation of RCC with a clear-cell component.

b) Advanced (not amenable to curative surgery or radiation therapy) or metastatic (AJCC Stage IV) RCC

c) No prior systemic therapy for RCC with the following exception:

i) One prior adjuvant or neoadjuvant therapy for completely resectable RCC if such therapy did not include an agent that targets VEGF or VEGF receptors and if recurrence occurred at least 6 months after the last dose of adjuvant or neoadjuvant therapy.

d) KPS of at least 70% (See Appendix 2)

e) Measurable disease as per RECIST v1.1 (See Appendix 3)

f) Tumor tissue (FFPE archival or recent acquisition) must be received by the central vendor (block or unstained slides) in order to randomize a subject to study treatment. (Note: Fine Needle Aspiration [FNA] and bone metastases samples are not acceptable for submission).

g) Patients with favorable, intermediate and poor risk categories will be eligible for the study. Patients must be categorized according to favorable versus intermediate/poor risk status at registration.

To be eligible for the intermediate or poor-risk cohort, at least one of the following prognostic factors as per the International Metastatic RCC Database Consortium (IMDC) criteria must be present:

i) KPS equal to 70%

ii) Less than 1 year from diagnosis to randomization

iii) Hemoglobin less than the lower limit of normal (LLN)

iv) Corrected calcium concentration greater than 10 mg/dL (Appendix 1)

v) Absolute neutrophil count greater than the ULN

vi) Platelet count greater than the ULN

If none of the above factors are present, subjects are only eligible for the favorable-risk cohort. The favorable-risk cohort may close to enrollment earlier than the intermediate- or poor-risk cohort.

3. Age and Reproductive Status

a) Males and Females, ≥ 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 breastfeeding

d) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for a period of 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo approximately five half-lives. The terminal half-life of the active metabolite of sunitinib is up to 110 hours.

i) WOCBP randomized to receive nivolumab + ipilimumab should use an adequate method to avoid pregnancy for 23 weeks (30 days plus the time required for nivolumab to undergo approximately five half-lives) after the last dose of investigational drug.

ii) WOCBP randomized to receive sunitinib should use an adequate method to avoid pregnancy for 8 weeks (30 days plus the time required for the active metabolite of sunitinib to undergo five half-lives)

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for a period of 90 days (duration of sperm turnover) plus the

time required for the investigational drug to undergo approximately five half-lives. The terminal half-life of the active metabolite of sunitinib is up to 110 hours.

i) Males randomized to receive nivolumab combined with ipilimumab who are sexually active with WOCBP must continue contraception for 31 weeks (90 days plus the time required for nivolumab to undergo approximately five half-lives) after the last dose of investigational drug.

ii) Males randomized to receive sunitinib who are sexually active with WOCBP must continue contraception for 16 weeks (90 days plus the time required for the active metabolite of sunitinib to undergo five half-lives) after the last dose of investigational drug.

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

Investigators shall counsel WOCBP and male subjects 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 subjects 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% when used consistently and correctly.

At a minimum, subjects must agree to the use of one highly effective method as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- Nonhormonal IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy
- Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

LESS EFFECTIVE (UNACCETPABLE) METHODS OF CONTRACEPTION

- Diaphragm with spermicide

- Cervical cap with spermicide
- Vaginal sponge
- Male Condom with or without spermicide
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Female Condom*
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicide only
- Lactation amenorrhea method (LAM)

* A male and female condom must not be used together.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Any history of or current CNS metastases. Baseline imaging of the brain by MRI (preferred) or CT scan is required within 28 days prior to randomization.

2. Medical History and Concurrent Diseases

a) Prior systemic treatment with VEGF or VEGF receptor targeted therapy (including, but not limited to, sunitinib, pazopanib, axitinib, tivozanib, and bevacizumab).

b) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

c) Any active or recent history of a known or suspected autoimmune disease or recent history of a syndrome that required systemic corticosteroids (> 10 mg daily prednisone equivalent) or immunosuppressive medications except for syndromes which would not be expected to recur in the absence of an external trigger. Subjects with vitiligo or type I diabetes mellitus or residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement are permitted to enroll.

d) Any condition requiring systemic treatment with corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days prior to first dose of study drug. Inhaled steroids and adrenal replacement steroid doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

e) Uncontrolled adrenal insufficiency.

f) Ongoing symptomatic cardiac dysrhythmias, uncontrolled atrial fibrillation, or prolongation of the Fridericia corrected QT (QTcF) interval defined as > 450 msec for males and > 470 msec for females, where $QTcF = QT / \sqrt[3]{RR}$

g) Poorly controlled hypertension (defined as systolic blood pressure (SBP) of ≥ 150 mmHg or diastolic blood pressure (DBP) of ≥ 90 mmHg), despite antihypertensive therapy.

h) History of any of the following cardiovascular conditions within 12 months of enrollment: cardiac angioplasty or stenting, myocardial infarction, unstable angina, coronary artery by-pass graft surgery, symptomatic peripheral vascular disease, class III or IV congestive heart failure, as defined by the New York Heart Association.

i) History of cerebrovascular accident including transient ischemic attack within the past 12 months.

j) History of deep vein thrombosis (DVT) unless adequately treated with low molecular weight heparin

k) History of pulmonary embolism within the past 6 months unless stable, asymptomatic, and treated with low molecular weight heparin for at least 6 weeks.

l) History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within the past 6 months.

m) Serious, non-healing wound or ulcer.

n) Evidence of active bleeding or bleeding susceptibility; or medically significant hemorrhage within prior 30 days.

o) Any requirement for anti-coagulation, except for low molecular weight heparin.

p) 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.

q) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

r) Any positive test for hepatitis B or hepatitis C virus indicating acute or chronic infection.

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

t) Major surgery (eg, nephrectomy) less than 28 days prior to the first dose of study drug.

u) Anti-cancer therapy less than 28 days prior to the first dose of study drug or palliative, focal radiation therapy less than 14 days prior to the first dose of study drug.

v) Presence of any toxicities attributed to prior anti-cancer therapy, other than alopecia, that have not resolved to Grade 1 (NCI CTCAE v4) or baseline before administration of study drug.

[redacted]

x) Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of sunitinib (eg, malabsorptive disorder, ulcerative disease, uncontrolled nausea, vomiting, diarrhea, or small bowel resection).

3. Physical and Laboratory Test Findings

a) Left ventricular ejection fraction (LVEF) less than the LLN as assessed by echocardiography or multigated acquisition (MUGA) scan.

b) Any of the following laboratory test findings:

i) WBC < 2,000/mm^3

ii) Neutrophils < 1,500/mm^3

iii) Platelets < 100,000/mm^3

iv) AST or ALT > 3 x ULN (> 5 x ULN if liver metastases are present)

v) Total Bilirubin > 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)

vi) Serum creatinine > 1.5 x upper limit of normal (ULN) or creatinine clearance < 40 mL/min (measured or calculated by Cockroft-Gault formula):

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

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

4. Allergies and Adverse Drug Reaction

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

5. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

b) Subjects 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 subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

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

3.3.3 Women of Childbearing Potential

A Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause 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 > 40mIU/mL to confirm menopause.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study:

- Immunosuppressive agents (except to treat a drug-related adverse event)
- Systemic corticosteroids > 10 mg daily prednisone equivalent (except as stated in Section 3.4.3 below or to treat a drug-related adverse event).
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for palliative radiation therapy (Section 3.4.2), surgical resection except for palliative surgical resection (Section 3.4.2), or standard or investigational agents for treatment of cancer).

Supportive care for disease-related symptoms may be offered to all subjects on the trial.

Note: Initiation of CYP3A4 inducers and inhibitors (Appendix 4) is not prohibited after dosing has begun, however Arm B subjects should follow sunitinib dose modification recommendations (Section 4.5.3.2).

3.4.2 Other Restrictions and Precautions

Palliative (limited-field) radiation therapy and palliative surgical resection are permitted, if the following criteria are met:

- The subject will be considered to have progressed at the time of palliative therapy and must meet criteria to continue with treatment beyond progression (Section 4.5.7)
- The case is discussed with the BMS Medical Monitor or Study Director.

3.4.3 Permitted Therapy

Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if > 10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

Concomitant medications are recorded at baseline and throughout the treatment phase of the study in the appropriate section of the CRF. All medications (prescriptions or over the counter medications) continued at the start of the study or started during the study and different from the study drug must be documented in the concomitant therapy section of the CRF.

3.5 Discontinuation of Subjects following any Treatment with Study Drug

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

- Subject's request to stop study treatment
- 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 subject
- Protocol defined disease progression (subjects may be permitted to continue treatment beyond initial disease progression see Section 4.5.7)
- 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
- Additional protocol specified reasons for discontinuation (see Section 4.5.5)

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject 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 drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.6 Post Study Drug Study Follow up

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

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug 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 subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects 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 drug 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 subject 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.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the 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 subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject'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 subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

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

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection.

Table 4-1: Study Drugs for CA209214

Product Description / Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
BMS-936558-01 (Nivolumab) Solution for Injection[a]	100 mg (10 mg/mL)	IP	Open Label	10 mL per vial (5 or 10 vials/carton)	Store at 2° - 8 °C. Protect from light and freezing.
Ipilimumab Solution for Injection	200 mg (5mg/mL)	IP	Open Label	40 mL per vial (4 vials/carton)	Store at 2° - 8 °C. Protect from light and freezing.
Sunitinib Malate Capsule[b]	12.5 mg	IP	Open Label	28 capsules per wallet card or 30 capsules per bottle	Store at 15° - 25 °C.

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

[b] Sunitinib may be obtained by the investigational sites in certain countries as local commercial product (which may be available as a different potency/package size than listed above) if local regulations allow and agreed to by BMS.

Premedications or medications used to treat infusion-related reactions should be sourced by the investigative sites if available and permitted by local regulations. Solutions used as diluent (ie, 0.9% Sodium Chloride Injection or 5% Dextrose Injection) should also be sourced by investigative sites if available and permitted by local regulations.

4.1 Investigational Product

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.

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 subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

4.2 Non-investigational Product

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.

In this protocol, non-investigational product(s) is/are: medications used to treat nivolumab infusion-related reactions (eg, steroids, anti-emetics); these non-investigational products should be sourced by the investigator sites if available and permitted by local regulations.

4.3 Storage and Dispensing

The product storage manager should ensure that the study drug 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 drug arise, the study drug should not be dispensed and contact BMS immediately.

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

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

Infusion-related supplies (eg, IV bags, in-line filters, 0.9% NaCl solution) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

For nivolumab and ipilimumab, please refer to the current version of the Investigator Brochures and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information.

Nivolumab is to be administered as an approximately 60-minute IV infusion. At the end of the infusion, flush the line with a sufficient quantity of normal saline. Ipilimumab is to be administered as an approximately 30-minute IV infusion. At the end of the infusion, flush the line with a sufficient quantity of normal saline or 5% dextrose solution. When both study drugs are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly

followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be ipilimumab, and will start at least 30 minutes after completion of the nivolumab infusion.

For sunitinib, please refer to the appropriate SmPC or package insert and/or pharmacy reference sheets for complete storage, handling, and administration information.

4.4 Method of Assigning Subject Identification

CA209214 is a randomized, open-label study. After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by calling an interactive voice response system (IVRS) to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IVRS. Specific instructions for using IVRS will be provided to the investigational site in a separate document. The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- Date that informed consent was obtained
- Date of birth
- Gender at birth

Once enrolled in IVRS, enrolled subjects that have met all eligibility criteria and the required tumor tissue has been received by the central laboratory will be ready to be randomized through the IVRS. The following information is required for subject randomization:

- Subject number
- Date of birth
- KPS less than 80 (ie, KPS equal to 70)? Yes/No
- Less than 1 year from initial diagnosis of RCC (eg, nephrectomy or first diagnostic biopsy) to randomization? Yes/No
- Hemoglobin less than the LLN? Yes/No
- Corrected calcium greater than 10 mg/dL? Yes/No (Appendix 1)
- Absolute neutrophil count greater than the ULN? Yes/No
- Platelet count greater than the ULN? Yes/No

Subjects meeting all eligibility criteria will be randomized in a 1:1 ratio to Arm A (nivolumab combined with ipilimumab) or Arm B (sunitinib), stratified by the following factors:

- IMDC Prognostic Score (Total Number of IMDC Adverse Prognostic Factors Present)
  - 0
  - 1-2
  - 3-6

- Region
  - US
  - Canada/W Europe/N Europe
  - Rest of World

No more than 820 intermediate/poor risk subjects and 250 favorable risk subjects will be randomized in this study. These restrictions will be implemented via the IVRS system

The randomization procedures will be carried out via permuted blocks within each stratum. The exact procedures for using the IVRS will be detailed in the IVRS manual.

