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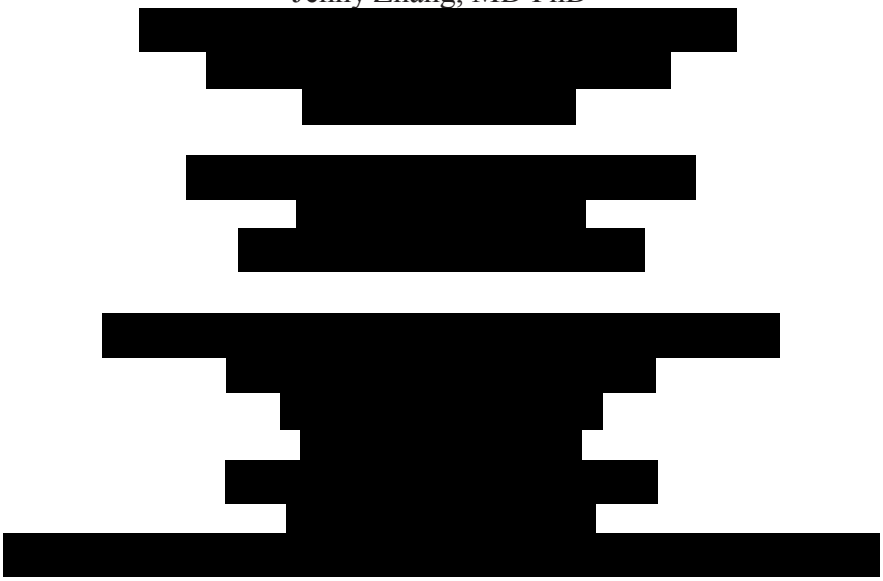
CLINICAL PROTOCOL CA209577

A Randomized, Multicenter, Double Blind, Phase III Study of Adjuvant Nivolumab or Placebo in Subjects with Resected Esophageal, or Gastroesophageal Junction Cancer

(**CheckMate 577**: **CHECKpoint** pathway and nivolu**M**ab clinical **T**rial **E**valuation 577)

Revised Protocol Number: 03
Administrative Letter 03

Study Director/Medical Monitor
Jenny Zhang, MD PhD



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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 03	06-Jun-2019	• Added exclusion criteria, on-study, and post-study requirements regarding live/attenuated vaccines. • Updated language regarding hepatitis B or C virus exclusion criteria. • Updated language for WOCBP in Section 3.3.3 and Appendix. • Moved OS from co-primary endpoint to secondary endpoint. • [redacted]. • Added language regarding monitoring for infusion-related reactions. • Added language regarding dose interruptions, delays, and discontinuation. • Added myocarditis to Grade 3 non-skin drug-related adverse events (AEs). • Removed AE assessment from survival follow-up visits. • Clarified language regarding diagnosis of recurrence. • Added option for review of reports by a blinded independent central review at a later date. • Replaced original sample-size determinations based on co-primary endpoints. • Added new section to provide data for the assumptions regarding DFS and OS in the control arm. • Added new section to provide data for the assumed treatment effect. • Added new section to update sample size and power estimates based on new assumptions. • Updated to provide new triggers and timing for the interim and final analyses. • Added explanation of how timing of DFS/OS analyses will be adjusted to maintain a strong control of type I error. • Moved discussion of addressing family-wise error rate across DFS and OS analyses at interim and final analyses to a new section. • Moved error-rate discussion to new section and removed mention of OS as a primary endpoint. • Added two separate sections to address each the DFS and OS analyses. • Made multiple updates to bring protocol in line with current program standards.
Administrative Letter 03	01-Aug-2017	Medical Monitor information updated
Revised Protocol 02	04-May-2017	Incorporates Amendment 06 and Administrative Letter 02

