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Date: 17-Mar-2016
Revised Date: 31-May-2018

Clinical Protocol CA209627

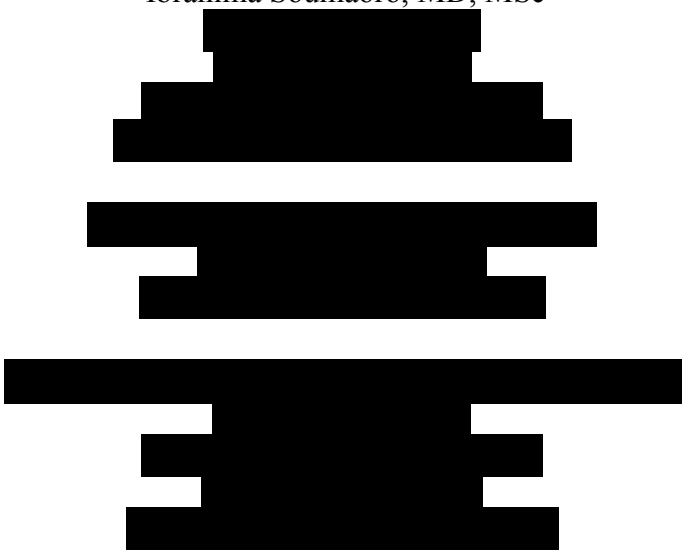
An Open-label Phase 2 Multi-cohort Trial of Nivolumab in Advanced or Metastatic Malignancies

(CheckMate 627: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 627)

Revised Protocol Number: 02

Study Director/Medical Monitor

Ibrahima Soumaoro, MD, MSc



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 02	31-May-2018	• Incorporated change as per Administrative Letter 03 • Updated Medical Monitor information • Added minor changes to statistical section • Added language that Oncology TA was responsible for the design and conduct of the study and decisions regarding the protocol will be made with consultation with the Steering Committee • Added language for early stopping considerations
Revised Protocol 01	18-Jan-2018	• Changed primary end point from Clinical Benefit Rate at week 16 (CBR16) to Objective Response Rate (ORR). • Statistical analysis is modified to include a pause rule and clarification of final analysis of each bin. • Adverse Events were updated to include Immune-Mediated Adverse Events (IMAEs) • Vital signs were added to follow-up assessments • 28 days screening window removed • Adenocarcinoma of the small bowel and Adrenocortical carcinoma were added to inclusion criteria • Additional tumor types were added to the exclusion criteria • Treatment duration for 24 months
Original Protocol	17-Mar-2016	Not applicable

[redacted]

[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 4.5.1: Dose Delay Criteria	The bullet point regarding Grade 3 lymphopenia was corrected to read "Grade 3 lymphopenia or asymptomatic amylase or lipase.."	[redacted]
Section 7: Data Monitoring Committee and other External Committees; Section 8: Statistical Considerations; Section 8.1: Sample Size Determination; Section 8.5: Interim Analysis; Section 8.5.1: Pause Rule; Appendix 1 - Statistical Analysis and Modeling, Section 3: Trial Logistics	Revised the decision rule that mandates stopping for early success to allow continuing enrollment for promising cohorts	[redacted]

SYNOPSIS

Clinical Protocol CA209627

Protocol Title: An Open-label Phase 2 Multi-cohort Trial of Nivolumab in Advanced or Metastatic Malignancies

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

Nivolumab (BMS-936558) 240 mg IV as a 30 minute infusion every 2 weeks for 8 cycles followed by nivolumab 480 mg as a 30 minute infusion every 4 weeks beginning at cycle 9 until 24 months, disease progression, unacceptable toxicity or withdrawal of consent.

Study Phase: 2

Research Hypothesis: Nivolumab monotherapy will improve objective tumor response in subjects with advanced or metastatic malignancies.

Objectives:

Primary objective:

To evaluate the investigator-assessed Objective Response Rate (ORR) of nivolumab monotherapy in advanced or metastatic malignancies

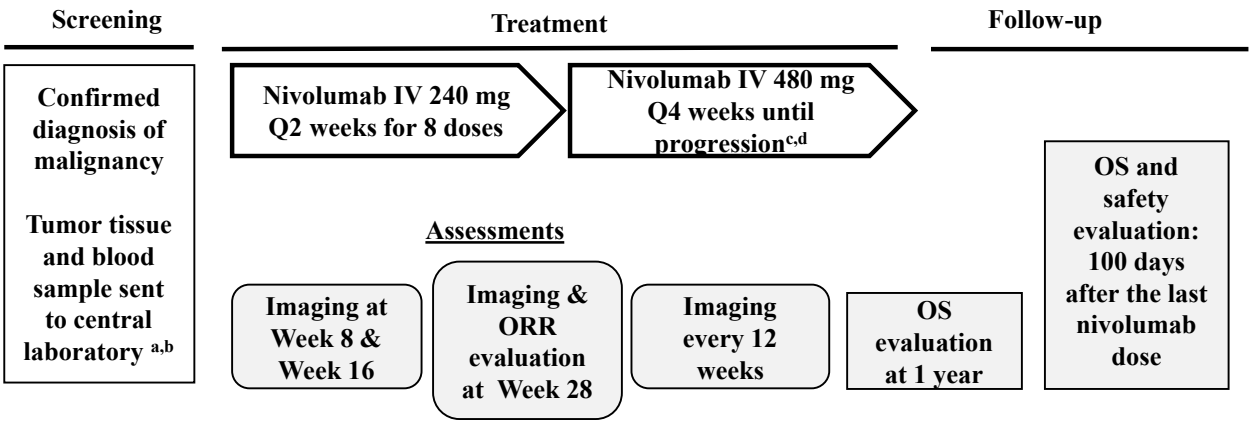
Secondary objectives:

- To assess duration of investigator-assessed clinical response (duration of response)
- To assess time to response (TTR)
- To assess clinical benefit rate (CBR)
- To assess overall survival (OS) at one year
- To assess safety of nivolumab in malignancies in this study
- To correlate clinical response and OS to programmed death-ligand 1 (PD-L1) expression
- To correlate clinical response and OS to MisMatch Repair (MMR) alterations

[redacted]

Study Design: This is an open-label, multicenter, phase 2 study of nivolumab monotherapy in subjects (≥ 18 years) with advanced or metastatic malignancies not previously evaluated with nivolumab. Enrollment includes up to 350 subjects. Subjects must have received previous standard of care for primary therapy or post primary therapy.

Study Design Schematic



[a] Tumor tissue will be evaluated for sufficient tumor that meet the minimum quality requirements, received by a central laboratory before first treatment

[b] Blood sample will be collected at screening or before first nivolumab administration

[c] Subjects will be treated until protocol-defined progression, unacceptable toxicity, 24 months of treatment, or withdrawal of consent

[d] Time interval between dose 8 and dose 9 is 2 weeks; time interval between dose 9 and dose 10 is 4 weeks

Study Population: Key Inclusion Criteria

- Cohorts are comprised of tumor types which may include but are not limited to the following advanced or metastatic malignancies:
  1. Adenocarcinoma of the small bowel
  2. Adrenocortical carcinoma
  3. adenoid cystic carcinoma
  4. anal cancer
  5. biliary tract cancer (intrahepatic or extrahepatic cholangiocarcinoma gallbladder cancer, ampullary carcinoma)
  6. carcinoid after somatostatin analogs (SSA) (Ki67 less than 20%)
  7. cervix cancer (exocervix, squamous cell pathology)
  8. endometrial cancer (after primary treatment that includes radiation therapy. Subjects with tumors greater than 10% estrogen receptor positive pathology in the primary tumor are excluded)
  9. histiocytoses (including Erdheim Chester disease, Langerhans cell histiocytosis)
  10. insulinoma
  11. Lynch syndrome associated cancers (excluding hereditary nonpolyposis colorectal cancer [HNPCC]).
  12. medullary thyroid cancer
  13. Merkel cell carcinoma (includes unresectable disease)
  14. nasopharyngeal carcinoma
  15. neuroendocrine tumors (poorly differentiated, Ki67 greater than 20%)
  16. neuroendocrine tumors (well to moderately differentiated, Ki67 less than 20%)
  17. non-lung small cell carcinoma (including small cell carcinoma of the ovary of pulmonary type or small cell ovarian cancer hypercalcemic type)
  18. non squamous cell cancer of the head and neck (including cancer of the salivary gland)

19. penile cancer
20. rare women's cancers (high grade, clear cell:-greater than 50% clear cell by pathology)
21. soft-tissue sarcoma (including liposarcoma, leiomyosarcoma)
22. malignant peripheral nerve sheath tumor-NF-1
23. testicular cancer (chemotherapy resistant or recurrent within 2 years of primary therapy)
24. thymic carcinoma or invasive thymoma
25. thyroid cancer (anaplastic thyroid cancer as primary therapy)
26. thyroid cancer (papillary or follicular, after failing radioactive iodine [RAI] and after approved kinase inhibition [lenvatinib])
27. uterine sarcoma (excluding endometrial stroma sarcoma)
28. vaginal cancer (squamous cell pathology)
29. vulvar cancer (squamous cell pathology)

- Other (consult with BMS Medical Monitor before screening subjects in this group - for US only)
- Adults ≥ 18 years of age
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Pathology report confirming diagnosis of malignancy. Subjects will have advanced or metastatic disease. In the case of anaplastic thyroid cancer, subjects may receive nivolumab as part of primary therapy.
- Subjects must have measurable disease by computed tomography (CT) or magnetic resonance imaging (MRI) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.
- Subjects must have received standard-of-care primary treatment for malignancy and standard-of-care for relapse or refractory disease, if treatment exists. For de novo metastatic disease, subjects with recurrent or refractory disease after standard-of-care (first-line or second-line [if treatment exists]) will be eligible for this trial. If there is no standard-of-care treatment for de novo metastatic disease (eg, metastatic carcinoid), subjects are eligible to enroll without prior first-line (or second-line) therapy.
- Mandatory tissue and blood collection for PD-L1 testing and MMR-deficiency testing. Tumor tissue (formalin-fixed, paraffin embedded archival [< 3 months old] or recent acquisition) must be received by a central laboratory before first treatment. In order to receive treatment, the sample must meet the minimum quality requirements, as determined by the central laboratory. If the archival tissue is > 3 months old, a fresh biopsy will be required to obtain sufficient tissue sample for PD-L1 testing. Archival tissue samples are acceptable for MMR testing. A blood sample must be obtained before the first dose of nivolumab. Test results are not required for enrollment. (Note: Fine Needle Aspiration [FNA] and bone metastases samples are not acceptable for submission.)