Amendment 14 Update:

IVRS will be amended to allow all subjects in the poor or intermediate cohorts previously randomized to Arm B (sunitinib) to receive treatment with nivolumab combined with ipilimumab. The IVRS will assign the nivolumab combined with ipilimumab treatment for all subjects eligible for the crossover extension phase. Procedural information will be provided in a separate document.

Subjects currently randomized to Arm B (sunitinib) may also continue obtaining treatment, as previously done so through the IVRS, as long as they are continuing to derive benefit from sunitinib in the judgement of the investigator.

[redacted]

[redacted]

Amendment 14 Update:

[redacted]

4.5.1 Antiemetic Premedications

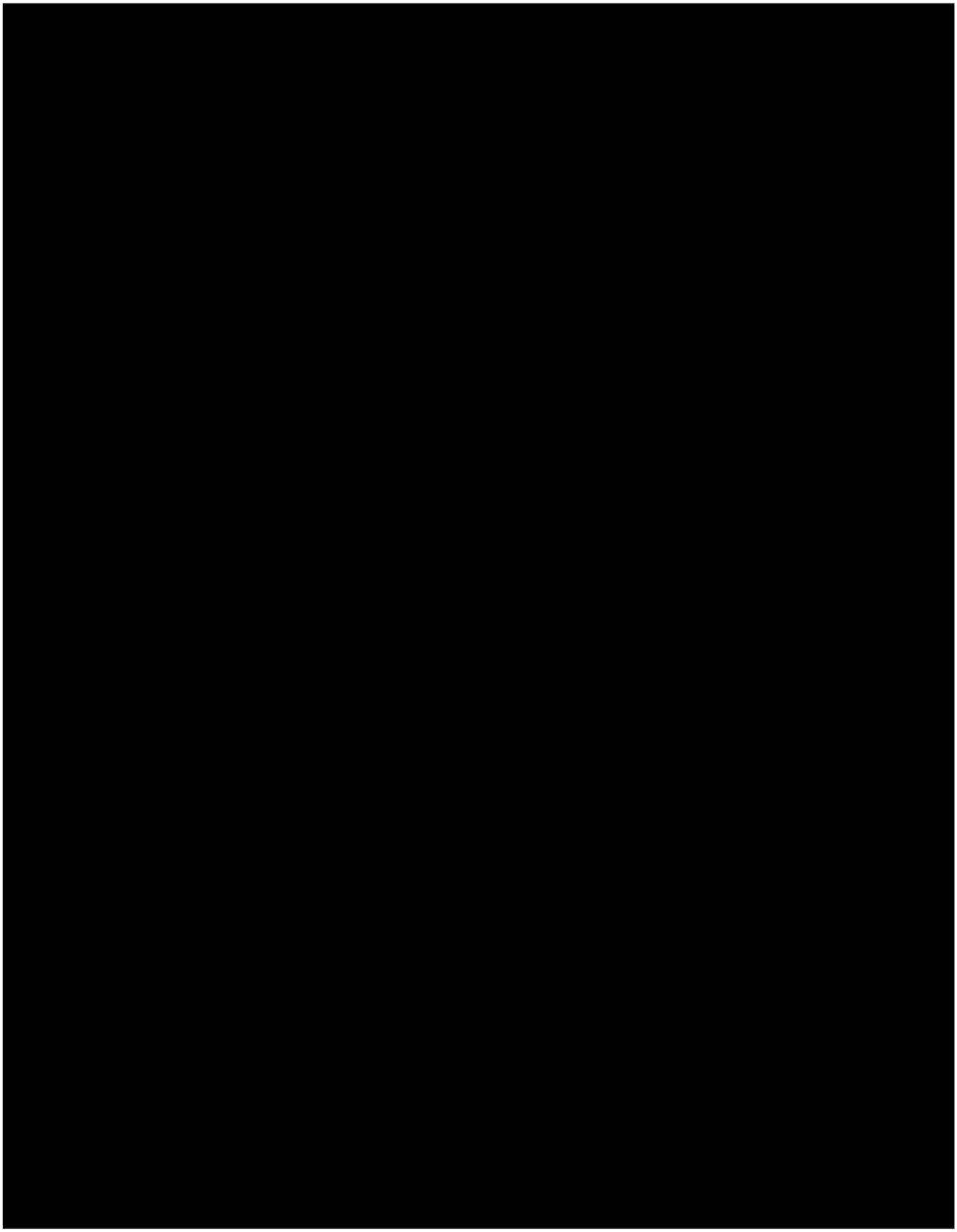
Antiemetic premedications should not be routinely administered prior to dosing of drugs. See section 4.5.6 for premedication recommendations following a nivolumab or ipilimumab-related infusion reaction.

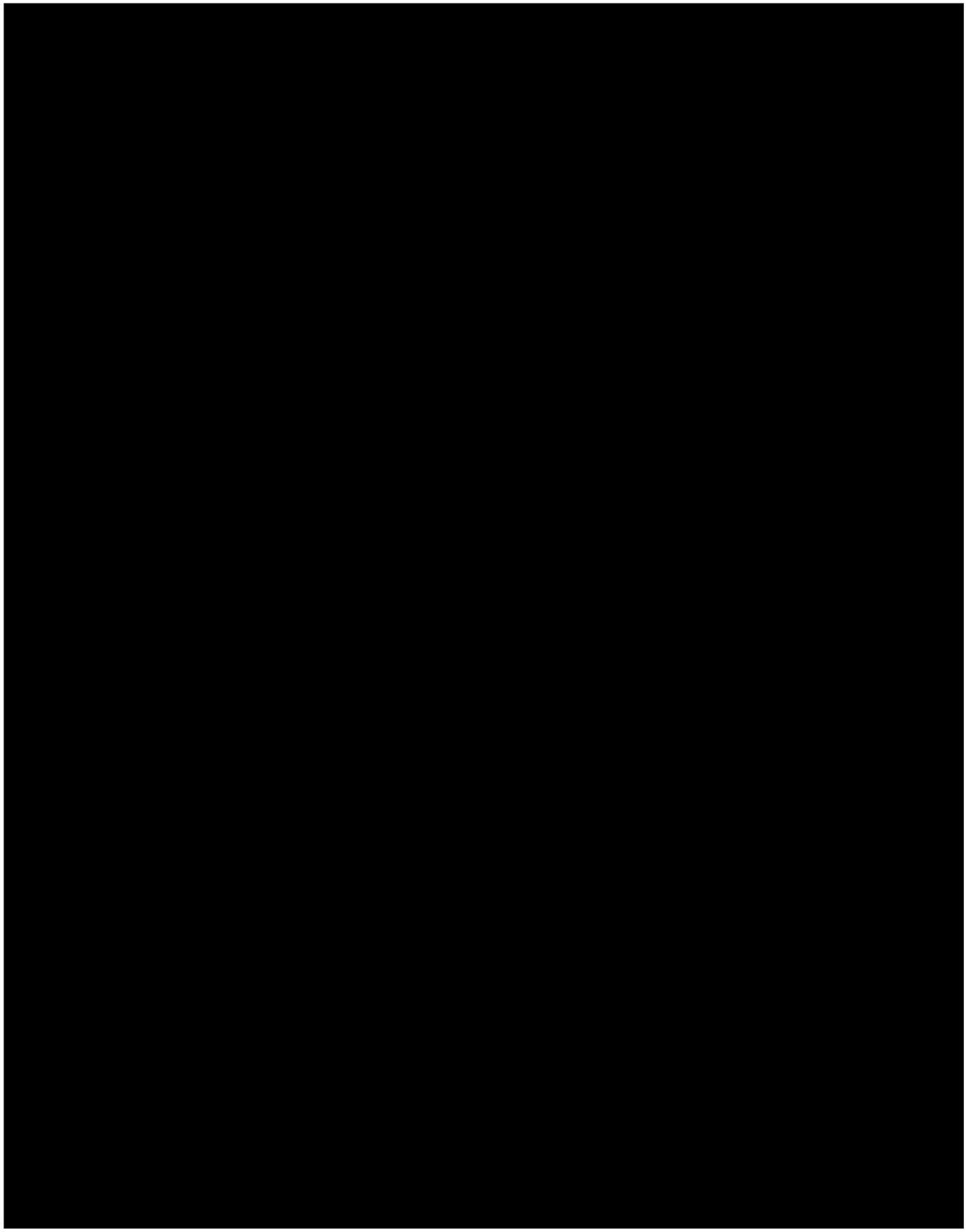
4.5.2 Dose Delay Criteria

Dose delay criteria apply for all drug-related adverse events (regardless of whether or not the event is attributed to nivolumab, ipilimumab, or both). All study drugs must be delayed until treatment can resume (see Section 4.5.4).

[redacted]

[redacted]





4.5.4 Criteria to Resume Treatment

4.5.4.1 Criteria to Resume Treatment on Arm A (Nivolumab combined with Ipilimumab)

Missed doses of nivolumab and/or ipilimumab should be administered as soon as the subject meets criteria to resume treatment. If a dose has been missed, the subject should not wait until the next scheduled dosing date.

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

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin.
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.5.5) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in Section 4.5.5.

During cycles 1 and 2, both nivolumab and ipilimumab must be resumed on the same day. All four doses of nivolumab combined with ipilimumab must be given prior to beginning nivolumab monotherapy (cycle 3 and beyond).

If the subject is unable to resume both nivolumab and ipilimumab, permanent discontinuation is required (Section 4.5.5).

4.5.4.2 Criteria to Resume Treatment on Arm B (Sunitinib)

Within a cycle, missed doses of sunitinib should be skipped and not replaced. Subjects should never be dosed during the 2-week off period of each 6-week cycle, even if treatment delays occurred earlier in the cycle and therapy is ready to be resumed. If treatment is delayed past the end of the 6-week cycle, the start of the next cycle should be delayed until treatment with sunitinib resumes.

If treatment is delayed > 6 weeks for any reason, the subject must be permanently discontinued from study therapy, except in cases where permission to resume treatment is granted by the BMS Medical Monitor or Study Director.

Criteria to resume treatment are dependent on the reason for delay and are included in Section 4.5.2.2.

4.5.5 Discontinuation Criteria

4.5.5.1 Discontinuation Criteria for Arm A (Nivolumab combined with Ipilimumab)

Treatment with nivolumab and ipilimumab should be permanently discontinued for any of the following:

- Any Grade 2 drug-related uveitis or 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, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, and infusion reactions:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - 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:
      - AST or ALT > 8 x ULN
      - Total bilirubin > 5 x ULN
      - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. It is recommended to consult with the BMS Medical Monitor or Study Director for Grade 4 amylase or lipase abnormalities.
  - 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
- Any dosing interruption lasting > 6 weeks unless the BMS Medical Monitor or Study Director is consulted and agrees with the rationale for resuming therapy after a delay > 6 weeks. Note that tumor assessments should continue as per protocol even if dosing is interrupted.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab or ipilimumab dosing

During cycles 1 and 2, both nivolumab and ipilimumab must be discontinued at the same time.