Document	Date of Issue	Summary of Change
Amendment 06	04-May-2017	The main purpose of the amendment was to modify the inclusion criteria to increase the time between complete resection and randomization from 4-14 weeks to 4-16 weeks. Other changes incorporated included: • Revised the term 'PD-L1 expression,' 'PD-L1 expression level,' and 'PD-L1 evaluable status' to 'PD-L1 status' to account for the inclusion of patients where the PD-L1 results are indeterminate or non-evaluable. Updated the stratifications to account for the inclusion of patients with a PD-L1 result of indeterminate or non-evaluable. • Revised the estimated enrollment and study duration, time to achieve 455 disease-free survival (DFS) events, and time to achieve 330 deaths and 440 deaths based on the current subject accrual rate • Revised the maximum dose delay window to 42 days during Cycles 1-8 and 70 days during Cycles 9-17 • Revised the study design/schematic to remove the reference to 'distant' recurrence • Revised the screening window from 28 days to 49 days • Revised the study drug dosing window. For Cycles 1-8, subjects may have study drug administered up to 2 days before or 3 days after the scheduled dosing date. For Cycles 9-17, subjects may be dosed within a +/- 3 day window. • [redacted] • Revised the Flow Chart/Time and Events Schedule to resolve minor inconsistencies and to provide clarifications • Fixed typos and resolved minor inconsistencies
Administrative Letter 02	30-Nov-2016	To correct a formatting issue with the indenting of the bullets in protocol Section 4.5.2 (Dose Delay Criteria).
Revised Protocol 01	24-Aug-2016	Incorporates Amendment 05 and Administrative Letter 01
Amendment 05	24-Aug-2016	The main purpose the amendment was to: • Modify the nivolumab Dose Delay Criteria (Section 4.5.2), Criteria to Resume Treatment (Section 4.5.4), and Discontinuation of Subjects from Treatment (Section 4.5.5) criteria to align with the US Package Insert and EU Summary of Product Characteristics Other changes incorporated included: • Change the BMS Medical Monitor • Revised the study schematic

Document	Date of Issue	Summary of Change
		• Clarify that subjects will receive their randomized treatment (nivolumab or placebo) for the duration of the On-Treatment Period • Changed the term BMS and BMS Medical Monitor to Sponsor or designee • Clarified that a blinded independent central review may occur during or at the end of the trial • Increased the time from complete resection to randomization to 4-14 weeks • Specified the order of priority of the imaging modalities for this trial • Specified that adverse events will be documented for a minimum of 100 days after last dose of study drug • Specified that during the Follow-Up phase survival visits may be may be accomplished by in-person visit or phone contact • Revised certain Inclusion/Exclusion criterion • Updated the duration of contraception use for WOCBP and males subjects with female partners that are WOCBP • Removed the methods of contraception from protocol Section 3.3 • Removed reference to unblinded site staff and an unblinded site monitor • Added information regarding resuming dosing following resolution of an AE or immunosuppression tapering • Increased the number of tumor slides from the surgically resected specimen from 10 to 20 slides • Specified that 5 slides would be required for the optional tumor samples • Added albumin to the list of analytes required at the Screening Visit • Allowed for Total T3/T4 to be reported by the lab if free T3/T4 are not available based on site capabilities • Updated the On-Treatment Procedural Outline notes to reflect that assessments should be performed prior to dosing at the required Cycles • Removed reference to the plasma samples in the On-Treatment Procedural Outline table • Clarified that urinalysis is required at the Follow-Up visits if clinically indicated • [redacted] • Specified the collection timepoints for the Outcomes Research Assessments during the On-Treatment Period • Added language that allows for additional pregnancy testing to be performed during the Follow-Up Period • Separated the Safety Assessment section of the protocol into sub-sections based on the study phase • Included information regarding pulmonary adverse events and treatment • [redacted] • Added information regarding immune-mediated adverse events • Added information regarding AE and SUSAR reporting • Added information that a female partner of a male subject must sign an informed consent form to disclose information regarding a pregnancy

Document	Date of Issue	Summary of Change
		• Updated terminology used for the statistical censoring scheme • Updated the abbreviations list • Revised the Appendix 2 (Safety Management Algorithms) • Added Appendix 3 (Women of Childbearing Potential and Methods of Contraception) • Other minor changes incorporated into this amendment include changes in document names, study materials that will be provided to sites, removal of duplicate statements, revisions to section numbering, and formatting changes
Administrative Letter 01	10-Feb-2016	• Fixed the protocol title • Removed the reference to neck as an anatomical imaging area for the CT/MRI scan • Updated a section number
Original Protocol	06-Jan-2016	Not applicable

SYNOPSIS

Clinical Protocol CA209577

Protocol Title: A Randomized, Multicenter, Double Blind, Phase III Study of Adjuvant Nivolumab or Placebo in Subjects with Resected Esophageal, or Gastroesophageal Junction Cancer