Key Exclusion Criteria

- Subjects who require ongoing treatment with more than 10 mg of prednisone (or steroid equivalent, excluding inhaled or topical steroids) daily
- Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibodies (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways).
- Subjects with the following malignancies are excluded:
  1. adenocarcinoma of the colon
  2. adenocarcinoma of the pancreas
  3. adenocarcinoma of the prostate
  4. adenocarcinoma of the rectum
  5. endometrial cancers with greater than 10% estrogen receptor positive pathology in the primary tumor
  6. epithelial ovarian cancer
  7. breast cancer that is ER, PR positive or HER2 positive or triple-negative
  8. esophageal cancer

9. gastric cancer
10. gastrointestinal stromal tumor (GIST)
11. hepatocellular carcinoma
12. Hodgkin's lymphoma
13. leptomeningeal disease
14. leukemia
15. melanoma
16. meningioma (low grade)
17. multiple myeloma
18. myelodysplastic syndrome
19. non-Hodgkin's lymphoma (except primary CNS lymphoma without leptomeningeal disease)
20. non-small cell lung cancer
21. peritoneal carcinoma
22. primary CNS lymphoma
23. renal cell carcinoma
24. small cell lung cancer
25. squamous cell carcinoma of the head and neck
26. squamous cell carcinoma of the skin
27. urothelial bladder cancer (urothelial [transitional cell] histology or mixed histologies)
28. carcinoma of unknown primary

- Subjects with an active, known, or suspected autoimmune disease (Subjects may enroll with type I diabetes mellitus, hypothyroidism [only requiring hormone replacement], vitiligo, psoriasis, or alopecia not requiring systemic treatment.)
- Subjects with previous malignancies (except non-melanoma skin cancers, and in situ cancers) are excluded unless a complete remission was achieved at least 2 years prior to study entry and no additional therapy is required or anticipated to be required during the study period.

Study Drug: includes Investigational [Medicinal] Products (IP/IMP) as listed:

Study Drug for CA209627		
Medication	**Potency**	**IP/Non-IP**
Nivolumab BMS936558-01	40 mg/4 mL and 100 mg/10 mL solution in a single-dose vial.	IP

Study Assessments: The primary endpoint of this trial is investigator-assessed ORR of nivolumab monotherapy which is based on tumor assessments at baseline and then at 28 weeks from first dose of nivolumab. Clinical benefit will be defined. Tumor assessments will occur at week 8, week 16, week 28, and then every 12 weeks until disease progression, regardless of any dose delays. Adverse events will be assessed continuously during the study and for 100 days after last trial dose of nivolumab.

Statistical Considerations:

Sample Size: Up to 350 subjects

Primary Endpoint: ORR analyses will be summarized for each tumor type.

Secondary Endpoints:

- Duration of the response
- TTR
- CBR
- Overall Survival (OS) at one year
- Safety and Tolerability

[redacted]

Analyses:

The final analysis for each group declares success if the Bayesian posterior probability that the treatment effect in that group (treatment compared to control) is above 80%.

DOR, TTR, CBR, and overall survival at 1 year will also be provided for each group.

Safety analyses will be performed by tumor group in all treated subjects. Descriptive statistics of safety will be presented using NCI CTCAE version 4.0. All AEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v4.0 criteria by system organ class and MedDRA preferred term. On-study lab parameters including hematology, chemistry, liver function, thyroid function, and renal function will be summarized using worst grade per NCI CTCAE v4.0 criteria.

[redacted]

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[redacted]

1.2 Research Hypothesis

Nivolumab monotherapy will improve objective tumor response in subjects with advanced or metastatic malignancies.

1.3 Objectives(s)

1.3.1 Primary Objectives

To evaluate the investigator-assessed ORR of nivolumab monotherapy in advanced or metastatic malignancies

1.3.2 Secondary Objectives

- To assess duration of investigator-assessed clinical response (duration of response)
- To assess time to response (TTR)

- To assess clinical benefit rate (CBR)
- To assess overall survival (OS) at 1 year
- To assess safety of nivolumab in malignancies in this trial
- To correlate clinical response and OS to PD-L1 expression
- To correlate clinical response and OS to MMR alterations

[redacted]

[redacted]

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS), International Ethical Guidelines Good Clinical Practice (GCP), as defined by the International 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) and applicable local requirements.

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

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

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (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, patient emergency cards, advertisements, etc), 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 BMS-936558 Nivolumab Investigator Brochure or product labeling information to be provided to subjects and any updates.

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

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

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

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
- 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.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
- If informed consent is initially given by a 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.
- 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, contracted representatives (eg, CRO), and regulatory authorities have direct access to subject records.

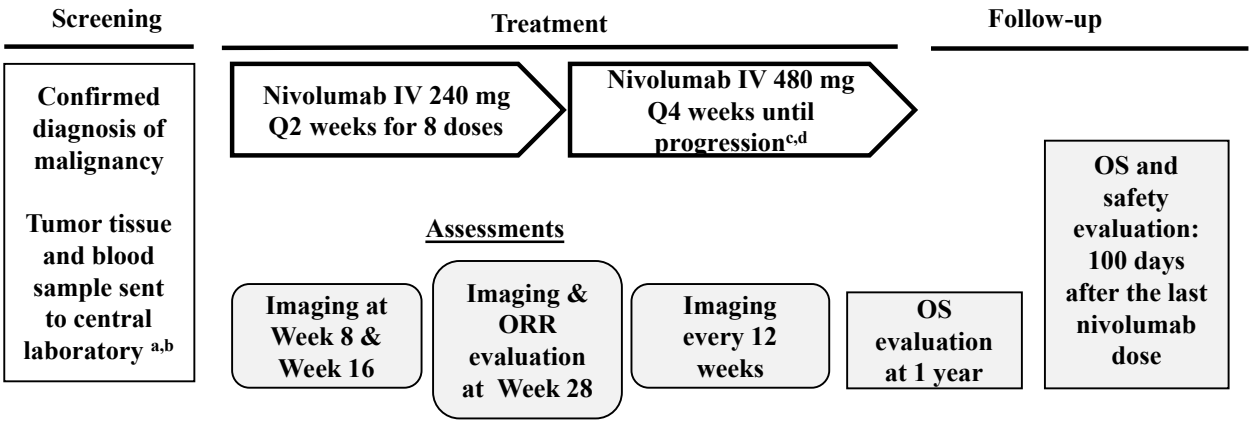
The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is an open-label, multicenter, phase 2 study of nivolumab monotherapy in adult (≥ 18 years) subjects with advanced malignancies. Subjects must have received previous standard-of-care therapies (for primary therapy or post primary therapy).

Figure 3.1-1: Study Design Schematic



[a] Tumor tissue will be evaluated for sufficient tumor tissue that meet the minimum quality requirements, received by a central laboratory before first treatment.

[b] Blood sample will be collected at screening or before first nivolumab administration

[c] Subjects will be treated until confirmed progression, unacceptable toxicity, or 24 months of treatment (see Section 4.5.3)

[d] Time interval between dose 8 and dose 9 is 2 weeks; time interval between dose 9 and dose 10 is 4 weeks

Enrollment of up to 350 subjects is expected to require approximately 24 months. Interim monitoring and final analyses are planned. Subjects will receive study drug **for the maximum treatment duration of 24 months.**

The start of the trial is defined as first visit for first subject screened. End of trial is defined as the last scheduled procedure shown in the Time & Events Schedule for the last subject. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

3.2 Post-Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study drug **for the maximum treatment duration specified in protocol Section 3.1**. 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 to comply with scheduled visits, treatment schedule, laboratory tests, mandatory collection of archival or fresh tumor tissue (primary or metastatic) specimens, blood, and other requirements of the study. Mandatory tissue and blood collection is required for PD-L1 testing and for MMR deficiency testing. Tumor tissue (formalin-fixed, paraffin embedded archival or recent acquisition [< 3 months old]) must be received by a central laboratory before first treatment. If the archival tissue is > 3 months old, a fresh biopsy will be required, to obtain sufficient tissue sample for PD-L1 testing. Archival tissue samples are acceptable for MMR testing. In order to receive treatment, the sample must meet the minimum quality requirements, as determined by the central laboratory. A blood sample must be obtained before the first dose of nivolumab. Test results are not required for enrollment. (Note: Fine Needle Aspiration (FNA) and bone metastases samples are not acceptable for submission

c) Subject Re-enrollment: This trial permits the re-enrollment of a subject that has discontinued the study as a screening failure (the subject will not have received nivolumab). If re-enrolled, the subject must be re-consented.