4.5.5.2 Discontinuation Criteria for Arm B (Sunitinib)

Treatment with sunitinib should be permanently discontinued for any of the following:

- Any requirement for more than 2 sunitinib dose reductions.
- Any Grade drug-related arterial thrombosis.
- Grade 4 drug-related hemorrhage or recurrent Grade 3 drug-related hemorrhage after dose reduction.
- Grade 4 drug-related symptomatic venous thrombosis.
- Grade 4 drug-related cardiac toxicity.
- Two or more symptomatic episodes of hypertension despite modification of antihypertensive medication(s) and reduction of sunitinib dose.
- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
    1. AST or ALT > 8 x ULN.
    2. Concurrent AST or ALT > 3 x ULN and total bilirubin >2 x ULN.
- Any dosing interruption lasting > 6 weeks unless the BMS Medical Monitor or Study Director is consulted and agrees with the rationale for resuming therapy after a delay > 6 weeks. Note that tumor assessments should continue as per protocol even if dosing is interrupted.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued sunitinib dosing.

4.5.6 Treatment of Nivolumab or Ipilimumab-Related Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, each 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, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor or Study Director and reported as an SAE if criteria are met. 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 subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg

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

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

Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid 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 subject closely. If symptoms recur then no further nivolumab or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab or ipilimumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]). Grade 4: (life-threatening; pressor or ventilatory support indicated).

Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 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. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

4.5.7 Treatment Beyond Disease Progression

Accumulating evidence[40] indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.

Subjects, regardless of study arm, will be permitted to continue treatment beyond initial investigator assessed progression as long as they meet the following criteria:

- Investigator-assessed clinical benefit
  and
- Subject is tolerating study drug.

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment.

All decisions to continue treatment beyond initial progression should be discussed with the BMS Medical Monitor or Study Director and documented in the study records.

Subjects must be re-consented with an ICF addendum to continue treatment.

Subjects should discontinue study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions).

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 measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm).

Amendment 14 Update:

Subjects enrolled in the nivolumab combined with ipilimumab crossover extension phase will be permitted to continue study therapy beyond initial investigator-assessed RECIST 1.1-defined progression, as defined in this section, up to a maximum of 2 years from the first dose of nivolumab combined with ipilimumab.

4.5.8 Immunotherapy Adverse Event Management

Because of the potential for clinically meaningful nivolumab or ipilimumab-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, GI toxicity, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity, and renal toxicity.

These adverse event management algorithms are included in Appendix 5.

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

Trained medical personnel will administer nivolumab and ipilimumab and dispense other study medication.

Treatment compliance will be monitored by drug accountability, as well as by recording administration of all medications in the CRF. The date and time of start and end of infusion and the exact amount given at each infusion will be recorded. Any missed doses or interruptions in sunitinib administration will be recorded. In case the treatment has to be interrupted during an infusion and the dosing is not resumed, the medical personnel should evaluate the percentage of dose received by the patient and document it in the patient record.

Any reason for non-compliance should also be documented.

4.8 Destruction of Study Drug

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

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

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

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study drug.

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

4.9 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible Study Monitor.

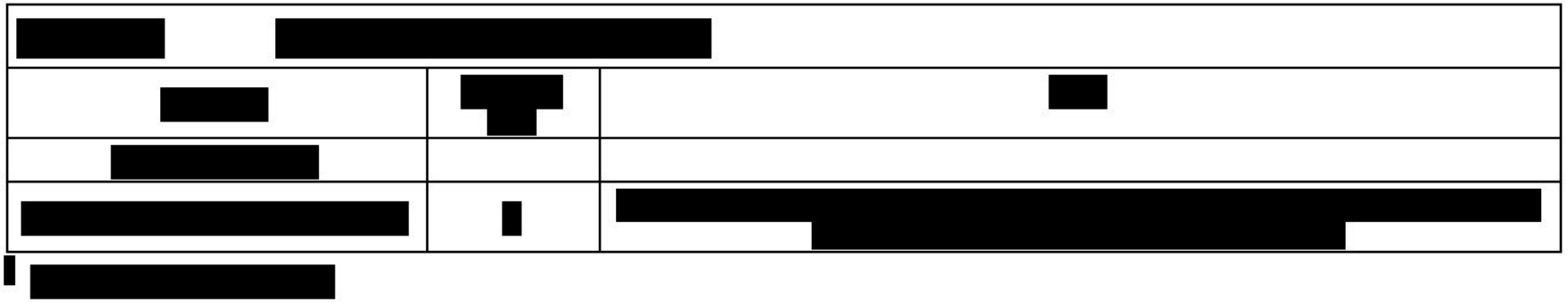
It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local,

and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

Arrangements for the return of study drug will be made by the responsible Study Monitor.

4.10 Retained Samples for Bioavailability / Bioequivalence

Not applicable.



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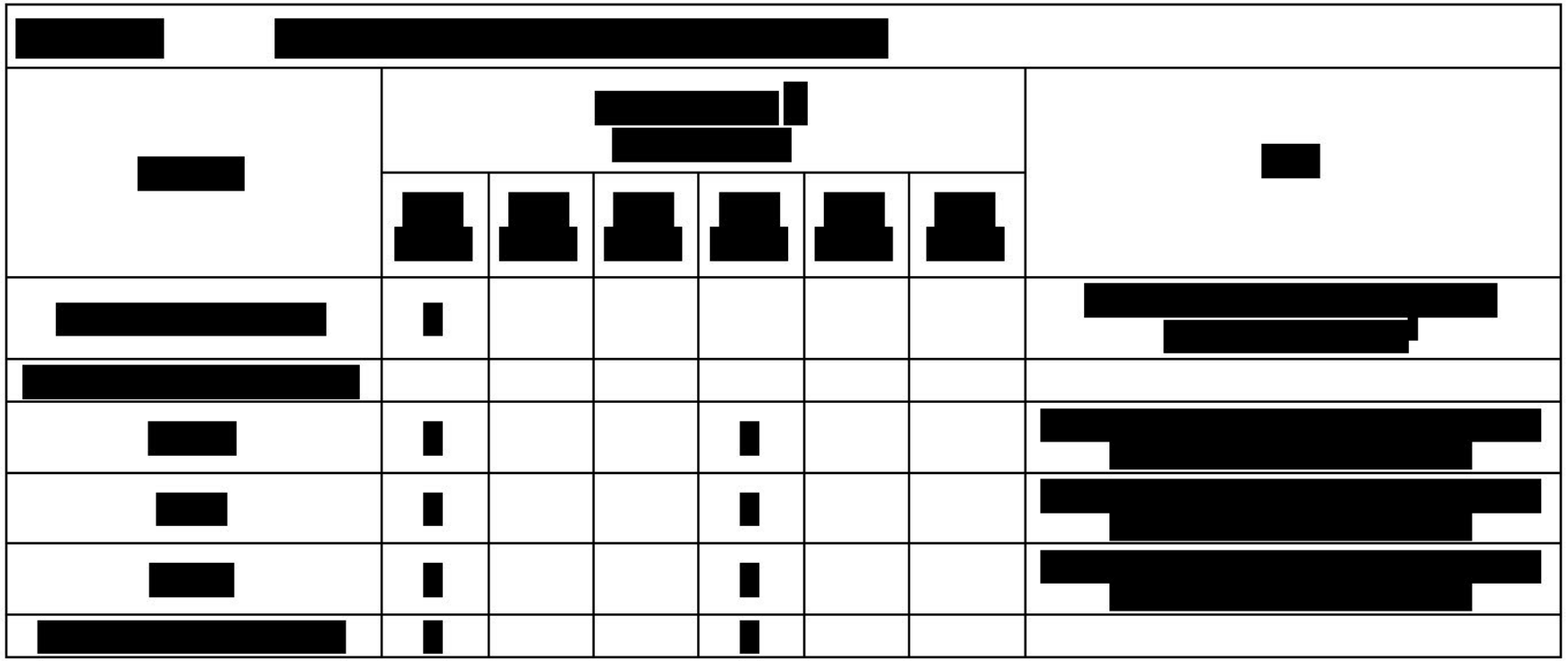

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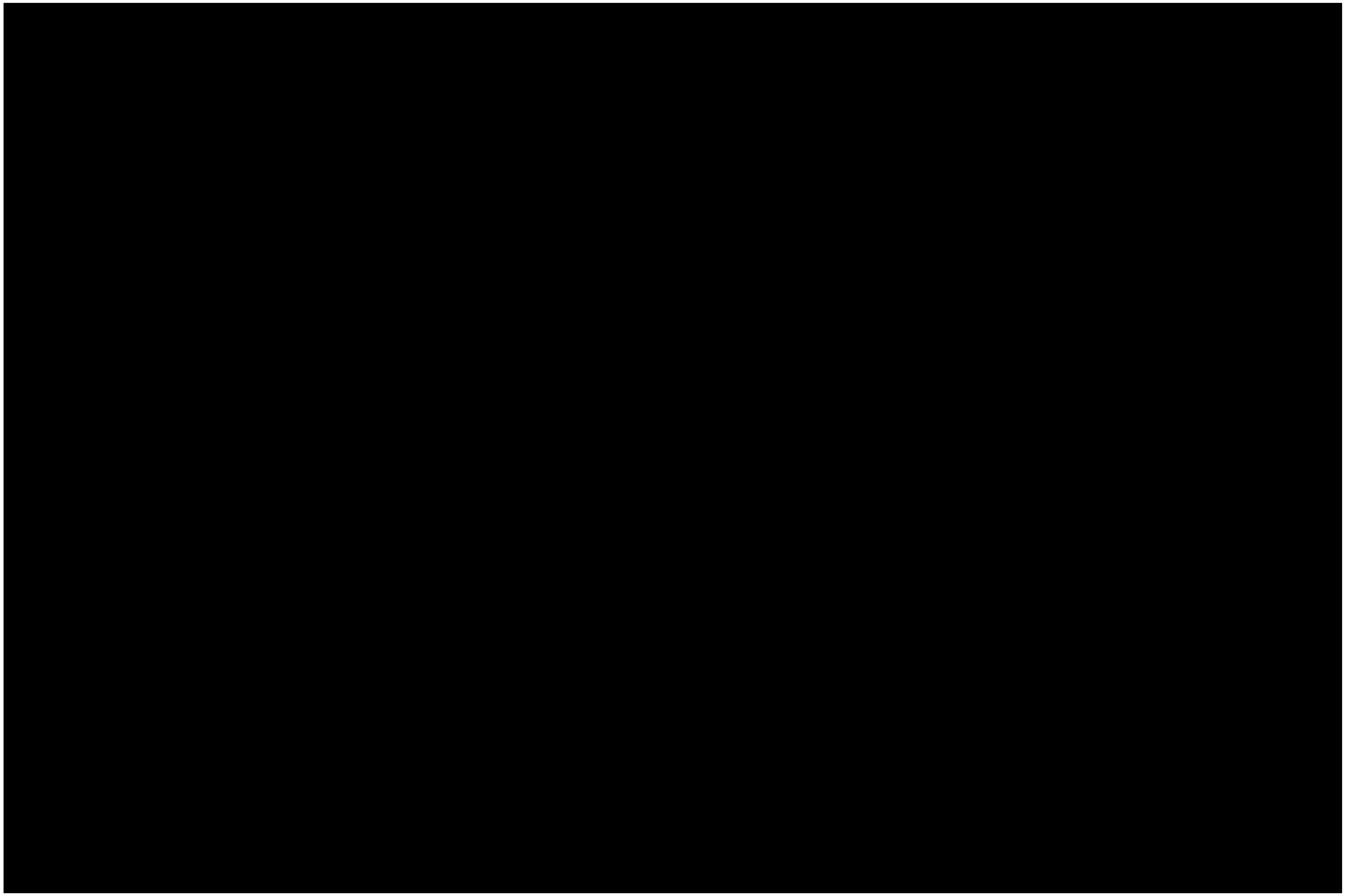