(**CheckMate 577: CHECKpoint** pathway and nivolu**M**ab clinical **T**rial **E**valuation 577)

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

Subject will be randomized to nivolumab (BMS-936558) or placebo monotherapy. Subjects randomized to nivolumab will receive 240 mg nivolumab administered as an IV infusion over 30 minutes every 2 weeks for 16 weeks (8 doses) followed by 480 mg nivolumab administered as an IV infusion over 30 minutes every 4 weeks beginning at Week 17 (2 weeks after the 8th dose). Subjects randomized to placebo will receive placebo administered as an IV infusion over 30 minutes every 2 weeks for 16 weeks (8 doses) followed by placebo as an IV infusion over 30 minutes every 4 weeks beginning at Week 17 (2 weeks after the 8th dose).

Treatment will continue until disease recurrence, unacceptable toxicity, or subject withdrawal of consent with a maximum of 1-year total duration of study medication.

Study Phase: Phase 3

Research Hypothesis:

In subjects with resected esophageal (EC) and gastroesophageal junction (GEJ) cancer, the administration of nivolumab will improve overall survival (OS), Disease-free survival (DFS) or both compared with placebo.

Objectives:

Primary objectives:

- To compare DFS of nivolumab versus placebo in subjects with resected EC or GEJ cancer.

Secondary objectives:

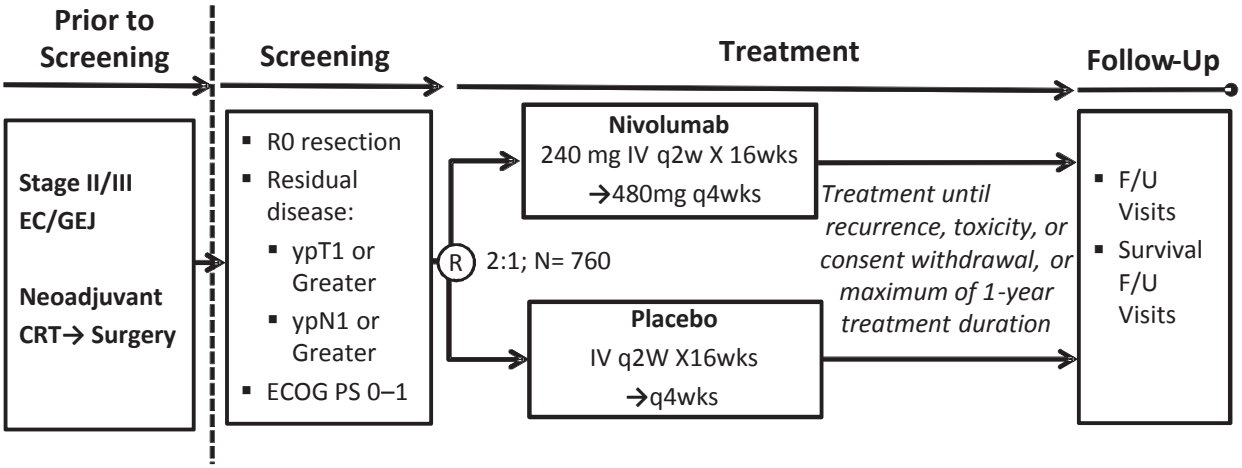
- To compare OS of nivolumab versus placebo in subjects with resected EC or GEJ cancer.
- To evaluate 1, 2, and 3 year survival rates of nivolumab versus placebo in subjects with resected EC or GEJ cancer.

[redacted]

[redacted]

Study Design:

This is a phase 3, randomized, double-blind, placebo controlled study of adjuvant nivolumab in subjects with resected esophageal cancer (EC), or gastroesophageal junction (GEJ) cancer who have received chemoradiotherapy (CRT) followed by surgery.



After CRT followed by surgery, subjects will sign the informed consent form. Subjects whose tumors do not achieve pathological complete response (non-pCR) will be randomized in a blinded fashion 2:1 ratio to two arms between nivolumab (BMS-936558) or placebo monotherapy. Subjects randomized to nivolumab will receive 240 mg nivolumab administered as an IV infusion over 30 minutes every 2 weeks for 16 weeks (8 doses) followed by 480 mg nivolumab administered as an IV infusion over 30 minutes every 4 weeks beginning at Week 17 (2 weeks after the 8th dose). Subjects randomized to placebo will receive placebo administered as an IV infusion over 30 minutes every 2 weeks for 16 weeks (8 doses) followed by placebo as an IV infusion over 30 minutes every 4 weeks beginning at Week 17 (2 weeks after the 8th dose).