2. Target Population

a) Subjects with pathologically confirmed locally advanced or metastatic disease. In the case of anaplastic thyroid cancer, subjects may receive nivolumab as part of primary therapy. Advanced or metastatic tumor types may include, but are not limited to the following:

- Adenocarcinoma of the small bowel
- Adrenocortical carcinoma
- adenoid cystic carcinoma
- anal cancer
- biliary tract cancer (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer, ampullary carcinoma)
- carcinoid after somatostatin analogs (SSA) (Ki67 less than 20%)
- cervix cancer (exocervix, squamous cell pathology)
- endometrial cancer (after primary treatment that includes radiation therapy. Subjects with tumors with greater than 10% estrogen receptor positive pathology in the primary tumor are excluded)
- histiocytoses (including Erdheim Chester disease, Langerhans cell histiocytosis)
- insulinoma

- Lynch syndrome associated cancers (excluding hereditary nonpolyposis colorectal cancer [HNPCC]) (Please see Section 10)
- medullary thyroid cancer
- Merkel cell carcinoma (includes unresectable disease)
- mesothelioma
- nasopharyngeal carcinoma
- neuroendocrine tumors (poorly differentiated, Ki67 greater than 20%)
- neuroendocrine tumors (well to moderately differentiated, Ki67 less than 20%)
- non-lung small cell carcinoma (including small cell carcinoma of the ovary of pulmonary type or small cell ovarian cancer hypercalcemic type)
- non squamous cell cancer of the head and neck (including cancer of the salivary gland)
- penile cancer
- rare women's cancers (high grade, clear cell:-greater than 50% clear cell by pathology)
- soft-tissue sarcoma [including liposarcoma, leiomyosarcoma])
- malignant peripheral nerve sheath tumor NF-1
- testicular cancer (chemotherapy resistant or recurrent within 2 years of primary therapy)
- thymic carcinoma or invasive thymoma
- thyroid cancer (anaplastic thyroid cancer as primary therapy)
- thyroid cancer (papillary or follicular, after failing radioactive iodine [RAI] and after approved kinase inhibition [lenvatinib])
- uterine sarcoma (excluding endometrial stroma sarcoma)
- vaginal cancer (squamous cell pathology)
- vulvar cancer (squamous cell pathology)

b) Other (please consult with BMS Medical Monitor before screening subjects in this group - US only)

c) Subjects must have received standard-of-care primary treatment for malignancy and standard-of-care for relapse or refractory disease, if treatment exists. For de novo metastatic disease, subjects with recurrent or refractory disease after standard-of-care (first-line or second-line [if treatment exists]) will be eligible for this trial. If there is no standard-of-care treatment for de novo metastatic disease (eg, metastatic carcinoid), subjects are eligible to enroll without prior first-line (or second-line) therapy.

d) For subjects with brain metastases, there must be ≥ 1 evaluable lesion outside the brain. Subjects must not be receiving corticosteroids for brain metastasis.

e) Screening laboratory values must meet the following criteria (using CTCAE v4):

i) WBC ≥ 2000/uL

ii) Neutrophils ≥ 1500/uL

iii) Platelets ≥ $100x10^3$/uL

iv) Hemoglobin ≥ 9.0 g/dL

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

Female CrCl = (140- age in years) x weight (kg) x 0.85/ (72 x serum creatinine in mg/dL)

Male CrCl = (140- age in years) x weight in kg x 1.00/ (72 x serum creatinine in mg/dL)

vi) AST ≤ 3.0 x ULN

vii) ALT ≤ 3.0 x ULN

viii) Total bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level of < 3.0x ULN).

f) Subjects must have measurable disease by CT or MRI per RECIST 1.1 criteria (see Appendix 4)

g) Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 1 (see Appendix 2)

h) Life expectancy ≥ 16 weeks

3. Age and Reproductive Status

a) Adults, ages ≥ 18

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) WOCBP should use an adequate method to avoid pregnancy for 5 months (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug.

e) Males who are sexually active with WOCBP must continue contraception for 7 months (90 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug.

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

Investigators shall counsel WOCBP, and male subjects who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception (Appendix 6), which have a failure rate of < 1% when used consistently and correctly.

3.3.2 Exclusion Criteria

1. Target Disease Exclusions

a) Subjects with:

- adenocarcinoma of the colon
- adenocarcinoma of the pancreas
- adenocarcinoma of the prostate
- adenocarcinoma of the rectum
- endometrial cancers with greater than 10% estrogen receptor positive pathology in the primary tumor
- epithelial ovarian cancer
- breast cancer that is ER, PR positive breast cancer OR HER2 positive OR triple-negative
- esophageal cancer
- gastric cancer
-
- hepatocellular carcinoma
- Hodgkin's lymphoma
- leptomeningeal disease
- leukemia
- melanoma
- meningioma (low grade)
- multiple myeloma
- myelodysplastic syndrome
- non-Hodgkin's lymphoma (except primary CNS lymphoma without leptomeningeal disease)
- non-small cell lung cancer
- peritoneal carcinoma
- primary CNS lymphoma
- renal cell carcinoma
- small cell lung cancer
- squamous cell carcinoma of the head and neck
- squamous cell carcinoma of the skin
- urothelial bladder cancer (urothelial [transitional cell] histology or mixed histologies)
- carcinoma of unknown primary

2. Medical History and Concurrent Diseases

a) Subjects with previous malignancies (except non-melanoma skin cancers, and in situ cancers) are excluded unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required or anticipated to be required during the trial period.

b) Active and untreated CNS metastases as determined by CT or MRI evaluation during screening and prior radiographic assessments. Subjects with CNS metastasis requiring corticosteroids are excluded from the trial.

c) Previously treated spinal cord compression must be clinically stable for ≥ 6 weeks prior to first dose of nivolumab

d) Uncontrolled pain

e) Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures

f) Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium or Ca > 12 mg/dL or corrected serum calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab

h) Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibodies (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways).

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

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

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

l) Prior allogeneic bone marrow transplantation or prior solid organ transplantation

m) Any disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a condition or event that contraindicates the use of the investigational drug or that may affect the interpretation of the results or render the subject at high risk from treatment complication

n) Subjects previously treated with investigational anticancer therapies less than 6 weeks prior to the first dose of nivolumab

o) Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results (eg, significant liver disease, cirrhosis, uncontrolled major seizure disorder, psychiatric disorders, superior vena cava syndrome)

p) Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within 3 months before first dose of nivolumab, unstable arrhythmias or unstable angina

q) Signs or symptoms of infection within 4 weeks before first dose of nivolumab, severe infections within 4 weeks before first dose of nivolumab including but not limited to

hospitalization for complications of infection, bacteremia or severe pneumonia, and/or received oral or IV antibiotics within 2 weeks before first dose of nivolumab

r) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug. Subjects with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enroll.

s) Major surgical procedure within 28 days before first dose of nivolumab or anticipation of need for a major surgical procedure during the course of the study

t) Treatment with botanical preparations (eg, herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment. Refer to Section 3.4.1 for prohibited therapies.

3. Physical and Laboratory Test Findings

a) Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection, and/or detectable virus
b) Positive test for human immunodeficiency virus (HIV)

4. Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components
b) Known hypersensitivity to dacarbazine (DTIC)

5. Other Exclusion Criteria

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

3.3.3 Women of Childbearing Potential

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 or bilateral salpingectomy) 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 > 40 mIU/mL to confirm menopause.

*Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The

duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

[redacted]

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
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply, and BMS approval is required).
- Any event found in the Discontinuation criteria as outlined in Section 4.5.3.

Subjects discontinuing study treatment will remain on study for documentation of progression and death for up to one year.

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

BMS may request that survival data be collected on all treated/randomized subjects outside of the protocol defined window (Table 5.1-4). At the time of this request, each subject will be

contacted to determine their survival status unless the subject has withdrawn consent for all contacts or is lost to follow-up.

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**, if 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

Subjects should receive nivolumab at a dose of 240 mg as a 30 minute infusion on Day 1 of each 2-week treatment cycle for 8 doses until progression, unacceptable toxicity, withdrawal of consent, the study ends, or until q4w dosing begins, whichever occurs first. Beginning with Dose 9, subjects should receive nivolumab 480 mg as a 30 minute infusion every 4 weeks (± 3 days) until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. Subjects will receive study drug **for the maximum treatment duration of 24 months.**

Study drug includes both Investigational [Medicinal] Product (IP/IMP) consist of the following:

Table 4-1: Study Drug for CA209627

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Nivolumab BMS-936558-01 Solution for Injection	40 mg/4 mL and 100 mg (10 mg/mL)	IP	Open Label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect from light and freezing

There will be no dose escalations or reductions of nivolumab allowed. Subjects may be dosed no less than 12 days from the previous dose during q2w cycles. For q4w dosing cycles, subjects may be dosed within a ± 3 day window. Premedications are not recommended for the first dose of nivolumab.

Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to Section 4.5.6.

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

Nivolumab Injection: 40 mg/4 mL and 100 mg/10 mL (10 mg/mL)

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL.

When the dose is fixed (eg, 240 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 120 mL. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

No incompatibilities have been observed between nivolumab injection and polyvinyl chloride (PVC), non-PVC/non-DEHP (di[2-ethylhexyl]phthalate) IV components, or glass bottles have been observed.

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

Not applicable for this study.

4.3 Storage of Study Drug

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.

Please refer to Section 9.2.2 for guidance on IP records and documentation.

4.4 Method of Assigning Subject Identification

The subject number will be assigned through an interactive voice response system (IVRS) once the subject has signed the informed consent form and is registered. 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 (year of birth only in Germany)
- Gender at birth
- Tumor type

Once enrolled in IVRS, subjects that have met all eligibility criteria will be ready for treatment and drug vial assignment through the IVRS. The following information is required for drug vial assignment and treatment:

- Subject number
- Date of birth (year of birth only in Germany)
- Tumor Type
- Confirmation of receipt of tumor tissue in archival (≤ 3 months old or new biopsy tissue) and blood samples by a central laboratory

4.5 Selection and Timing of Dose for Each Subject

Subjects will receive treatment with nivolumab 240 mg as a 30 minute IV infusion on Day 1 of a treatment cycle every 2 weeks (14 days) for 8 doses until progression, unacceptable toxicity, withdrawal of consent, the study ends, or until Q4W dosing begins, whichever occurs first. Participants should begin study treatment within 3 calendar days of treatment assignment. Beginning with dose 9 (2 weeks following the 8th dose), subjects will receive treatment with nivolumab 480 mg as a 30 minute IV infusion every 4 weeks (28 days) (± 3 days) until progression, unacceptable toxicity, withdrawal of consent, maximum of 24 months of treatment, or the study ends, whichever occurs first.

If required for clinic scheduling, subjects may be treated up to 3 days before or after the scheduled date, ie, at intervals of not less than 12 days from the previous dose during Q2W cycles. For Q4W dosing cycles, participants may be dosed within a ±3 day window. A dose given more than 3 days after the intended dose date will be considered a delay. Subsequent treatments should be based on the actual date of administration of the previous dose of drug.

No dose escalations or reductions of nivolumab are allowed. Dosing visits are not skipped, only delayed.

There are no premedications recommended for nivolumab until infusion reactions have been observed in the subject. Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to Section 4.5.6.

Dose delay criteria, criteria to resume treatment, and treatment discontinuation criteria can be found in Section 4.5.1, Section 4.5.2, and Section 4.5.3, respectively.