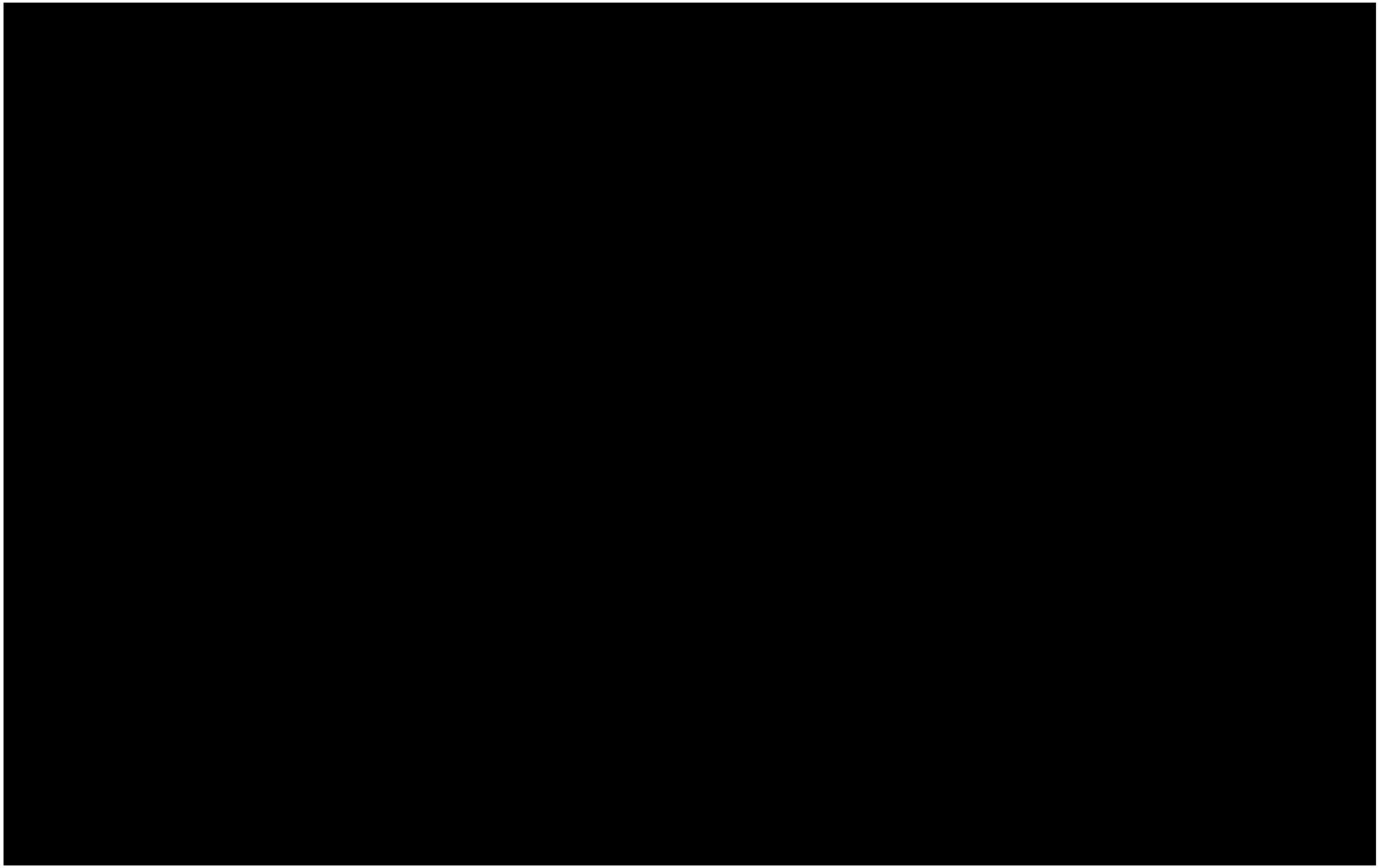

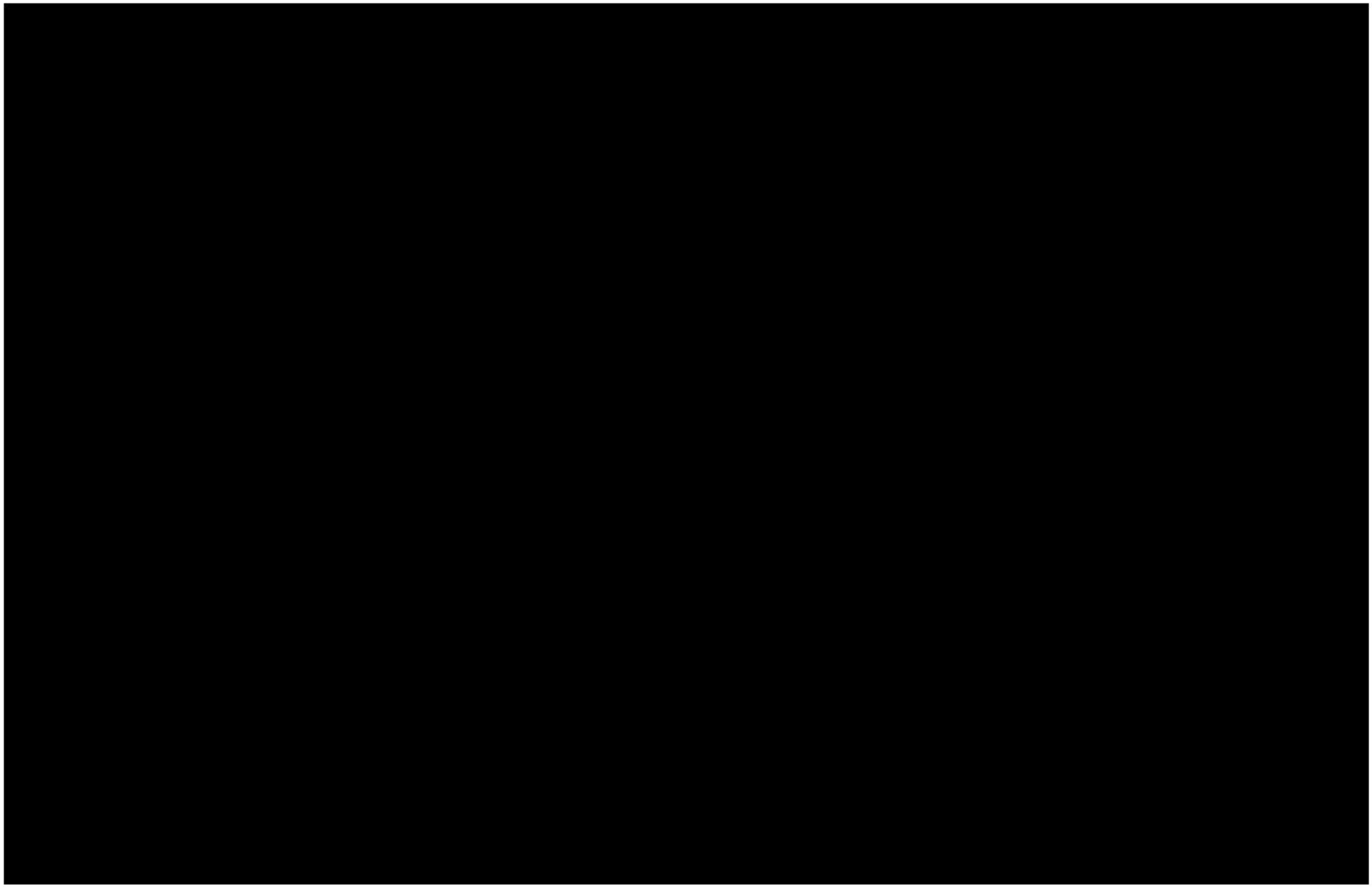

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5.1.1 Retesting During Screening or Lead-in Period

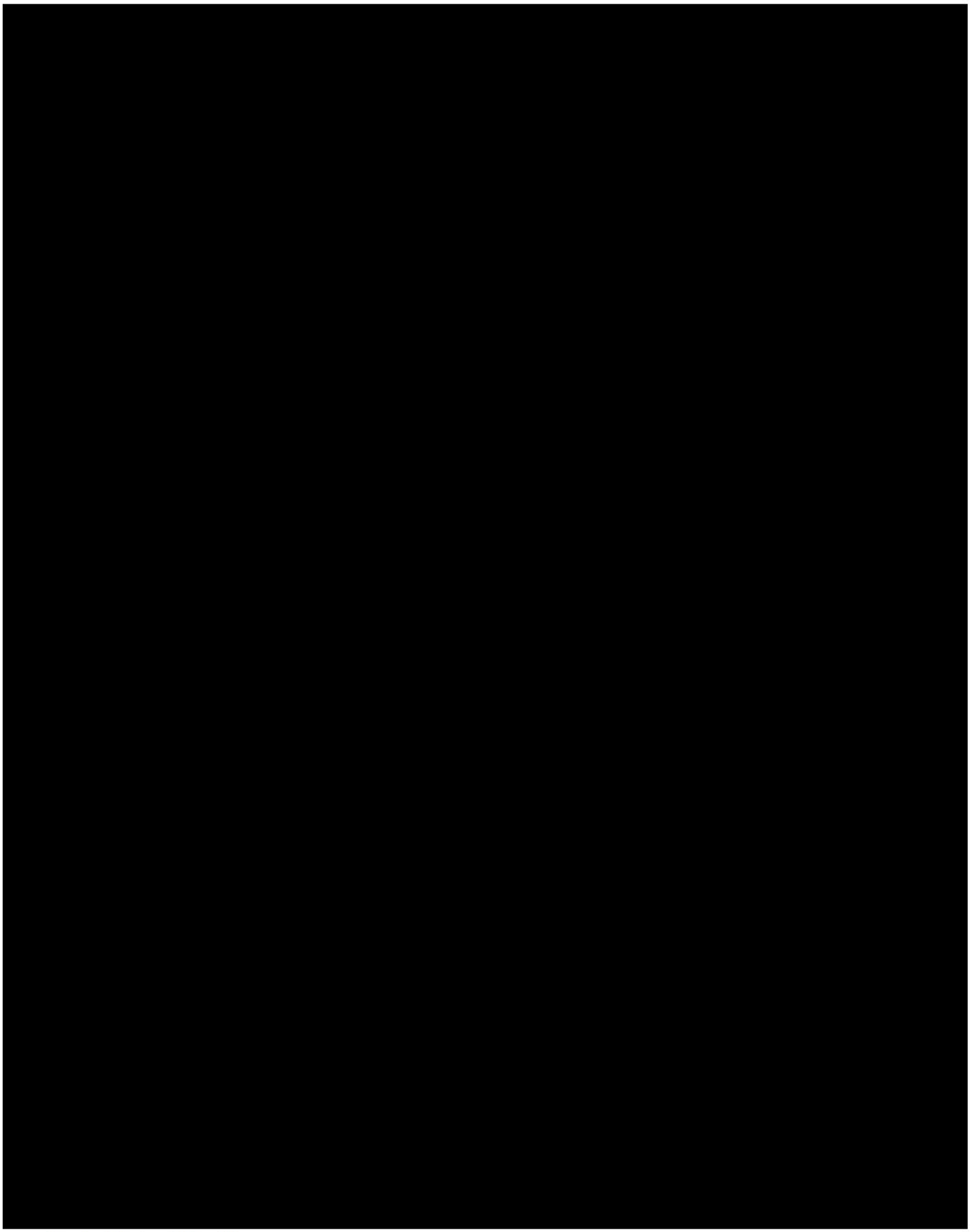
Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

Any new result will override the previous result (ie, the most current result prior to Randomization) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

5.2 Study Materials

- NCI CTCAE version 4.0
- Nivolumab Investigator Brochure
- Ipilimumab Investigator Brochure
- Pharmacy Binder
- Laboratory manuals for collection and handling of blood (including PK, biomarker and immunogenicity) and tissue specimens
- Site manual for operation of interactive voice response system, including enrollment/randomization worksheets
- Manual for entry of local laboratory data
- Pregnancy Surveillance Forms
- CA209214 Imaging Manual

[redacted]



Amendment 14 Update:

For subjects moving into the nivolumab combined with ipilimumab crossover extension phase, please refer to Table 5.1-4, Table 5.1-5, and Table 5.1-6 for the schedule of screening and on-study assessments.