The treatment will be given until disease recurrence, unacceptable toxicity, or subject withdrawal of consent with a maximum of 1-year total duration of study medication.

Stratification factors:

1) PD-L1 status (≥ 1% vs. < 1% or indeterminate or non-evaluable)
2) Pathologic lymph node status (positive ≥ ypN1 vs. negative ypN0)
3) Histology (squamous vs. adenocarcinoma)

Study Population: Subjects must meet all eligibility criteria specified in Section 3.3 of the protocol, including the following:

Key Inclusion Criteria

- All subjects must have Stage II or Stage III (per AJCC 7th edition) carcinoma of the esophagus or gastroesophageal junction and have histologically confirmed predominant adenocarcinoma or squamous cell carcinoma esophageal or gastroesophageal junction cancer at the time of initial diagnosis.
- Subjects must complete pre-operative chemoradiotherapy followed by surgery prior to randomization. Platinum based chemotherapy should be used. Chemotherapy and radiation regimens can be followed as local standards of care per NCCN or ESMO guidelines.
- Subject must have complete resection (R0), have been surgically rendered free of disease with negative margins on resected specimens defined as no vital tumor present within 1 mm of the proximal, distal, or circumferential resection margins. Subject must have residual pathologic disease, i.e. non-pathologic complete response (non-pCR) of their EC or GEJ, with at least ypN1 or ypT1 listed in the pathology report of resected specimens. For any cases of uncertainty (e.g. ypNx), it is recommended that the Medical Monitor or designee be consulted prior to randomization. The pathology reports of detectable lesion(s) confirming malignancy must be reviewed, dated, and signed by the investigator prior to randomization.
- Complete resection must be performed in a window of 4-16 weeks prior to randomization.
- ECOG performance status score of 0 or 1.
- All subjects must have disease-free status documented by a complete physical examination and imaging studies within 4 weeks prior to randomization. Imaging studies must include CT/MRI scan of chest and abdomen.

- Tumor tissue from the resected site of disease must be provided for biomarker analyses. In order to be randomized, a subject must have a PD-L1 status classification (≥ 1%, < 1% or indeterminate or non-evaluable) as determined by the central lab. If insufficient tumor tissue content is provided for analysis, acquisition of additional archived tumor tissue (block and /or slides) for the biomarker analysis is required.

Key exclusion criteria

- Subjects with cervical esophageal carcinoma. Location of tumor as it relates to eligibility can be discussed with BMS medical monitor.
- Subjects who do not receive concurrent CRT prior to surgery. Subjects who only receive chemotherapy or only radiation prior to surgery are not eligible.
- Subjects with Stage IV resectable disease.
- Subjects with an active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

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

Study Drug for BMS-936558		
Medication	**Potency**	**IP/Non-IP**
Nivolumab	10 mg/ml	IP
placebo	-	IP

Study Assessments:

- Disease-free survival (DFS) is the primary endpoint of this study. Subjects will be assessed for recurrence (until distant recurrence) by CT or MRI as follows:
- Baseline assessment should be performed 4 weeks prior to the randomization.
- Subjects on treatment will be evaluated for recurrence every 12 weeks ± 7 days
- Subjects who discontinue treatment for reasons other than distant recurrence will continue to have surveillance assessments (until distant recurrence) every 12 weeks ± 7 days during the first year after randomization, every 12 weeks ± 14 days during the second year, after that

follow local standard in the range of 6-12 months between year 3 and year 5 with the last assessment at year 5.

OS will be followed continuously while subjects are on the study drug and every 3 months or more frequently as required via in-person or phone contact after subjects discontinue the study drug.

Statistical Considerations:

Sample Size: The sample size determination takes into consideration the comparison of the primary endpoint of DFS and the first secondary endpoint of OS between the 2 treatment arms.