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

4.5.1 Dose Delay Criteria

Nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related adverse event with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT, or total bilirubin abnormalities
- Any Grade 3 skin, drug-related AE
- Any Grade 3 drug-related laboratory abnormality with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Any Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation (See Section 4.5.3 for Treatment Discontinuation Criteria).
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met.

4.5.2 Criteria to Resume Treatment

Subjects may resume treatment with nivolumab when the drug-related AE(s) resolve(s) to Grade ≤1 or baseline, 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
- For subjects with Grade 2 AST, ALT, and/or total bilirubin abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the Medical Monitor or designee.
- Subjects with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor or designee. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

4.5.3 Treatment Discontinuation Criteria

Nivolumab treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related AE lasting > 7 days, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, myocarditis, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Grade ≥ 3 drug-related AST, ALT or total bilirubin requires discontinuation*
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN
- * In most cases of Grade 3 AST or ALT elevation, study drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that

warrants continuation of study drug(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.

- Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or total bilirubin), except for the following events which do not require discontinuation:
- Grade 4 neutropenia ≤ 7 days
- Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
- Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy adverse events, such hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks from the previous dose, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

4.5.4 Nivolumab Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[48] Subjects treated with nivolumab will be permitted to continue nivolumab treatment beyond initial RECIST 1.1 defined PD until the maximum of 24 months from the first treatment, assessed by the investigator, as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Tolerance of study drug

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

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

If the investigator believes the subject would receive clinical benefit by continuing nivolumab treatment after scans showing disease progression, the subject may continue to receive nivolumab treatment, remain on the trial, and monitored according to the Time and Events Schedule in Section 5.

When a subject receives nivolumab therapy beyond disease progression, further progression from initial progressive disease evaluation is defined as an additional 10% increase in tumor burden (with a minimum 5 mm absolute increase). This includes an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the initial progressive disease evaluation. Nivolumab treatment should be discontinued permanently upon determination of further progression.

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

[redacted]

4.5.6 Treatment of Nivolumab-Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthalgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4) guidelines.

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

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

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

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

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further BMS-936558 will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

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

- Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

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

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

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

4.8 Destruction or Return of Investigational Product

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

If	Then
IP supplied by BMS (including its vendors)	Any unused IP supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless IP containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

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

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.

- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

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

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

Please refer to Section 9.2.2 for additional guidance on IP records and documentation.

4.9 Retained Samples for Bioavailability / Bioequivalence

Not applicable

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline CA209627

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose
Medical History	X	Including diagnostic pathology report
Prior Systemic Therapy	X	
Safety Assessments		
Physical Examination	X	Within 14 days prior to first dose
Physical Measurements	X	Include Height and Weight Within 14 days prior to first dose
Vital Signs	X	Temperature, BP, HR, and RR within 3 days of first dose
Performance Status (ECOG)	X	Within 14 days prior to first dose. See Appendix 2 for ECOG scale
Assessment of Signs and Symptoms	X	After obtaining Informed Consent, assess all signs and symptoms within 14 days prior to first dose.
Concomitant Medication Collection	X	Within 14 days prior to first dose
Serious Adverse Events assessment		Assessed using NCI CTCAE v. 4 (continuously evaluate after subject signs ICF)
Laboratory Tests	X	Screening local laboratory assessments should be done within 14 days prior to first dose and are to include: CBC with differential, Chemistry panel including LFTs (ALT, AST, total bilirubin, alkaline phosphatase), albumin, BUN or serum urea level, creatinine, Ca, Na, K, Cl, phosphate, LDH, glucose, and thyroid panel including TSH, free T3, and free T4. The following screening local laboratory assessments should be done prior to first dose: Hepatitis B and C testing (HBV sAg and HCV Ab or HCV RNA).
HIV testing (Germany only)	X	

Table 5.1-1: Screening Procedural Outline CA209627

Procedure	Screening Visit	Notes
Pregnancy Test	X	Serum or urine pregnancy testing at screening visit and repeated within 24 hours of first dose.
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
IVRS/Clinical Drug Supplies		
Phone calls to IVRS	X	Phone calls must be made to IVRS as follows: • For subject number assignment at the time informed consent is obtained. • Prior to dosing for study drug vial assignment (call should be made within 3 days prior to dosing).

Table 5.1-2: On-Treatment Assessments - Nivolumab 240mg/Q2 weeks CA209627

Procedure	Cycle 1 Day 1 (C1D1) (First dose)	Each Cycle (every 2 weeks) on Day 1	Notes:
Safety Assessments			
Physical Examination (including weight)	X		
Targeted Physical Examination		X	Targeted examination must include at a minimum the following body systems: Cardiovascular, Gastrointestinal, and Pulmonary. Weight must be collected. Within 3 days prior to dosing
Vital Signs	X	X	Temperature, BP, RR, and HR. Obtain vital signs within 3 days prior to dosing.
ECOG Performance Status	X	X	See Appendix 2 for ECOG scale
Adverse Events Assessment	------- Continuously -------		Assessed using NCI CTCAE v. 4
Serious Adverse Event Assessments	------- Continuously -------		Assessed using NCI CTCAE v. 4.
Review of Concomitant Medications	X	X	
Laboratory Tests	X	X	On-study local laboratory assessments should be done within 3 days prior to dosing for every cycle and to include: CBC with differential, Chemistry panel including LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Na, K, Cl, phosphate, LDH, and glucose. If > 14 days from screening, labs must be repeated.
Thyroid Function Testing		See Notes	TSH (reflex to free T3 and free T4 if abnormal result) to be performed every 6 weeks (± 1 week).
Pregnancy Test	X	See Notes	Serum or urine within 24 hours prior to first dose and then at least once every 4 weeks regardless of dosing schedule.

Table 5.1-2: On-Treatment Assessments - Nivolumab 240mg/Q2 weeks CA209627

Procedure	Cycle 1 Day 1 (C1D1) (First dose)	Each Cycle (every 2 weeks) on Day 1	Notes:
Efficacy Assessments			
Radiographic Tumor Assessment		See notes	See Appendix 4 (RECIST 1.1 Guidelines) for details regarding imaging methodology requirements and assessments Radiographic tumor assessment must be performed on Week 8 (± 5 days), prior to the next cycle, at Week 16 prior to the start of 480 mg dosing, and at Week 28 prior to dosing. Cycles beyond Week 16 may be ± 5 days.
[redacted]			
[redacted]	[redacted]		[redacted]
Clinical Drug Supplies			
Administer Study Drug	X	X	Within 3 days from vial allocation, the subject must receive the first dose of study medication. Subjects may be dosed no less than 12 days between doses and no more than 3 days from the scheduled dose. Contact with IVRS for drug vial assignment.

Table 5.1-3: On-Treatment Assessments - Nivolumab 480mg/Q4 weeks CA209627

Procedure	Each Cycle (every 4 weeks) on Day 1	Notes
Safety Assessments		
Targeted Physical Examination	X	Targeted examination must include at a minimum the following body systems: Cardiovascular, Gastrointestinal, and Pulmonary. Weight must be collected. Within 3 days before dosing
Vital Signs	X	Temperature, BP, RR, and HR. Obtain vital signs within 3 days before dosing.
ECOG Performance Status	X	See Appendix 2 for ECOG scale
Adverse Events Assessment	X	Assessed using NCI CTCAE v. 4.0.
Serious Adverse Event Assessments	X	Assessed using NCI CTCAE v. 4.0.
Review of Concomitant Medications	X	
Laboratory Tests	X	On-study local laboratory assessments should be done within 3 days prior to dosing for every cycle and to include: CBC with differential, Chemistry panel including LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Na, K, Cl, phosphate, LDH, and glucose.
Thyroid Function Testing	X	TSH (reflex to free T3 and free T4 if abnormal result) to be performed every 8 weeks (± 1 week).
Pregnancy Test	X	Serum or urine every 4 weeks regardless of dosing schedule.
Efficacy Assessments		
Radiographic Tumor Assessment	Every 12 weeks	See Appendix 4 (RECIST 1.1 Guidelines) for details regarding imaging methodology requirements and assessments Radiographic tumor assessment must be performed q12 weeks ±5 days. Timing of radiographic assessments is based on timing from first dose.
[redacted]		
[redacted]	[redacted]	[redacted]

Table 5.1-3: On-Treatment Assessments - Nivolumab 480mg/Q4 weeks CA209627

Procedure	Each Cycle (every 4 weeks) on Day 1	Notes
Clinical Drug Supplies		
Administer Study Drug	X	Within 3 days of schedule dose. Contact with IVRS for drug vial assignment.

Table 5.1-4: Follow-Up Assessments - All Subjects CA209627

Procedure	Follow-Up Visits X01 (Day 35) (±7 Days) and X02 (Day 100) [a] (±7 Days) after last dose	Survival Follow-Up Visits [b] Every 12 weeks	Notes
Safety Assessments			
Targeted Physical Examination	X		Targeted examination must include the Cardiovascular, Gastrointestinal, and Pulmonary body systems and examination to specific malignancy To assess for potential late emergent study drug related findings.
Vital Signs	X	X	
Adverse Events and Serious Adverse Events Assessment	X		All AEs and SAEs must be collected up to 100 days after study drug discontinuation. SAEs that relate to any later protocol specified procedure must be collected.
Review of Medical History and Subsequent Cancer Therapy Information	X	X	
Laboratory Tests	X		CBC with differential, Chemistry panel including LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Na, K, Cl, phosphate, LDH, and glucose.
Thyroid Function Testing	X		TSH (reflex to free T3 and free T4 if abnormal result)
Pregnancy Test	X		Serum or urine

Table 5.1-4: Follow-Up Assessments - All Subjects CA209627

Procedure	Follow-Up Visits X01 (Day 35) (±7 Days) and X02 (Day 100) [a] (±7 Days) after last dose	Survival Follow-Up Visits [b] Every 12 weeks	Notes
Efficacy Assessments			
Radiographic Tumor Assessment	See notes		Only for subjects without progression and no longer on study therapy. If subject starts subsequent treatment, no assessment required Subjects with a history of brain metastasis may have surveillance MRI approximately every 12 weeks or sooner if clinically indicated
Subject Status			
Survival Status	X	X	Every 3 months after X02; may be accomplished by visit or phone contact, to update survival information and assess subsequent anti-cancer therapy.