5.3.1 Imaging Assessment for the Study

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.

Scans will be submitted to an Imaging Corelab by an IRCC.

5.3.1.1 CT/MRI

Both contrast-enhanced Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) scans acquired on dedicated CT/MRI equipment are adequate imaging modalities for this study.

CT with contrast (or MRI) of the chest, abdomen, pelvis and all other known sites of disease are to be performed for tumor assessments at baseline (Table 5.1-1), at 12 weeks (±1 wk) after randomization and then every 6 weeks (± 1 wk) as per Table 5.1-2 and Table 5.1-3, until disease progression or treatment is discontinued (whichever occurs later).

CT scans should be acquired with 5 mm slices with no intervening gap (contiguous). Should a subject 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. MRIs should be acquired with slice thickness of ≤ 5 mm with no gap (contiguous).

Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging time.

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 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.

5.3.1.2 MRI/CT Brain

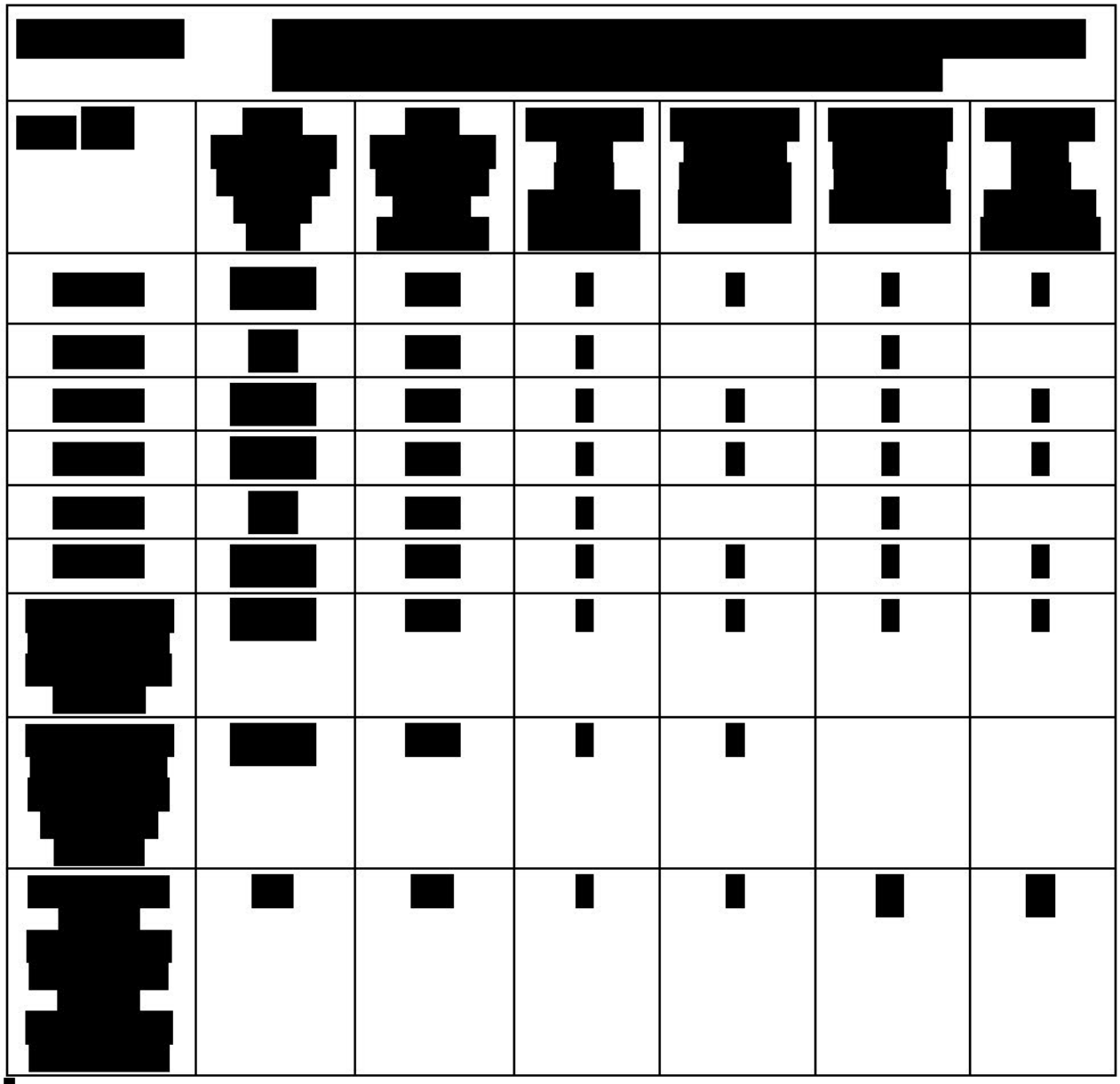
MRI (preferred) or CT of brain is required at screening in order to rule out active metastatic disease (subjects with a history of brain metastasis are excluded from the study). MRI or CT

brain scans during on-study treatment and follow up periods are required only if clinically indicated for new signs and symptoms that suggest central nervous system (CNS) involvement.

[redacted]

purposes; exploratory results will not be reported. Serum samples designated for PK or

[redacted]



[redacted]

[redacted]

[redacted]

The NCCN FKSI-19 is a 19-item scale that measures tumor specific HrQoL in kidney cancer [redacted]

5.7.1 Healthcare Resource Utilization

Healthcare resource utilization data (eg, hospitalizations, non-protocol specified medical visits, etc) will be collected for all randomized subjects. Specifically, healthcare resource utilization is evaluated based on the number of medical care encounters such as hospital admissions and their duration, outpatient visits, diagnostic tests and procedures, concomitant medications and reasons for the encounters.

[redacted]

5.8 Other Assessments

[redacted] oods samples for immunogenicity will NOT be collected in the crossover extension phase.

5.9 Results of Central Assessments

Not Applicable.

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject 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.

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.

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

6.1 Serious Adverse Events

A S***erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject 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)
- 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 subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency 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 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug 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 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details).

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 (eg, 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 (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. **All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing**. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

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

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours. 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. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. 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.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should 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, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug and continue until 100 days from the last dose of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug 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.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

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

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

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during approximately 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 and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor or Study Director of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

All occurrences of overdose must be reported as SAEs (see Section 6.1.1 for reporting details).

6.6 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 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

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

AND

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

AND

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.

6.7 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.

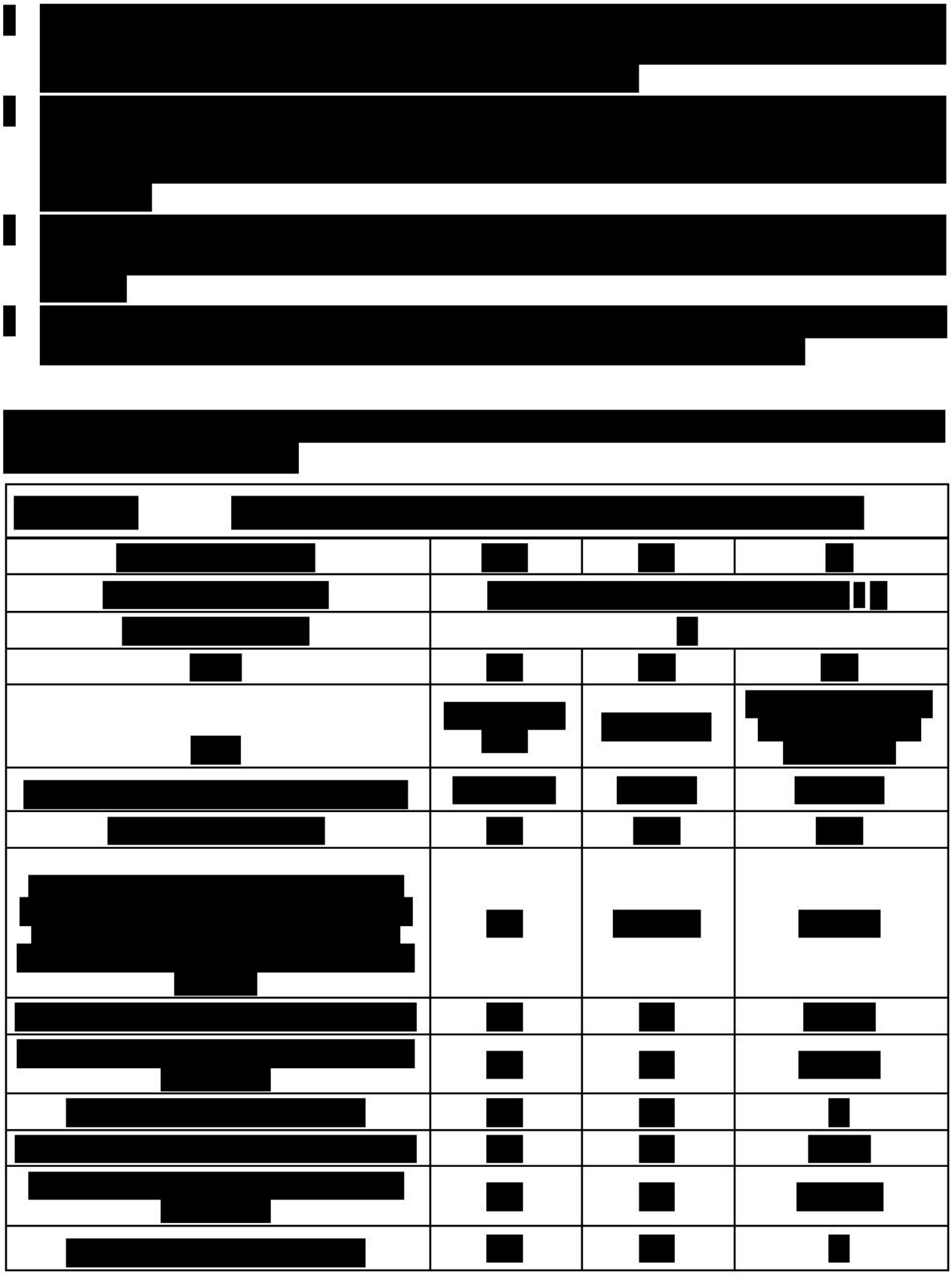
7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

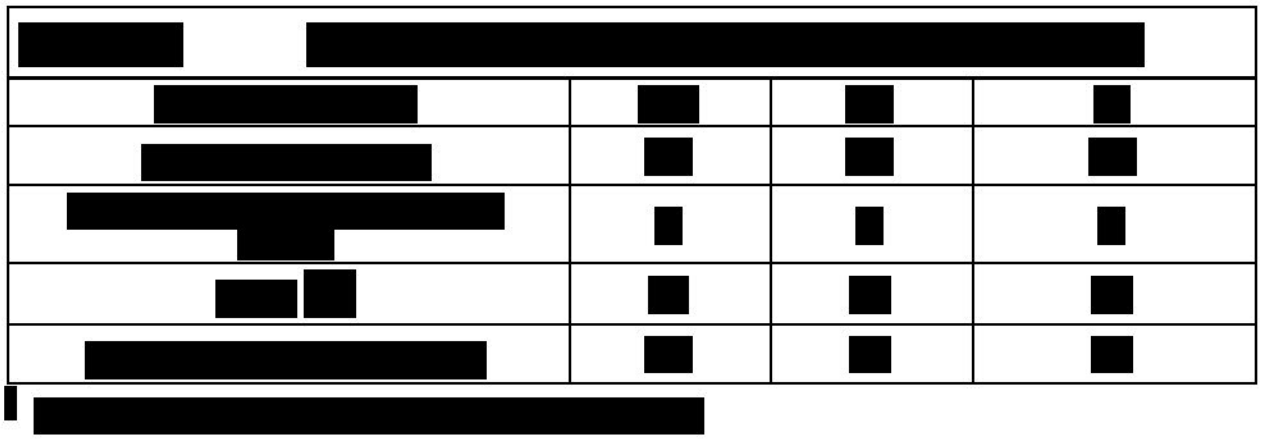
To provide independent oversight of safety, efficacy, and study conduct, a data monitoring committee (DMC) will be instituted. The DMC will meet regularly to ensure that subject safety is carefully monitored. The DMC will convene additional ad hoc meetings if necessary. Following each meeting, the DMC will recommend continuation, modification, or discontinuation of the study based on observed toxicities. The DMC will also review the interim analysis results and inform BMS whether stopping criteria for superiority are met at that time. A separate DMC charter will describe the activities of this committee in more detail.