The study will require approximately 760 subjects to be randomized at a 2:1 ratio to nivolumab and placebo and observations of at least 440 DFS events in order to achieve approximately 91% power to detect an average hazard ratio (HR) of 0.72 at a 2-sided alpha of 0.05. The sample-size determination accounts for 1 DFS interim analysis.

It is estimated that these 760 subjects will be accrued and randomized within 36 months from the first-patient first-visit.

Overall survival will be tested following the overall hierarchical testing procedure upon demonstration of superiority in DFS at either interim or final analyses for all randomized subjects.

With the sample size of 760, it is required to observe at least 460 OS events at the final OS analysis in order to achieve approximately 90% power to detect an average HR of 0.73 at a 2-sided alpha of 0.05. The power of the OS final analysis accounts for 2 OS interim analyses that occur at the same time as the DFS interim and DFS final analyses, respectively.

Endpoints:

Primary endpoints: DFS is the primary endpoint of this study.

Disease-Free Survival is time between randomization date and first date of recurrence or death, whichever occurs first. Recurrence is defined as the appearance of one or more new lesions, which can be local, regional, or distant in location from the primary resected site (by imaging or pathology whichever comes first). All deaths without prior recurrence will be included as DFS event - regardless of cause or of how long it has been since the last known disease evaluation. For subjects who remain alive and without recurrence, DFS will be censored on the date of last evaluable disease assessment.

Secondary endpoint: Overall survival and overall survival rates are secondary endpoints.

Overall Survival is time between the date of randomization and the date of death. For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive.

The overall survival rate at 1, 2, and 3 years is defined as the probability that a subject is alive at 1, 2, and 3 years, respectively, following randomization.

Analyses: DFS will be compared between treatment arms using a 2-sided log rank test, stratified by the 3 randomization stratification factors as recorded in Interactive Web Response System

(IWRS). The HR for DFS with its corresponding 2-sided 100 x (1 - adjusted α)% confidence intervals (CI) will be estimated via a stratified Cox model with treatment arm as the only covariate in the model.

DFS for each treatment arm will be estimated and plotted using the Kaplan-Meier (KM) product-limit method. Median survival time will be computed using the KM estimate and a 95% CI for the median will be computed based on a log-log transformation of the survivor function.

Overall survival will be estimated and plotted using the KM product-limit method for each treatment arm. Median survival time along with the 95% CI will be constructed based on a log-log transformed CI for the survival function. The HR for OS with its corresponding 2-sided 100x (1 - adjusted α)% CIs will be estimated via a stratified Cox model with treatment arm as the only covariate in the model.

Overall Survival will only be tested if superiority has been demonstrated in DFS. Overall Survival will be compared between treatment arms using a 2-sided log rank test, stratified by the 3 randomization stratification factors as recorded in IWRS.

Survival rate analysis will be carried out only for those time points which are mature enough by the time of the given database-lock. Point estimates will be provided using KM product-limit method. For each survival rate per treatment arm, 2-sided 95% CIs using log-log transformation will be computed.

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1.2 Research Hypothesis

In subjects with resected esophageal and gastroesophageal junction cancer, the administration of nivolumab will improve overall survival (OS), Disease-free survival (DFS) or both compared with placebo.

1.3 Objectives(s)

1.3.1 Primary Objective

- To compare disease-free survival (DFS) of nivolumab versus placebo in subjects with resected EC or GEJ cancer.

1.3.2 Secondary Objectives

- To compare overall survival (OS) of nivolumab versus placebo in subjects with resected EC or GEJ cancer.
- To evaluate 1, 2, and 3 year survival rates of nivolumab versus placebo in subjects with resected EC or GEJ cancer.

[redacted]

[redacted]

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

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

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

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

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

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

2.2 Institutional Review Board/Independent Ethics Committee

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

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

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.

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

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

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the 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 and regulatory authorities have direct access to subject records.