NOTES:

[a] Subjects must be followed for at least 100 days after last dose of study treatment. Follow-up visit #1 occurs approximately 35 days (± 7 days) after the last dose or coinciding with the date of discontinuation (± 7 days) if date of discontinuation is greater than 30 days after last dose. Follow-up visit #2 occurs approximately 100 days (± 7 days) from last dose

[b] Survival Follow-up visits to occur every 3 months from Follow-up Visit 2. At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contact. Vital signs not required if follow-up is performed via telephone contact.

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.

Laboratory parameters and/or assessments that are included in Table 5.1-1, Screening Procedural Outline may be repeated in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

5.2 Study Materials

- National Cancer Institute Common Terminology Criteria for Adverse Events NCI CTCAE version 4.0
- BMS-936558 Nivolumab Investigator Brochure
- Laboratory Manuals for collection and handling of blood and tissue specimens
- Pharmacy Binder
- Site manual for operation of interactive voice response system, including enrollment worksheets
- Serious Adverse Event CRFs/eCRFs

5.3 Safety Assessments

At screening, a medical history will be obtained to capture relevant underlying conditions. The screening examinations should include weight, height, ECOG Performance Status, blood pressure (BP), heart rate (HR), respiration rate (RR), and temperature.

Screening local laboratory assessments should be done within 14 days prior to treatment and are to include: CBC with differential, Chemistry panel including LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Na, K, Cl, phosphate, LDH, glucose, albumin, and thyroid panel including TSH, free T3, and free T4.

Screening pregnancy tests for WOCBP must be performed within 24 hours prior to the initial administration of study drug.

The following screening local laboratory assessments should be done prior to treatment: Hepatitis B and C testing (HBV sAg and HCV Ab or HCV RNA).

While on-study the following local laboratory assessments will occur within 3 calendar days prior to each dose: CBC with differential, chemistry panel including LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Na, K, Cl, phosphate, LDH, glucose.

Thyroid function testing (TSH; reflexive fT3 and fT4 if abnormal during on-treatment testing) is to be done every 6 weeks (every 3 doses) for subjects receiving nivolumab at 240 mg q2w, then every 8 weeks (± 1 week) for subjects receiving nivolumab at 480 mg q4w (every other dose). If the patient demonstrated an active endocrinopathy during the nivolumab 240 mg dosing period, then thyroid function testing will be performed every 6 weeks (± 1 week) at the discretion of the treating physician.

On treatment pregnancy tests should be performed as per the schedule in the Time & Events table.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase as well as during the first 2 safety follow-up visits. Once subjects reach the survival follow-up phase, either in-person visits or documented telephone calls/email correspondence to assess the subject's status are acceptable.

Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.

The start and stop time of the study therapy infusions and any interruptions or infusion rate reductions should be documented.

Physical examinations are to be performed as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

On treatment local laboratory assessments are to be completed within 3 calendar days prior to dosing.

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

If a subject shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary adverse events, the subject should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the BMS-936558 Nivolumab Investigator Brochure and Appendix 3.

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

5.3.1 Imaging Assessment for the Study

Images will be collected centrally and may be reviewed by blinded independent central review (BICR) at a later date, or at any time during the study. Image acquisition guidelines and submission process will be outlined in the CA209-627 Imaging Manual to be provided by the core lab.

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

Study evaluations will take place in accordance with Table 5.1-1, Table 5.1-2, Table 5.1-3, and Table 5.1-4 according to RECIST 1.1. CT with IV contrast are the preferred imaging modalities for assessing radiographic tumor response. In cases where contrast is contraindicated, a non-contrast scan will suffice. Screening (baseline) tumor assessments of, chest, abdomen, pelvis, and all known / suspected sites of disease are to be performed prior to first dose. Subsequent assessments should include chest, abdomen, pelvis, and all known / suspected sites of disease using the same imaging method and technique as was used at baseline.

For evaluating CNS metastasis, brain MRI is the required imaging method, and assessment is required during screening in subjects with a known history of treated brain metastases. All known sites of disease (including CNS) should be assessed at baseline and subsequent assessments using the same imaging method and technique. If more than 1 method is used at screening, then the most accurate method according to RECIST 1.1 should be used when recording data, and should again be used for all subsequent assessments. Bone scan, PET scan, or ultrasound is not adequate for assessment of RECIST 1.1 response. Previously treated CNS metastases are not considered measurable lesions for purposes of RECIST 1.1 determined response. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks or sooner if clinically indicated.

Radiographic tumor response will be assessed at Week 8 (± 5 days), Week 16 (± 5 days), and Week 28 (± 5 days), then every 12 weeks (± 5 days) until disease progression, beyond progression, lost to follow-up, or withdrawal of consent. Tumor assessments for all subjects should continue as per protocol even if dosing is interrupted. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Change in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the investigator using the RECIST 1.1 criteria (see Appendix 4 for details of RECIST 1.1).[49] Independent adjudication will resolve equivocal interpretations of imaging results.

Local radiologic assessment of tumor measurements will be used during the study for clinical management and investigator-assessed disease progression using RECIST 1.1 criteria. The same imaging modality used in screening must be used in all subsequent imaging assessments. 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.

5.4 Efficacy Assessments

5.4.1 Objective Response Rate (ORR)

The primary endpoint is investigator-assessed ORR in all treated subjects. See Section 8.3.1.

Please see Appendix 4 for RECIST 1.1.

5.4.2 Secondary Efficacy Assessments

Secondary endpoints are DOR, TTR, CBR, and OS at 1 year. See Section 8.3.2 for the definitions of these endpoints.

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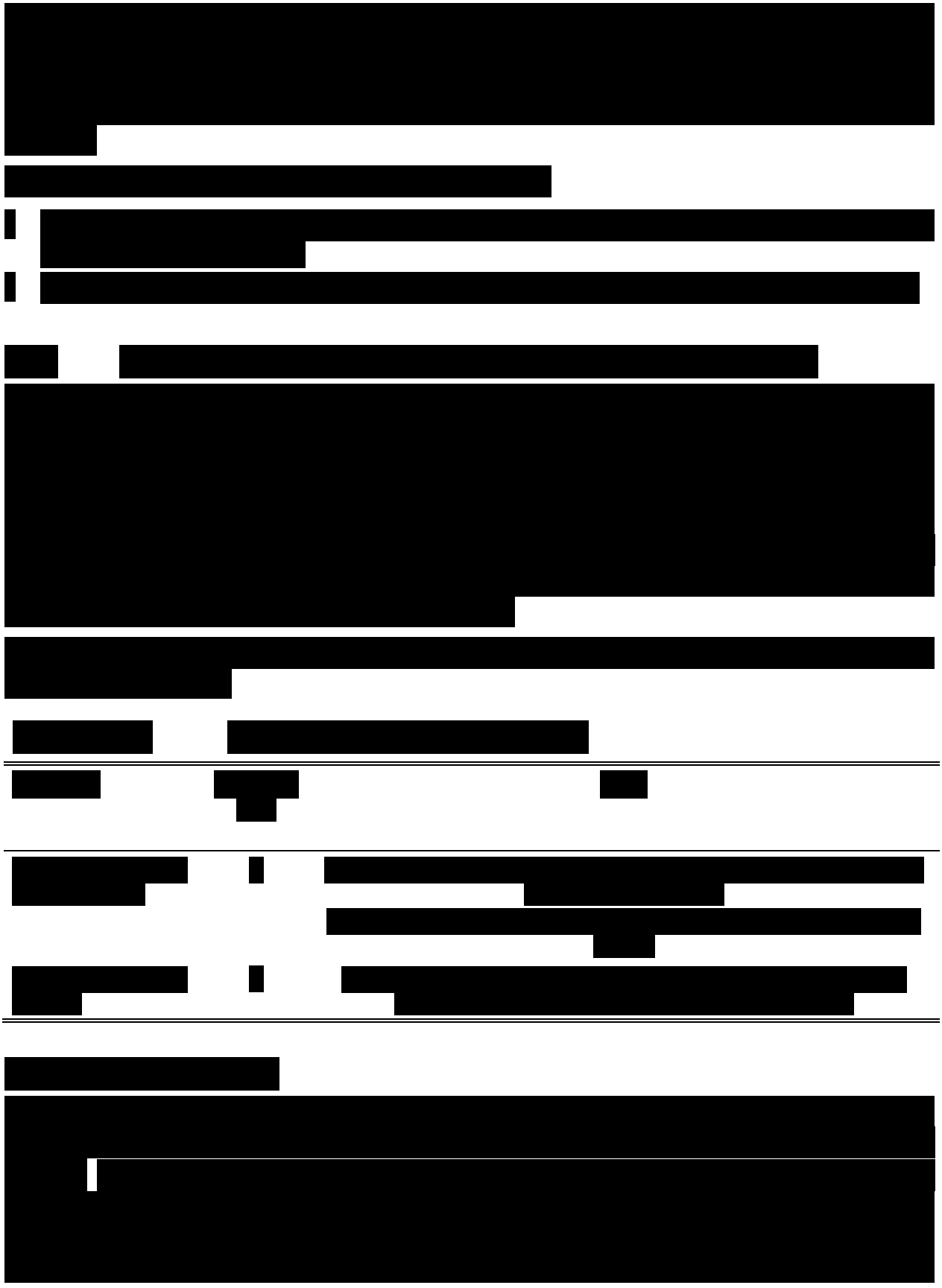


5.7 Retention of Tissue for Additional Research

All residual blood and tissue samples will be retained by the BMS Biorepository for additional research purposes. No additional sampling is required. Additional research retention is mandatory for all subjects, except where prohibited by local laws and regulations. Details of sample collection and processing will be provided to the site in the procedure manual.

5.8 Outcomes Research Assessments

Not applicable.

5.9 Other 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.) Care should be taken not to introduce bias when collecting AE and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known adverse events, when appropriate for the program or protocol.

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320.

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

6.1 Serious Adverse Events

A ***Serious 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.)
- Admission for administration of anticancer therapy in the absence of any other SAEs

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 BMS-936558 Nivolumab Investigator Brochure 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 the last dose of nivolumab. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

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

An SAE report must 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 must 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 Sponsor or designee within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system

is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

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

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

All SAEs must be followed to resolution or stabilization.