IRRC assessments will be utilized in this study for determination for PFS and ORR endpoints. The IRRC will review all available tumor assessment scans for all randomized subjects. Details of IRRC responsibilities and procedures will be specified in the IRRC charter.

[redacted]

Assuming a 21% screen failure rate, it is estimated that approximately 1355 subjects will be





8.2 Populations for Analyses

- **All enrolled subjects**: All subjects who signed an informed consent form and were registered into the IVRS.
- **All randomized subjects (any risk subjects)**: All subjects who were randomized to any treatment arm in the study. This population is considered as the secondary efficacy analysis population. Analysis of demography, protocol deviations, baseline characteristics, secondary efficacy analysis and outcome research analysis will be performed for this population.
- **Intermediate/poor risk subjects**: All randomized subjects with baseline IMDC prognostic score ≥ 1 at the time randomization. This is the primary efficacy analysis population. Analysis of demography, protocol deviations, baseline characteristics and primary efficacy analysis will be performed for this population.
- **All treated subjects**: All subjects who received any dose of study therapy. This is the primary dataset for drug exposure and safety analysis.
- **Favorable risk subjects**: All randomized subjects with baseline IMDC prognostic score = 0 at the time randomization. This population would be used for conducting exploratory analysis of efficacy endpoints.
- **PK subjects**: All subjects with available serum time-concentration data from randomized subjects dosed with nivolumab.
- **Immunogenicity subjects**: All subjects with available data from randomized subjects dosed with nivolumab.

All analyses will be performed using the treatment arm as randomized (intent to treat), with the exception of dosing and safety, for which the treatment arm as received will be used.

8.3 Endpoints

The primary objectives of this study to describe ORR and is to compare PFS (based on IRRC assessment) and OS of nivolumab combined with ipilimumab to sunitinib monotherapy in intermediate and poor-risk subjects with previously untreated mRCC. This is measured by the three co-primary endpoints defined in Section 8.3.1.

The first secondary objective of this study is to compare PFS (based on IRRC assessment) in the two treatment arms in the all randomized population. This would be measured by the same definitions of PFS, as specified in sections 8.3.1.1 and 8.3.1.3 respectively, in the all randomized population.

The second secondary objective of this study is to compare OS in the two treatment arms in the all randomized population. This would be measured by the same definition of OS, as specified in section 8.3.1.4, in the all randomized population.

The third secondary objective of this study is assessing ORR in the two treatment arms in all randomized population. This would be measured by the definition of ORR as specified in section 8.3.2.1, in intermediate/poor risk subjects and all randomized population respectively.

8.3.1 Co-Primary Endpoints

Object response rate, progression free survival, and overall survival are the co-primary endpoints.

8.3.1.1 Objective Response Rate

Objective response rate is defined as the proportion of randomized subjects who achieve a best response of complete response (CR) or partial response (PR) using the RECIST1.1 criteria based on IRRC assessment. BOR is defined as the best response designation, as determined by the IRC, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. As described in Section 5.4, confirmation of response is required. Duration of response (DOR) is defined as the time between the date of first documented response (CR or PR) to the date of the first documented progression as determined by the IRC (per RECIST 1.1), or death due to any cause, whichever occurs first. For subjects who neither progress nor die, the duration of objective response will be censored at the same time they will be censored for the primary definition of PFS (Section 8.3.1.3). Time to Objective Response (TTR) is defined as the time from randomization to the date of the first confirmed documented response (CR or PR), as assessed by the IRC. DOR and TTR will be evaluated for responders (confirmed CR or PR) only.

8.3.1.2 Primary Definition of Progression-Free Survival

The primary definition PFS is specified as the time between the date of randomization and the first date of documented progression, based on IRRC assessment (as per RECIST 1.1 criteria), or death due to any cause, whichever occurs first. Subjects who die without a reported progression will be considered to have progressed on the date of their death. The following censoring rules will be applied for the primary definition of PFS.

- Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment.
- Subjects who did not have any on study tumor assessments and did not die will be censored on their date of randomization.

- Subjects who receive subsequent systemic anti-cancer therapy prior to documented progression will be censored at the date of the last tumor assessment prior to the initiation of the new therapy.

8.3.1.3 Secondary Definition of Progression-Free Survival

The secondary definition of PFS is defined as the time between the date of randomization and the first date of documented progression, based on IRRC assessment (as per RECIST 1.1 criteria), or death due to any cause, whichever occurs first. Subjects who die without a reported progression will be considered to have progressed on the date of their death. The following censoring rules will be applied for the primary definition of PFS.

- Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment.
- Subjects who did not have any on study tumor assessments and did not die will be censored on their date of randomization.

8.3.1.4 Overall Survival

Overall survival is defined as the time from randomization to the date of death from any cause. For subjects that are alive, their survival time will be censored at the date of last contact ("last known alive date"). Overall survival will be censored for subjects at the date of randomization if they were randomized but had no follow-up.

8.3.2 Secondary Endpoint(s)

8.3.2.1 Adverse Event Incidence Rate

Adverse events incident rate is defined as the proportion subjects with any grade adverse events among subjects treated in each treatment arm. Events reported from the first dose and up to and including 100 days following the last dose of study treatment could be included in estimating this incidence rate.

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8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment arm as randomized using descriptive statistics for intermediate/poor risk subjects as well as all randomized subjects.

[redacted]

8.4.2.1 Objective Response Rate: Co-primary Endpoint

One of the primary objectives of the study is to describe the objective response rate per IRRC in the two treatment arms among intermediate and poor risk subjects. The ORR analysis will occupy a 0.001 administrative allocation of alpha.

The number and percentage of subjects in each category of best overall response per IRRC (complete response [CR], partial response [PR]], stable disease [SD], progressive disease [PD], or unable to determine [UD]) according to the IRRC will be presented, by treatment group. An estimate of the response rate and an associated exact two-sided 95% CI (Clopper and Pearson[44]) will be presented, by treatment group.

Sensitivity analysis based on investigator-determined ORR may also be performed. DOR and TTR will also be evaluated. Descriptive analysis of the response in the investigator's choice group (ie, subjects treated with investigator's choice among ORR population) will also be provided.

At the time of the formal ORR analysis, no PFS or OS analysis will be conducted because of the immaturity of those specific endpoints. A reduced analysis will be defined in the data presentation plan.

8.4.2.2 Progression-Free Survival Analysis: Co-primary Endpoint

One of the primary objectives of the study is to compare the progression-free survival (based on IRRC assessment) of nivolumab combined with ipilimumab to sunitinib monotherapy in intermediate and poor-risk subjects with previously untreated mRCC. All analyses specified in this section will be conducted for PFS derived as per primary and secondary definitions.

The primary formal comparison of PFS will be conducted using a two-sided 0.009 stratified log-rank test, with IMDC Prognostic Score (1-2 vs 3-6) and Region (US vs Canada/W Europe/N Europe vs ROW) as stratification factors among intermediate/poor risk subjects.

Median PFS will be estimated via the Kaplan-Meier product limit method. Two-sided 95% CI for the median PFS will be computed for each randomized arm. Kaplan-Meier plots of PFS will be presented. Hazard ratios (HR) and corresponding two-sided 99.1% confidence intervals (CI) will be estimated using a Cox proportional hazards model, with treatment arm as a single covariate, stratified by the stratification factors, corresponding to the comparison of PFS.

The totality of PFS results will be presented in a single graphical display that includes Kaplan-Meier curves for the two treatment arms, the log-rank p-values for the formal comparison, the HRs and corresponding CI, and the median PFS estimates and corresponding CIs.

The following supportive analyses of PFS will also be conducted:

A stratified multivariate Cox regression model will be used in order to estimate the treatment effect after adjustment for possible imbalances in known or potential prognostic factors. The covariates included in this model will be specified in the statistical analysis plan.

PFS using an un-stratified log rank test. The hazard ratio associated with treatment will be presented along with the associated two-sided 95% CIs.

8.4.2.3 Overall Survival Analysis: Co-primary Endpoint

One of the primary objectives of the study is to compare the overall survival of nivolumab combined with ipilimumab to sunitinib monotherapy in intermediate and poor-risk subjects with previously untreated mRCC. OS will be compared between the treatment arms using a two sided, $\alpha = 0.04$ level log-rank test (adjusted for interim analyses), stratified using the same factor as in PFS. A similar analysis as in PFS will be conducted for OS. Hazard ratios (HR) and corresponding two-sided 96% confidence intervals (CI) will be estimated using a Cox

proportional hazards model, with treatment arm as a single covariate, stratified by the stratification factors, corresponding to the comparison of OS.

8.4.2.4 Progression-Free Survival Analysis: Secondary Objective

One of the secondary objectives of the study is to compare the progression-free survival (based on IRRC assessment) of nivolumab combined with ipilimumab to sunitinib monotherapy in all randomized with previously untreated mRCC. All analyses specified in this section will be conducted for PFS derived as per primary and secondary definitions.

A formal comparison of PFS in all randomized subjects will be conducted using a two-sided 0.009 stratified log-rank test, with IMDC Prognostic Score (0 vs 1-2 vs 3-6) and Region (US vs Canada/W Europe/N Europe vs ROW) as stratification factors among all randomized subjects, only if the PFS comparison among intermediate/poor risk subjects towards the primary objective assessment is found to be statistically significant. Analyses of PFS among all randomized subjects will be similar to those conducted towards the assessment of the primary PFS objective.

8.4.2.5 Overall Survival Analysis: Secondary Objective

One of the secondary objectives of the study is to compare the overall survival of nivolumab combined with ipilimumab to sunitinib monotherapy in all randomized with previously untreated mRCC.

A formal comparison of OS in all randomized subjects will be conducted using a two-sided 0.04 stratified log-rank test, with IMDC Prognostic Score (0 vs 1-2 vs 3-6) and Region (US vs Canada/W Europe/N Europe vs ROW) as stratification factors among all randomized subjects, only if the OS comparison among intermediate/poor risk subjects towards the primary objective assessment is found to be statistically significant. Analyses of OS among all randomized subjects will be similar to those conducted towards the assessment of the primary OS objective.

8.4.2.6 Objective Response Rate Analysis: Secondary Objective

One of the secondary objectives of the study is to estimate the objective response rate in the two treatment arms among all randomized subjects.

Estimates of response rate, along with its exact two-sided 95% CI by Clopper-Pearson method, will be computed within each treatment arm. A two sided, 95% CI for difference of response rate between the treatment arms will also be computed.

8.4.3 Safety Analyses

The safety analysis will be performed in all treated subjects. Descriptive statistics of safety will be presented using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment arm. All AEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using the worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, coagulation, chemistry, liver function and renal function will be summarized using worse grade per NCI CCAE v 4.0 criteria.

8.4.3.1 AE Incidence Rate Analysis: Secondary Objective

One of the secondary objectives of the study is to estimate the adverse event incidence rate in the two treatment arms among treated subjects.

Estimates of AE incidence rate, along with its exact two-sided 95% CI by Clopper-Pearson method, will be computed within each treatment arm.

[redacted]

Biomarkers will be summarized graphically as they relate to efficacy and safety endpoints, as

[redacted]

8.4.7.2 Resource Utilization

Resource Utilization analysis will be described in a separate statistical analysis plan.