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

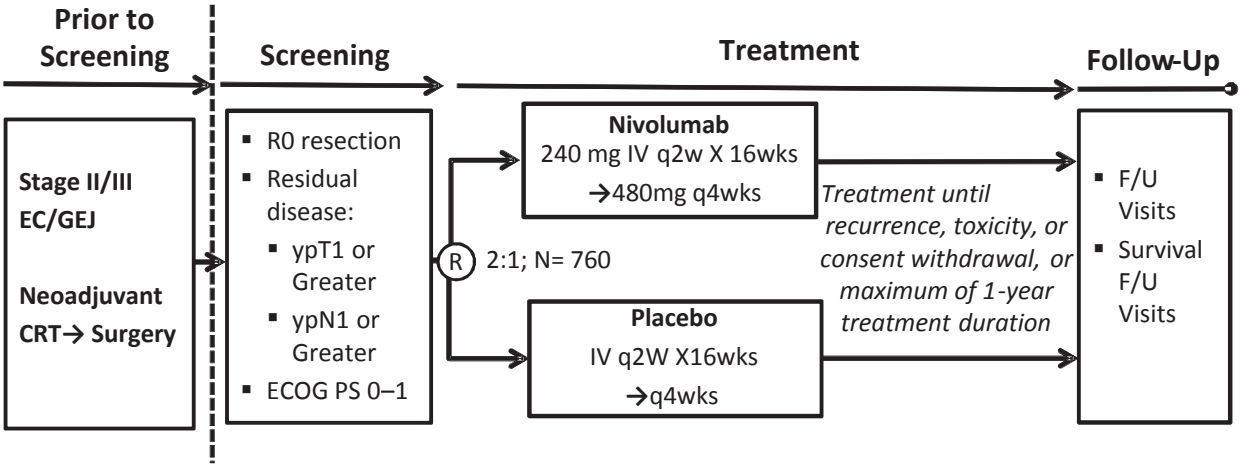
The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

The study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Study Design Schematic



This is a phase 3, randomized, double-blind, placebo controlled study of adjuvant nivolumab in subjects with resected esophageal cancer (EC), or gastroesophageal junction (GEJ) cancer who have received chemoradiotherapy (CRT) followed by surgery.

After CRT followed by surgery, subjects will sign the informed consent form (ICF). Approximately 760 subjects whose tumors do not achieve pathological complete response (non-pCR) will be randomized in a blinded fashion in a 2:1 ratio to two arms between nivolumab (BMS-936558) or placebo monotherapy. Subjects randomized to nivolumab will receive 240 mg nivolumab administered as an IV infusion over 30 minutes every 2 weeks for 16 weeks (8 doses) followed by 480 mg nivolumab administered as an IV infusion over 30 minutes every 4 weeks beginning at Week 17 (2 weeks after the 8th dose). Subjects randomized to placebo will receive placebo administered as an IV infusion over 30 minutes every 2 weeks for 16 weeks (8 doses) followed by placebo as an IV infusion over 30 minutes every 4 weeks beginning at Week 17 (2 weeks after the 8th dose). The treatment will be given until disease recurrence, unacceptable toxicity, or subject withdrawal of consent with a maximum of 1-year total duration of study medication.

Randomization stratification factors:

1. PD-L1 status (≥ 1% vs. < 1% or indeterminate or non-evaluable)
2. Pathologic lymph node status (positive ≥ ypN1vs. negative ypN0)
3. Histology (squamous vs. adenocarcinoma).

This study will consist of three phases: screening, treatment, and follow-up.

For a complete list of study required procedures, please refer to Section 5.

Screening phase:

- Begins by establishing the subject's initial eligibility and signing of the ICF. Subject must receive pre-operative CRT followed by curative surgery.
- Subjects must have been surgically rendered free of disease with negative margins on resected specimens defined as no vital tumor present within 1 mm of the proximal, distal, or circumferential resection margins, ie, R0. Subjects whose tumors do not achieve pCR, ie, pathological status ≥ ypN1 or ≥ ypT1 are eligible.
- The pathology reports of detectable lesion(s) confirming malignancy must be reviewed, dated, and signed by the investigator prior to randomization
- Subjects must have PD -L1 IHC testing, with results, performed by the central lab during the Screening period. Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections, with an associated pathology report, must be submitted for biomarker evaluation prior to randomization. The resected tumor tissue sample must be obtained within 16 weeks prior to randomization but after completion of CRT treatment, and there can have been no systemic therapy (eg, adjuvant) given after the sample was obtained. Tissue must be a core needle biopsy, excisional or incisional biopsy. Fine needle biopsies are not considered adequate for biomarker review and randomization. Additional details regarding these requirements can be found in the lab manual.
- Archive tumor tissues at pre-neoadjuvant chemoradiotherapy (ie, the initial diagnosis biopsy) for PD-L1 status biomarker analysis is optional. Additionally details regarding these requirements can be found in the lab manual.
- All subjects must have disease-free status documented by a complete physical examination and imaging studies within 4 weeks prior to randomization. Imaging studies must include CT/MRI scan of chest and abdomen.