BMS will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320.

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. 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.

All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of dosing.

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 electronic) as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the 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 at least 5 half-lives after product administration, the investigator must immediately notify the Sponsor or designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in 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). Please call the Sponsor or designee within 24 hours of awareness of the pregnancy.

The investigator must immediately notify the Sponsor or designee of this event and complete and forward a Pregnancy Surveillance Form to Sponsor or designee within 24 hours of awareness of the event 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 Sponsor or designee. In order for BMS to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details.).

6.6 Potential Drug Induced Liver Injury (DILI)

Hepatotoxicity, such as transaminase elevations and hepatitis, has been identified as an important risk for nivolumab.

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:

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

   AND

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

   AND

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

A hepatic AE management algorithm that has been established (Appendix 3) and applied across the nivolumab program remains appropriate for managing drug-induced liver injury (DILI) cases. The experience to date shows that hepatic AEs, including possible DILI cases, were manageable using the established management algorithm and thus do not meaningfully alter the benefit/risk of nivolumab in the advanced malignancy populations.

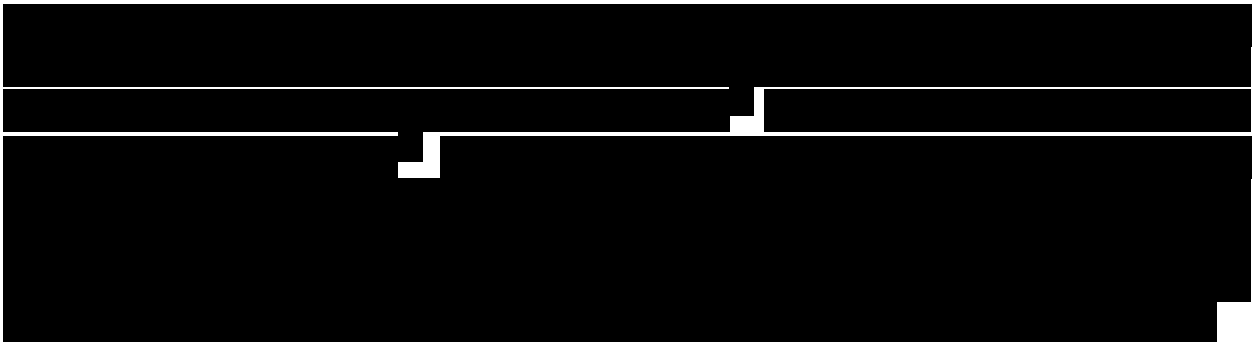
6.7 Other Safety Considerations

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

A Steering Committee comprised of trial investigators, trial statisticians, and BMS physicians will be created to design the trial and govern the trial's conduct, scope, and execution. No DMC will be formed for this trial. The oncology therapeutic area of BMS has primary responsibility for overall design and conduct of the study. Decisions regarding the study protocol will be made by the sponsor upon consultation with the steering committee.

8 STATISTICAL CONSIDERATIONS



Overview: This is a Phase 2 single-arm clinical trial that investigates nivolumab across multiple cancer types. At least 25 tumor types (groups) will be considered. If additional groups are identified in the course of the trial, they will be enrolled and will be included within the statistical analysis provided reasonable estimates of the control response rates can be identified. The trial is designed to estimate the underlying ORR of nivolumab in each tumor type (πg). Supporting secondary objectives include the duration of response, TTR, CBR, OS, and safety. All subjects will receive nivolumab.

A hierarchical model that borrows information across tumor subgroups will be used to strengthen the overall evidence within each subgroup. Using the hierarchical model, both continuous monitoring for futility and success will be undertaken throughout the study.

Regularly scheduled trial update analyses occur at most every 4 weeks. At each of these analyses, a Bayesian hierarchical model is fit across the data in all cohorts. For each cohort we determine the Bayesian posterior probability that the treatment effect in that cohort (treatment compared to historical control) is greater than 0 (eg, that treatment is better than control). Formally, if θ_g is the true log odds treatment effect for cohort g, we compute $Pr(\theta_g>0 \mid data)$ for each cohort g. At the regularly scheduled trial update analyses, each cohort may stop enrollment for success or futility. If a cohort stops enrollment, subjects currently in the cohort are all still followed to their primary endpoint.

Separate final analyses will be conducted for each cohort. A final analysis for a group will occur after enrollment in that group is complete and after all subjects in that group have at least 28 weeks follow-up. Once a group is stopped early for futility, the group will not be re-opened for further enrollment. The final analysis for a cohort declares success if the Bayesian posterior probability that the treatment effect in that cohort (treatment compared to historical control) is above 80%. For example, cohort g will be declared a success at cohort g's final analysis if $Pr(\theta_g>0 \mid data) > 0.80$. This posterior probability will incorporate the entire dataset at the time of analysis through the Bayesian Hierarchical Model.

Statistical Hypotheses: Let Yi be the response indicator for the ith subject. Define πg = Pr(Yi = 1 | gi = g) as the underlying probability of response for group g for the experimental treatment and Rg as the assumed probability of response for group g within the (historical) control population. Transformation to the logit scale is applied for modeling purposes. Let θg be the mean log odds treatment effect, ie,

$$\theta_g = log\ (\pi_g/(1-\pi_g)) - log\ (R_g/(1-R_g)).$$

Thus, θg is the logistic regression coefficient for the treatment within tumor group g. The primary analysis is a set of group specific tests of θg>0 (equivalently, πg > Rg) meaning that the treatment is better than the assumed control rate within that group. Thus, the following hypotheses are tested for each tumor group g:

$$H0g : \theta g \leq 0,$$

$$H1g : \theta g > 0.$$

The assumed control ORRs (Rg) vary by group and are provided in the Table 8-1 below.

Table 8-1: Historical Control ORRs

Group Index	Tumor Type	Assumed Control ORR (R_g)
1	Anal Cancer (squamous cell histology)	15%
2	Biliary Tract Cancer (includes nonresectable disease), intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer, and ampullary carcinoma	10%
3	Carcinoid after SSAs (Ki67 < 20%)	7.5%
4	Squamous Cell Cancer of the Cervix (exocervix), Squamous Cell Cancer of the Vagina	20%
5	Endometrial Cancer (after primary treatment including RT). Subjects with tumors > 10% estrogen receptor positive pathology in the primary tumor are excluded.	20%
6	Non-squamous Cell Cancer of the Head and Neck (including Cancer of the Salivary Gland, Adenoid Cystic Carcinoma)	10%
7	Histiocytoses (including Erdheim Chester Disease [macrophage disorder], Langerhans Cell Histiocytosis [LCH, dendritic cell disorder]	15%
8	Lynch Syndrome Associated Cancers (excluding HNPCC)	12.5%
9	Medullary Thyroid Cancer (after TKI [vandetanib or cabozantinib])	20%
10	Merkel Cell Carcinoma (includes unresectable disease)	15%
11	Mesothelioma	10%
12	Nasopharyngeal Carcinoma	17.5%
13	Neuroendocrine Tumors (poorly differentiated, Ki67 > 20%)	10%
14	Neuroendocrine Tumors (well to moderately differentiated) after SSAs or everolimus, including insulinomas	15%
15	Non-Lung Small Cell Carcinoma (includes Small Cell Carcinoma of the ovary of pulmonary or hypercalcemic type)	10%
16	Penile Cancer	15%
17	Rare Women's Cancers: Clear Cell (> 50% clear cell by pathology)	5%
18	Soft-Tissue Sarcoma (including Liposarcoma, Leiomyosarcoma), Malignant	10%

Table 8-1: Historical Control ORRs

Group Index	Tumor Type	Assumed Control ORR (R_g)
	Peripheral Nerve Sheath Tumor, NF-1	
19	Testicular Cancer (chemotherapy resistant disease or relapsed within 2 years of primary therapy)	10%
20	Thymic Carcinoma or Invasive Thymoma	10%
21	Thyroid Cancer (papillary or follicular), after failing RAI and approved kinase inhibition [lenvatinib]	15%
22	Thyroid Cancer: anaplastic first-line. In BRAF V600e positive subjects, investigators may administer nivolumab after vemurafenib.	5%
23	Uterine Sarcoma (excluding endometrial stromal sarcoma)	15%
24	Vulvar Cancer (post vulvectomy, cisplatin and radiotherapy)	15%
25	Adenoid Cystic Carcinoma	10%

8.1 Sample Size Determination

The maximum overall sample size across all tumor groups is 350 subjects. In addition, the maximum permitted sample size per group is 25 subjects, although a group with high posterior probability of success may be permitted a larger sample size at Sponsor discretion. Some groups will enroll more subjects than others. Simulation studies were conducted to evaluate the performance of the analysis under various assumptions for the distribution of true underlying ORRs across the tumor types. Operating characteristics including power and type I error were assessed.

When the treatment effects are similar across all tumor types, estimation efficiencies, due to borrowing, result in strong trial performance. When all groups are in truth effective, the individual groups generally exhibit power between 86.8% and 98.0%, under the scenario of odds ratio improvement of 3. When all groups are ineffective, the individual groups have between a 2.1% and 9.5% chance of mistakenly declaring group success. In addition, the global type I error (proportion of trials that declare at least 1 group successful when none is effective) is controlled at 0.539. Full presentation and discussion of the simulation parameters, corresponding simulation results, and example trials are included in the Appendix 1.

8.2 Populations for Analyses

- All enrolled subjects: all subjects who signed an informed consent form and were registered into the IVRS.
- All treated subjects: all subjects who received at least 1 dose of nivolumab.

[redacted]

8.3 Endpoints

8.3.1 Primary Endpoint

ORR is defined as the number of participants with a best overall response of confirmed CR or PR divided by the number of all treated participants. Best overall response is defined as the best response designation, as determined by investigator, recorded between the date of first dose and the date of objectively documented progression per tumor-specific response criteria or the date of subsequent therapy, whichever occurs first. For participants without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination.