8.5 Interim Analyses

Two interim analyses of OS are planned. First interim analysis is scheduled at the time of final PFS analysis and it is expected after observing 370 deaths (approx 58% of the targeted OS events) and the second interim analysis is scheduled after 478 deaths (approx 75% of total deaths) have been observed among intermediate/poor risk subjects based on above accrual rate and the exponential distribution in each arm. These formal comparisons of OS will allow for early stopping for superiority, and the boundaries for declaring superiority will be derived based on the actual number of deaths using Lan-DeMets spending function with O'Brien and Fleming type of boundary in EAST v5.4. If the first interim analysis is performed exactly at 370 deaths , the boundary in terms of statistical significance for declaring superiority would be 0.0045 (HR=0.744 , 6.9 months improvement in median OS) and if the second interim analysis is performed at exactly 479 deaths, the boundary in terms of statistical significance at the interim analysis for declaring superiority would be 0.0131 (or 0.8 with regard to HR boundary, which corresponds to 5.1 months improvement in median OS under the assumed control arm hazard

function). The boundary for declaring superiority in terms of statistical significance for the final analysis after 639 events would be 0.0354. An independent statistician external to BMS will perform interim analysis.

In addition to the formal planned interim analysis for OS, the DMC will have access to periodic un-blinded interim reports of efficacy and safety to allow a risk/benefit assessment. Details will be included in the DMC charter.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC and Regulatory Authority(ies), if required by local regulations, of an amendment, 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 IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (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).

9.1.2 Monitoring

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

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

In addition, the study may be evaluated by BMS 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 BMS.

9.1.2.1 Source Documentation

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.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator 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, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

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

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (inventoried and dispensed) is maintained at the study site. 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 subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, 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.

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

9.2.3 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 BMS 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 paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

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, including any paper or electronic 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 .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 BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 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:

- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. **Expanded definition** Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical

Term	Definition
	trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence

11 LIST OF ABBREVIATIONS

Abbreviation	Term
ADA	Anti-drug antibody
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALT	Alanine transaminase
AST	Aspartate transaminase
BMS	Bristol-Myers Squibb
BOR	Best overall response
BUN	Blood urea nitrogen
CMV	Cytomegalovirus
CR	Complete response
CRC	Colorectal cancer
CrCl	Creatinine clearance
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCF	Data clarification form
DILI	Drug-induced liver injury
DLT	Dose-limiting toxicity
DMC	Data monitoring committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
EOI	End of infusion
FFPE	Formalin-fixed paraffin-embedded
FKSI	Functional Assessment of Cancer Therapy-Kidney Symptom Index
FPFV	First Patient First Visit
FSH	Follicle-stimulating hormone
FU	Follow-up

Abbreviation	Term
GCP	Good clinical practices
GMP	Good manufacturing practices
HCV	Hepatitis C virus
HBV	Hepatitis B virus
HDL	High-density lipoprotein
HIFα	Hypoxia inducible factor α
HIPAA	Health Information Portability and Accountability Act
HRT	Hormone replacement therapy
HRU	Health Resource Utilization
ICF	Informed consent form
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
IMDC	International Metastatic RCC Database Consortium
ITIM	Immunoreceptor tyrosine inhibitory motif
ITSM	Immunoreceptor tyrosine-based switch motif
IV	Intravenous
IFN	Interferon
IRB/IEC	Institutional review board/independent ethics committee
IRRC	Independent Radiology Review Committee
IVRS	Interactive voice response system
KPS	Karnofsky Performance Score
LDL	Low-density lipoprotein
LFT	Liver function test
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MEL	Metastatic melanoma
miRNA	Micro-ribonucleic acid
MLR	Mixed lymphocyte reaction
MRI	Magnetic resonance imaging
MSKCC	Memorial Sloan-Kettering Cancer Center

Abbreviation	Term
MTD	Maximum-tolerated dose
mTOR	Mammalian target of rapamycin
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PFS	Progression-free survival
PK	Pharmacokinetics
PO	Per os (by mouth)
PR	Partial response
PRO	Patient-reported outcome
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase - polymerase chain reaction
SAE	Serious adverse event
sAg	Surface antigen
SD	Stable disease
SNP	Single nucleotide polymorphism
SOP	Standard operating procedures
TCR	T-cell receptor
TKI	Tyrosine kinase inhibitor
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States

Abbreviation	Term
VEGF	Vascular endothelial growth factor
VEGFr	Vascular endothelial growth factor receptor
WOCBP	Women of child bearing potential

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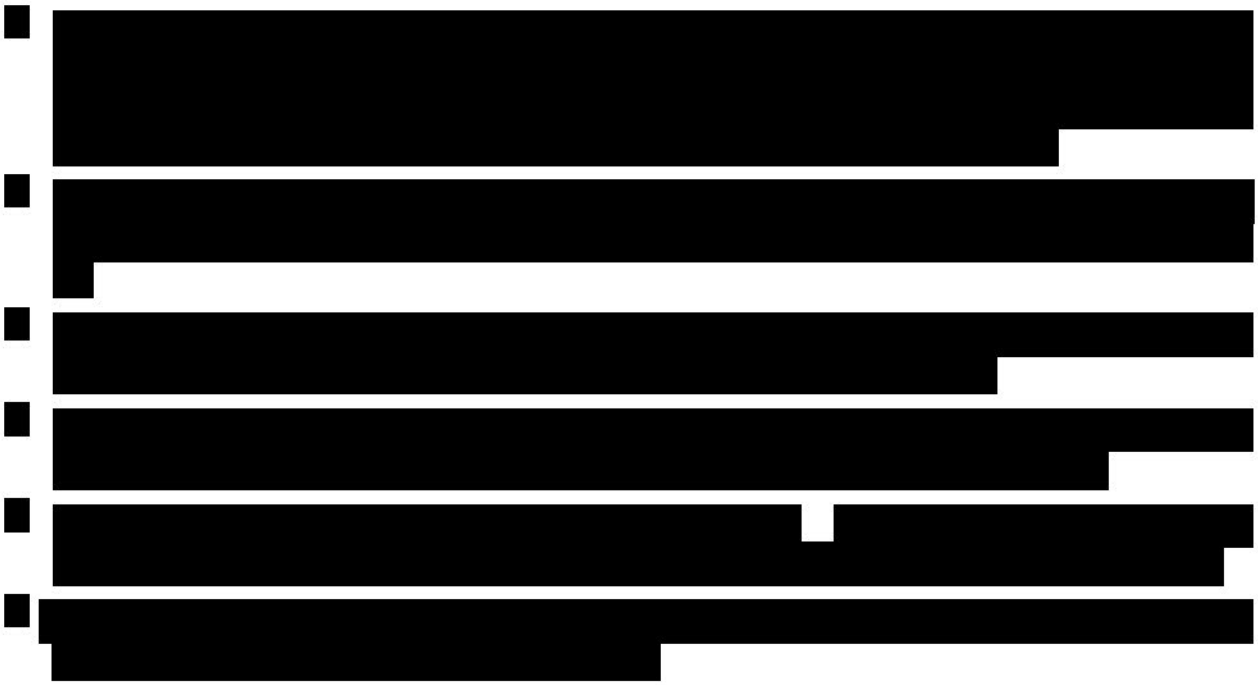

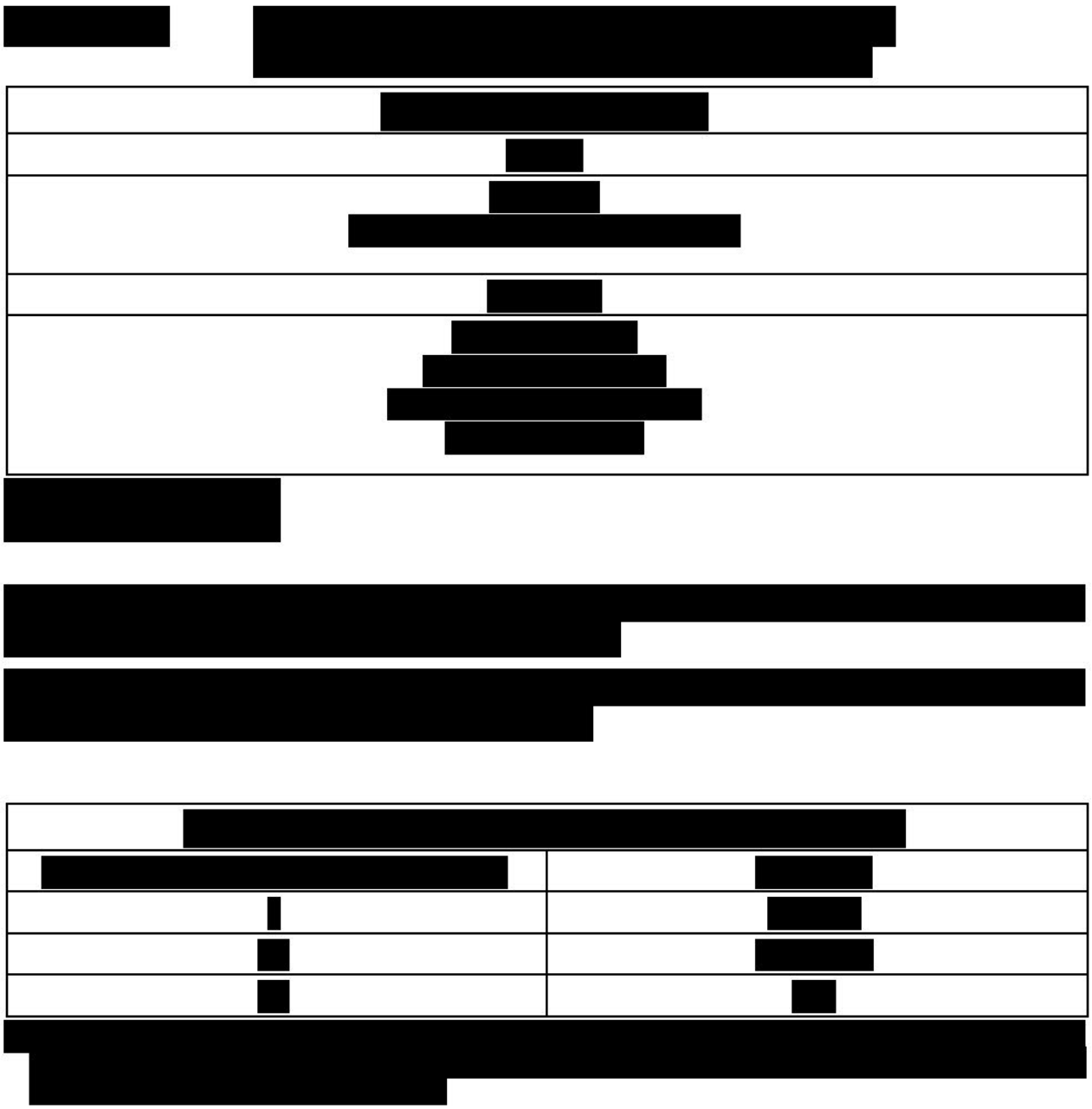

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APPENDIX 3 RECIST 1.1 GUIDELINES

1 EVALUATION OF LESIONS

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

1.1 Measurable

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

1. 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
2. 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
3. 20 mm by chest x-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT 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 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, saggital 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.

1.2 Non-Measurable

All other lesions are considered non-measurable, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, 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.

2 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).

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 nontarget lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3 RESPONSE CRITERIA

3.1 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.

3.1.1 Special Notes on the Assessment of Target Lesions

3.1.1.1 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.

3.1.1.2 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 (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.

3.1.1.3 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'.

3.2 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 and normalization of tumor marker level. 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) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

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

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

3.2.1.1 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 (see examples in Appendix 2 and further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. 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.

3.2.1.2 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 a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols 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.

3.2.2 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.

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.

If a new lesion is equivocal, for example because of its small size, continued therapy and 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.

3.3 Response Assessment

3.3.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. 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.

3.3.2 Time Point Response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 3.3.2-1 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 3.3.2-2 is to be used.

Table 3.3.2-1: 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 3.3.2-2: 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.

3.3.3 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 later. In this circumstance, the best overall response can be interpreted as in Table 3.3.3-1.