8.3.2 Secondary Endpoints

8.3.2.1 Duration of Response

DOR is defined as the time from first confirmed response (CR or PR) to the date of the first documented tumor progression as determined by investigator or death due to any cause, whichever occurs first. Participants who start subsequent therapy without a prior reported progression will be censored at the last evaluable tumor assessments prior to initiation of the subsequent anticancer therapy. Participants who die without a reported prior progression will be considered to have progressed on the date of their death. Participants who neither progress nor die will be censored on the date of their last evaluable tumor assessment.

8.3.2.2 TTR

TTR is defined as the time from first dosing date to the date of the first confirmed response, as assessed by investigator.

8.3.2.3 CBR

CBR is defined as the number of participants with a best overall response of confirmed CR or PR, or stable disease divided by the number of all treated subjects.

8.3.2.4 Overall survival

OS is defined as the time from the first dosing date to the date of death. A participant who has not died will be censored at last known date alive. OS rate at 1 year is measured as the survival rate at 1 year from Kaplan-Meier curve of OS.

8.3.2.5 Safety and Tolerability

Safety and tolerability will be measured by the incidence of deaths, adverse events, serious adverse events, adverse events leading to discontinuation, immune-mediated adverse events, select adverse events, adverse events leading to dose delay, and specific laboratory abnormalities (worst grade) in each tumor group. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographics and baseline disease characteristics including age, sex, race, weight, baseline disease diagnosis, and medical condition will be summarized using descriptive statistics by disease type.

8.4.2 Efficacy Analyses

The final analysis for each group declares success if the Bayesian posterior probability that the treatment effect in that group (treatment compared to control) is above 80%. Formally:

$$Pr(\theta\pi_g > R_g) > 0.80.$$

DOR, TTR, CBR, and overall survival at 1 year will also be provided for each group.

8.4.3 Safety Analyses

Safety analyses will be performed by tumor group in all treated subjects. Descriptive statistics of safety will be presented using NCI CTCAE version 4.0. All AEs, drug-related, AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v4.0 criteria by system organ class and MedDRA preferred term. On-study lab parameters including hematology, chemistry, liver function, thyroid function, and renal function will be summarized using worst grade per NCI CTCAE v4.0 criteria.

[redacted]

8.4.6 Outcomes Research Analyses

Not applicable.

8.4.7 Other Analyses

Not applicable.

8.5 Interim Analyses

Interim Monitoring will be conducted, at most, every 4 weeks. At each analysis, the groups will be evaluated for futility and success by comparing posterior quantities for the overall response rate to pre-specified early stopping criteria based on the hierarchical model based on population of subjects with at least 28 weeks of follow-up. The design may limit the maximum number of subjects per group to 25 subjects within the trial. Available resources will be used more effectively by enrolling subjects in groups that offer greater promise of efficacy. Internal assessment of the program will also take into consideration for the final decision of early stopping.

Early Futility: If there is a sufficiently low probability (20%) that the ORR in a group exceeds the historical rate R_g by at least 10%, then the group will stop enrollment early for futility. Formally, enrollment will stop early for futility if:

$$Pr(\pi g > Rg+0.10) < 0.20$$

A group is only eligible for early stopping for futility once a minimum of 5 subjects have been evaluated for ORR in that group.

Early Success: If there is a sufficiently high probability (95%) that the ORR in a group exceeds the historical rate Rg, then the group may stop enrollment early for success. Formally, enrollment may stop early for success if:

$$Pr(\pi g > Rg) > 0.95$$

A group is only eligible for early stopping for success once a minimum of eligible 8 subjects have been evaluated for ORR in that group.

8.5.1 Pause Rule

The Bayesian hierarchical model incorporates information from all cohorts into each analysis, however the primary driver of the analysis for each cohort is the data from that specific cohort. Thus, it is important that enough data is available in each cohort where possible. To minimize the possibility of excessive enrollment imbalance between the groups, enrollment may be paused in a cohort at any time where 12 or more patients have enrolled, but have not had, yet, an opportunity to complete their 28 week evaluation visit (dropouts are not included in this calculation if they have no post-baseline tumor assessment). The pause may continue until at least 75% of the subjects in the cohort have reached 28 weeks follow-up or have discontinued due to disease progression.

In addition, based on considerations such as emerging external data, cohorts may be paused by Sponsor decision in consultation with Steering Committee.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects. If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s), the deviation or change will be submitted as soon as possible to:

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

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority, must be sent to BMS. 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 or designee representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

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

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

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

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.

9.2 Records

9.2.1 Records Retention

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

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

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

9.2.2 Study Drug Records

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

If...	Then...
Supplied by BMS (or its vendors):	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 (e.g., lost, wasted) amount destroyed at study site, if applicable amount returned to BMS retain samples for bioavailability/bioequivalence, if applicable

If...	Then...
	dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

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

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

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

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

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:

- Study Steering Committee chair or their designee

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

10 GLOSSARY OF TERMS

Table 10-1: Glossary of Terms

Term	Definition
Clinical Benefit Rate	**Percentage of subjects who have achieved complete response, partial response, and stable disease to a therapy**
Lynch Syndrome associated malignancies.	**Subjects without a diagnosis of Lynch Syndrome, but with variations in the mismatch repair genes MLH1, MSH2, MSH6, PMS2, or germline deletions in the EPCAM gene** **or** **Subjects in whom molecular testing demonstrates the presence of MSI and/or abnormal expression of MMR proteins on IHC testing of tumors, without presence of characteristic germline mutations seen in LS.**
Pseudoprogression	Pseudoprogression is paradoxical tumor growth which mimics tumor progression. Imaging and corresponding signs and symptoms identify pseudoprogression.

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	aminotransaminases
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CI	confidence interval
CNS	central nervous system
CRC	Colorectal cancer
CRF	case report form (paper or electronic)
eCRF	electronic case report form
CT	computed tomography
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
eg	exempli gratia (for example)
FDA	Food and Drug Administration
FFPE	formalin fixed paraffin embedded
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVab	hepatitis C virus antibody
HIV	human immunodeficiency virus
HNPCC	Hereditary nonpolyposis colorectal cancer
HR	heart rate; hazard ratio

Term	Definition
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IU	international unit
IV	intravenous
LDH	lactate dehydrogenase
LFT	liver function test
mg	milligram
min	minute
mL	milliliter
MMR	mismatch repair
MRI	magnetic resonance imaging
µg	microgram
N	number of subjects or observations
N/A	not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIMP	non-investigational medicinal products
ORR	Objective response rate
OS	overall survival
PD-L1	Programmed death-ligand 1
RECIST	Response Evaluation Criteria in Solid Tumors
RR	respiration rate
SAE	serious adverse event
t	temperature
TSH	thyroid stimulating hormone
WBC	white blood cell

Term	Definition
WOCBP	women of childbearing potential

[redacted]

APPENDIX 2 ECOG PERFORMANCE STATUS

Table 1: ECOG Performance Status

ECOG PERFORMANCE STATUS	
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

APPENDIX 4 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) 1.1

1 EVALUATION OF LESIONS

Changes in tumor measurements and tumor responses will be assessed by the investigator using the RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) criteria. (Eisenhauer, et al 2009.)

Source: Eisenhauer et al New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1), European Journal of Cancer, 2009, Vol. 45, p 228-247

1.1 Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable tumor lesion. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

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

1.2 Measurable lesions

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

. 10 mm by CT/MRI scan - (CT/MRI scan slice thickness no greater than 5 mm)

. 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)

 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). At baseline and in follow-up, only the ***short*** axis will be measured and followed.

1.3 Non-measurable lesions

 All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions.

 Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that in not measurable by reproducible imaging techniques.

1.4 Special considerations regarding lesion measurability

1.4.1 Bone lesions

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

1.4.2 Cystic lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

1.4.3 Lesions with prior local treatment

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

1.5 Specifications by methods of measurements

1.5.1 Measurement of lesions

All measurements should be recorded in metric notation (mm). All baseline evaluations should be performed as close as possible to the beginning of the treatment.

1.5.2 Method of assessment

The **same method of assessment and the same technique should be used** to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

1.5.2.1 CT/MRI scan

CT/MRI is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT/MRI scan is based on the assumption that CT/MRI slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

1.5.2.2 Chest X-ray

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

1.5.2.3 Clinical lesions

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As previously noted, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

1.5.2.4 Ultrasound

Ultrasound is ***not*** useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

1.5.2.5 Endoscopy, laparoscopy

The utilization of these techniques for objective tumor evaluation is ***not*** advised.

1.5.2.6 Tumor markers

Tumor markers ***alone*** cannot be used to assess objective tumor response.

1.6 Baseline documentation of 'target' and 'non-target' lesions

1.6.1 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.

Target lesions should be selected on the basis of their **size** (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to ***reproducible repeated measurements*.**

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 below, 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.

1.6.2 Lymph nodes

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.

Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

1.7 Non-target lesions

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'.** In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

1.8 Tumor Response evaluation

1.8.1 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.

1.8.2 Special notes on the assessment of target lesions

1.8.2.1 Lymph nodes

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. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

1.8.2.2 Target lesions that become 'too small to measure'

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If the radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5 mm.

However, when such a lesion becomes difficult to assign an exact measure to then:

- 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: in case of a lymph node believed to be present and 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).

1.8.2.3 Target 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.
- 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'.

1.9 Evaluation 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 (< 10 mm 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* of existing non-target lesions. (*Note:* the appearance of one or more new lesions is also considered progression).

1.9.1 Special notes on assessment of non-target lesions

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

1.9.1.1 When the subject also has measurable disease

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status.

1.9.1.2 When the subject has only non-measurable disease

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

- A modest ‘increase’ in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable) a useful test that can be applied when assessing subjects 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: i.e. 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 subject should be considered to have had overall PD at that point.

1.9.1.3 Tumor markers

Tumor markers *alone* cannot be used to assess objective tumor responses. If markers are initially above the upper normal limit, however, they must normalize in order for a subject to be considered as having attained a complete response.

1.10 New lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: i.e. 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 subject’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 subject who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered which reveals metastases. The subject’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.*

1.10.1 FDG-PET evaluation

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of the qualitative assessment 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:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up might be a sign of PD based on a new lesion. However, other reasons for newly detected lesions with increased FDG-PET uptake, such as inflammatory lymphnodes, should be taken into consideration.
- 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 positive 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.
  - Other reasons for newly detected lesions with increased FDG-PET uptake, such as inflammatory lymphnodes, should be taken into consideration.

1.11 Response Criteria

1.11.1 Time point response

A response assessment should occur at each time point specified in the protocol.

For subjects who have **measurable disease** at baseline Table 2 provides a summary of the overall response status calculation at each time point.

Table 2: Time point response: subjects 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

Table 2: Time point response: subjects with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE =not evaluable.

For subjects who have **non-measurable** (therefore non-target) disease only, Table 3 is to be used.

Table 3: Time point response: Subjects 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

[a] 'Non-CR/non-PD' is preferred over 'stable disease' 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.
CR = complete response, PD = progressive disease, and NE = not evaluable.

1.11.2 Missing assessments and not evaluable designation

When no imaging/measurement is done at all at a particular time point, the subject is **not evaluable (NE)** at that time point. If only a subset of lesion measurements are made at an assessment, the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not have changed the assigned time point response.

1.11.3 Confirmation of Scans and External Evaluation

- **Verification of Response:** Confirmation of response (CR or PR) is required. Confirmed CR or PR will be claimed only if the criteria for each are met at a subsequent timepoint (minimum 4 weeks after criteria for an objective response are first met).
- **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 not to have progressive disease per RECIST 1.1.
- **External Evaluation of scans:** For all subjects, BMS will request the transfer of anonymized scans for a BMS internal or external evaluation through a third party. For tumor types where data from study CA209-032 will potentially be used for future NDA submissions, BMS will request the transfer of anonymized scans from all subjects with this tumor type for a BMS internal or external evaluation through a third party.

1.12 Best overall response: All time points

The best overall response is determined once all the data for the subject is known. It is defined as the best response designation, as determined by the investigator, recorded between the date of first treatment and the date of objectively documented progression per RECIST 1.1 or the date of subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. The subject'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.

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point (minimum 4 weeks after criteria of objective response are first met). In this circumstance, the best overall response can be interpreted as in Table 4.

Table 4: Best overall response when confirmation of CR and PR is required

Overall response	Overall response	BEST overall response
First time point	**Subsequent time point**	
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD

Table 4:	Best overall response when confirmation of CR and PR is required	
Overall response	**Overall response**	**BEST overall response**
First time point	**Subsequent time point**	
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable.

[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 subject 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.

For purposes of this study, the minimum scan time from baseline for determination of SD will be 6 weeks.

1.13 Duration of response

1.13.1 Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

1.13.2 Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

1.13.3 Immune related Response Criteria

Immune related response criteria using unidimensional measurements may be used to describe tumor shrinkage following RECIST 1.1 defined disease progression Appendix 4. The methodology is the same as described above for RECIST 1.1 except:

- New lesions do not automatically denote disease progression
- The measurement of longest diameter of new measurable lesions are in included in the sum of the measurements of the original target lesions.

Best immune related responses, for subjects who have progression followed by tumor shrinkage are classified as irCR (disappearance of all lesions) or irPR (≥ 30% reduction from baseline).

APPENDIX 5 NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION

Class I. Patients with cardiac disease, but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.

Class III. Patients with marked limitation of physical activity. They are comfortable at rest. Less that ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.

Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

APPENDIX 6 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

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

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

Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Unacceptable Methods of Contraception*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide

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

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

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

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

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

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 6.4 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting

APPENDIX 7 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

[redacted]

[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Cover page	Changed the Medical Monitor and associated contact information.	[redacted]
Synopsis, Investigational Product; Section 3.1, Study Design and Duration; Section 3.2, Post-study Access to Therapy; Section 4, Study Drug; Section 4.5.4, Nivolumab Treatment Beyond Disease Progression	Added 24 month maximum duration	[redacted]
Synopsis, Research Hypothesis; Synopsis, Primary Objective; Section 1.2, Research Hypothesis; Section 1.3.1, Primary Objectives; Section 8.3.1, Primary Endpoint	Changes the primary objective from clinical benefit rate to investigator-assessed objective response rate.	[redacted]
Synopsis, Secondary Objectives; Section 1.3.2, Secondary Objectives;	Added duration of response and time to response.	[redacted]
	Removed characterizing disease progression.	[redacted]
Synopsis, Schematic; Section 3.1, Study Design and Duration	Aligned the frequency of scans and the primary objective to reflect the changes made to the protocol.	[redacted]
Synopsis, Study Population, Key Inclusion Criteria; Section 3.3.1, Inclusion Criteria	Added adenocarcinoma of the small bowel and adrenocortical carcinoma to the possible tumor types for inclusion.	[redacted]
	Removed option for measurable disease by disease-specific criteria	[redacted]
	Provided additional information regarding required previous treatment.	[redacted]
	Changed the age of tissue sample from 4 months to 3 months.	[redacted]
Synopsis, Study Population, Key Exclusion Criteria; Section 3.3.2, Exclusion Criteria	Added adenocarcinoma of the colon, prostate, or rectum; gastrointestinal stromal tumor; meningioma; peritoneal carcinoma; primary CNS lymphoma, squamous carcinoma of the head and neck; squamous carcinoma of the skin; and carcinoma of unknown primary to	[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	the excluded malignancies. Removed gliomas.	
Synopsis, Study Assessments; Section 1.1.3, Rationale for Clinical Assessments at 28 Weeks; Table 5.1-1, Flow Chart/Time and Events Schedule, Table 5.1-2, On-treatment Assessments - Nivolumab 240mg/Q2W CA209627	Changed the evaluation of the response at 16 weeks to 28 weeks. The actual assessment timing have not changed.	[redacted]
Synopsis, Primary Endpoint; Secondary Endpoints.	The primary and secondary objectives were updated to align with the changes made to the primary and secondary objectives.	[redacted]
Synopsis, Analysis	The analyses were revised.	[redacted]
Section 1.1.6, Duration of Treatment with Nivolumab	Section was added.	[redacted]
Section 3.1, Study Design and Duration	Removed the sentence about survival data being collected for 1 year after the first nivolumab dose.	[redacted]
Section 3.3.1, Inclusion Criteria	Changed duration of contraception use from 23 weeks to 5 months for women and 31 weeks to 7 months for men.	[redacted]
Section 3.3.2, Exclusion Criteria; Section 3.4.1, Prohibited and/or Restricted Treatments	Added a criterion to exclude treatment with botanical preparations	[redacted]
Section 4, Study Design	Added directions to flush the infusion line after administration.	[redacted]
Section 4.4, Method of Assigning Subject Identification	Clarified that only year of birth is collected in Germany.	[redacted]
	Provided additional details regarding tumor tissue collection.	[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 4.5, Selection and Timing of Dose for Each Subject	Added additional details regarding the dosing of the every 2 weeks regimen and the every 4 week regimen.	[redacted].
Section 4.5.1, Dose Delay Criteria	Updated the dose delay criteria	[redacted] a.
Section 4.5.2, Criteria to Resume Treatment	Updated the criteria to resume treatment	[redacted]
Section 4.5.3, Treatment Discontinuation Criteria	Updated the criteria to discontinue treatment.	[redacted]
Section 4.5.4, Nivolumab Treatment Beyond Disease Progression	Language was revised	[redacted]
Section 5.1, Flow Cart/Time and Events Schedule; Table 5.1-1, Screening Procedural Outline	Added a row for Serious Adverse Event Collection	[redacted]
	Changed the age of tissue samples from 4 months to 3 months	[redacted]
Section 5.1, Flow Cart/Time and Events Schedule; Table 5.1-2, On-treatment Assessments - Nivolumab 240mg/Q2 weeks CA209627	Added thyroid function testing and pregnancy testing beyond Cycle 1.	[redacted]
	Added notes regarding the timing of tumor assessments at Week 16 and 28. The frequency of the assessments did not change.	[redacted]
Section 5.1, Flow Cart/Time and Events Schedule, Table 5.1-4, Follow-up Assessments - All Subjects CA209627	Added vital signs	[redacted]
Section 5.3, Safety Assessments	Removed requirement for screening assessments to be performed within 28 days.	[redacted]
Section 5.3.1, Imaging Assessments for the Study	Added details regarding the collection and review of the Blinded Independent Central Review	[redacted]
Section 5.4.1, Objective Response Rate	Provided definition for the new primary endpoint.	[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.4.2, Secondary Assessments	Provided the new secondary endpoints and the location of the definitions.	[redacted]
Section 5.6.1, Collection of Tumor Tissue and Blood for Biomarker Analysis	Changes the age of tumor tissue sample to 3 months	[redacted]
Section 6, Adverse Events	Added text to caution against introducing bias.	[redacted]
	Added the definition of immune-mediated adverse events	[redacted]
Section 8, Statistical Considerations; Section 8.1, Sample Size Determination	Change in primary endpoint and provided additional detail on the analysis.	[redacted]
Section 8.2, Populations for Analysis	Removed the all evaluable analysis and removed the table of historical control benefit rates.	[redacted]
Section 8.3.2.1, Duration of Response; Section 8.3.2.2, TTR, Section 8.3.2.3, CBR, Section 8.3.2.4, Overall Survival.	Sections were added.	[redacted]
Section 8.3.2.5, Safety and Tolerability	Clarified how safety and tolerability would be presented.	[redacted]
[redacted]	[redacted]	[redacted]
Section 8.4, Analysis	Interim Monitoring was moved to Section 8.5, Interim Analyses.	[redacted]
Section 8.4.2, Efficacy Analysis	Section was revised.	[redacted]
Section 8.4.3, Safety Analyses	More detail was added.	[redacted]
Section 8.5, Interim Analyses	Incorporates text originally appearing in Section 8.4.	[redacted]
Section 8.5.1, Pause Rule	Section was added.	[redacted]
Appendix 1, Statistical Analysis and Modeling	Changed primary analysis to ORR	[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 2	ECOG Scale, Management Algorithms, RECIST Criteria, and New York Heart Association (NYHA) Functional Classification were separated into individual appendices.	[redacted]
	Removed Response Criteria for Primary Central Nervous System	[redacted]
Appendix 3	Management Algorithms were updated.	[redacted]
Appendix 6, Methods of Contraception	Updated the methods of contraception.	[redacted]
All	Minor formatting and typographical corrections	[redacted]