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 3.3.3-1: Best Overall Response (Confirmation of CR&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[b] met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration[b] met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration[b] met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration[b] met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration [b]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.

[b] Minimum criteria for SD duration is 6 weeks.

3.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than 28 days after the criteria for response are first met. For this study, the next scheduled tumor assessment can meet this requirement.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered to not have progressive disease.

APPENDIX 5 MANAGEMENT ALGORITHMS FOR IMMUNO-ONCOLOGY AGENTS

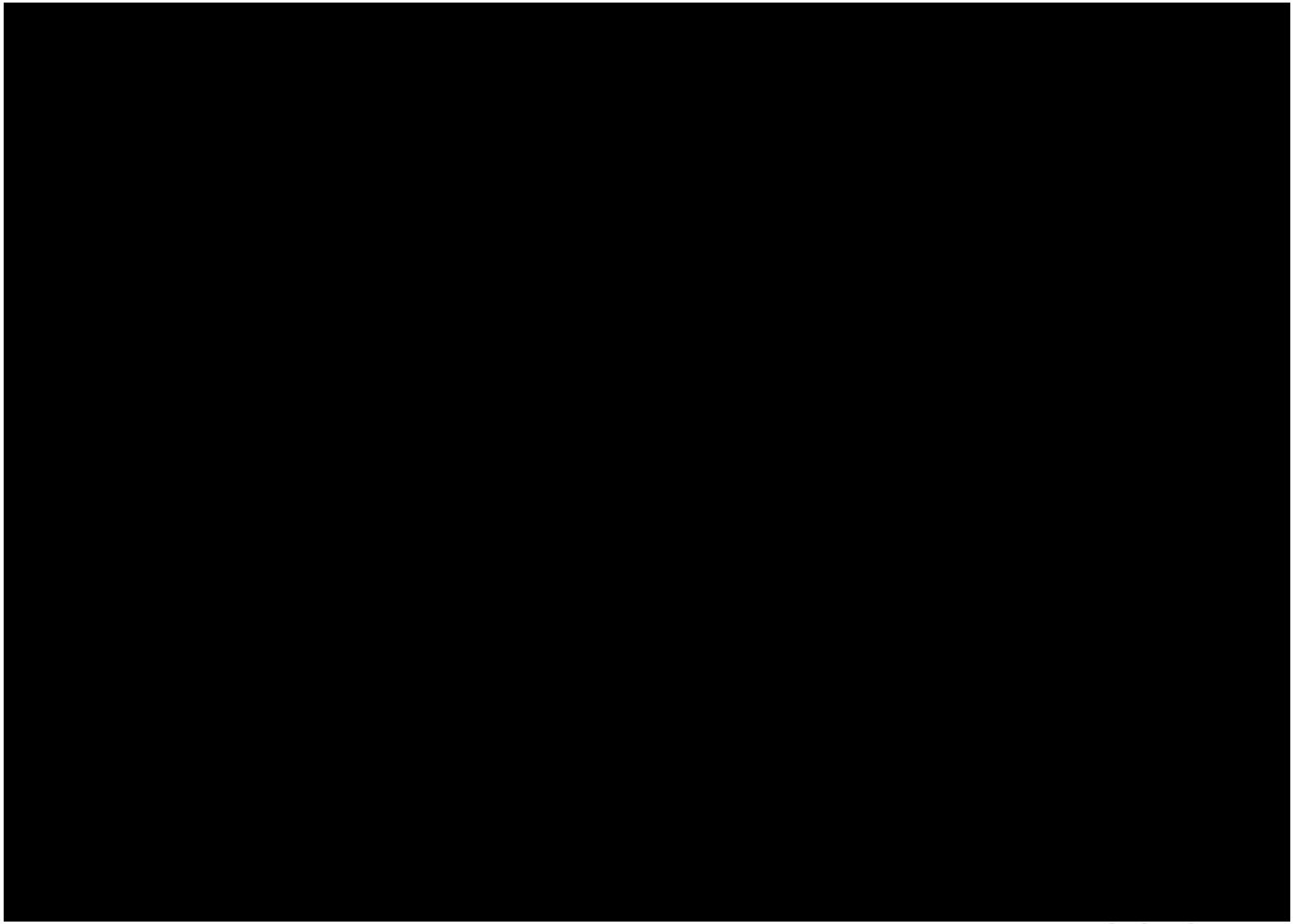
These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

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.



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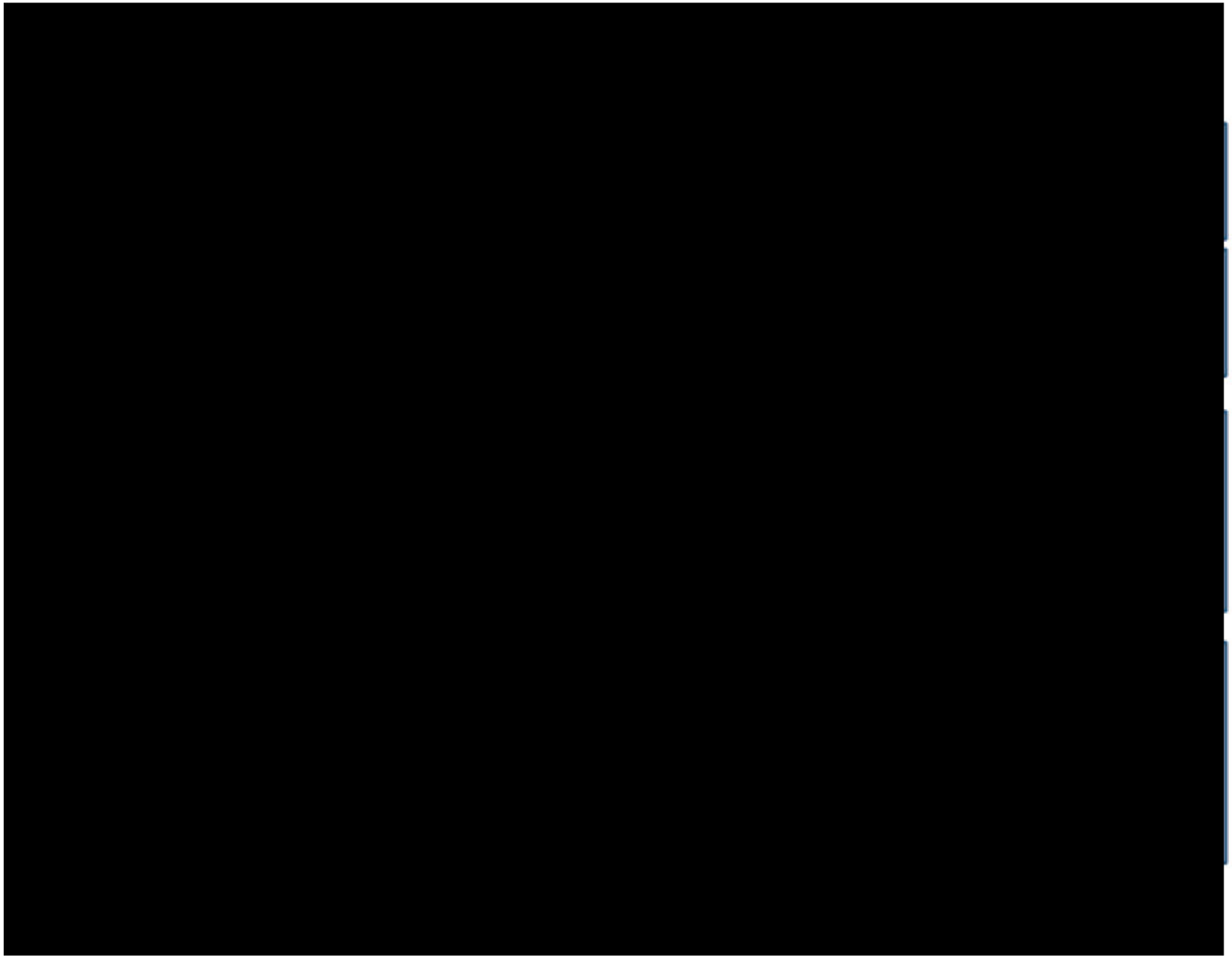

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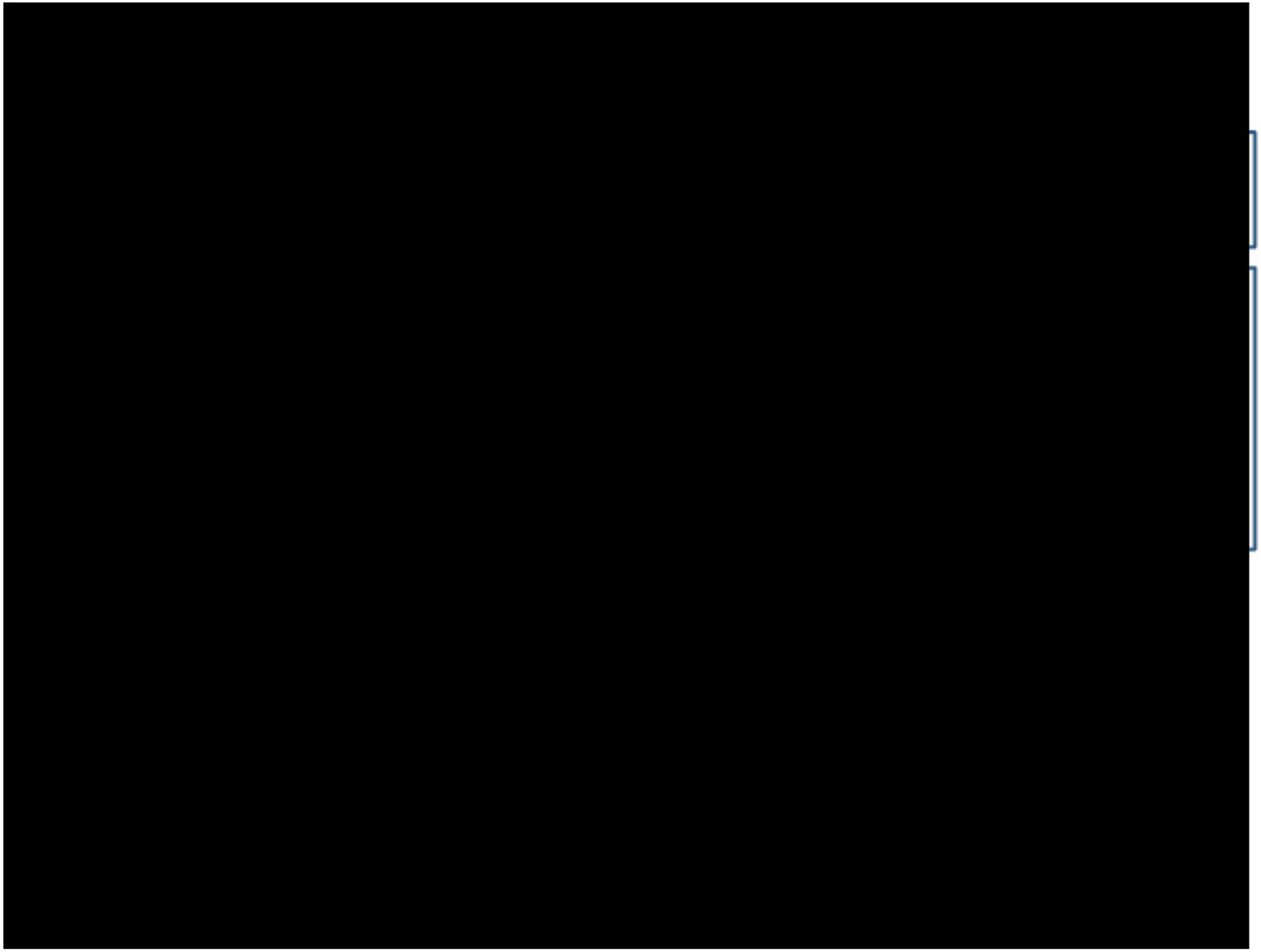

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