Treatment phase:

- Following confirmation of the subject's eligibility, the randomization entry to the IWRS can be made. The subject is randomly assigned in a 2:1 ratio to the nivolumab or to the placebo arm.
- Administration of nivolumab or placebo is to begin within 3 calendar days of randomization as an IV infusion over 30 minutes at 240 mg every 2 weeks for 16 weeks (8 doses) followed by nivolumab 480 mg as a 30 minute infusion every 4 weeks beginning at Week 17 (2 weeks after the 8th dose).
- Adverse event assessments should be documented at each clinic visit and WOCBP must have a pregnancy test every 4 weeks ± 1 week, see the details in Table 5.1-2
- Treated subjects will be evaluated for recurrence every 12 weeks ± 1 week, see the details in Table 5.1-2. At the sponsor's discretion, scans may be collected centrally for a blinded independent central review (BICR) during the study or at a later date.
- [redacted]

[redacted]

- This phase ends when the subject is discontinued early from study therapy (ie, disease recurrence, unacceptable toxicity, or subject withdrawal of consent) or at a maximum of 1 year of treatment.

Follow up phase:

- Begins after 1 year of treatment or when the decision is made to discontinue a subject from study therapy.
- After completion of the first two follow -up visits (FU 1 at day 30 days ± 1 week and FU 2 at 84 days ± 1 week from FU1), subjects will be followed every 3 months or more frequently as needed for survival. Survival visits may be accomplished by in-person visit or phone contact. See the details in Table 5.1-3
- Subjects who discontinue treatment for reasons other than distant recurrence will continue to have surveillance assessments (until distant recurrence) every 12 weeks ± 1 week during the first year after randomization, every 12 weeks ± 2 week during the second year, after that follow local standard in the range of 6-12 months between year 3 and year 5 with the last assessment at year 5. See the details in Table 5.1-3
- All adverse events will be documented for a minimum of 100 days after the last dose of study drug Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. See the details in Table 5.1-3
- [redacted]

Assuming an increasing monthly accrual rate, the accrual will take approximately 36 months.

The study will end once survival follow-up has concluded. Survival visits may continue for up to 5 years from the last patient last treatment.

3.2 Post Study Access to Therapy

At the end of the study, BMS will not continue to provide BMS supplied study drug to subjects/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

3.3 Study Population

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

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care

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

2. Target Population

a) All subjects must have Stage II or Stage III (per AJCC 7th edition) carcinoma of the esophagus or gastroesophageal junction and have histologically confirmed predominant adenocarcinoma or squamous cell carcinoma esophageal or gastroesophageal junction cancer at the time of initial diagnosis.

b) Subjects must complete pre-operative (neoadjuvant) chemoradiotherapy followed by surgery prior to randomization. Platinum based chemotherapy should be used. Chemotherapy and radiation regimens can be followed as local standards of care per NCCN or ESMO guidelines.

c) Subject must have complete resection (R0), have been surgically rendered free of disease with negative margins on resected specimens defined as no vital tumor present within 1 mm of the proximal, distal, or circumferential resection margins.

d) Subject must have residual pathologic disease, ie, non-pathologic complete response (non-pCR) of their EC or GEJ, with at least ypN1 or ypT1 listed in the pathology report of the resected specimens. For any cases of uncertainty (eg, ypNx), it is recommended that the Medical Monitor or designee be consulted prior to randomization. The pathology reports of detectable lesion(s) confirming malignancy must be reviewed, dated, and signed by the investigator prior to randomization.

e) Complete resection must be performed in a window 4-14 weeks prior to randomization. **Inclusion Criteria 2e is no longer applicable per Protocol Amendment 06. Refer to Inclusion Criteria 2l**

f) Surgery requiring local/epidural anesthesia must be completed at least 72 hours before study drug administration.

g) ECOG performance status score of 0 or 1.

h) All subjects must have disease-free status documented by a complete physical examination and imaging studies within 4 weeks prior to randomization. Imaging studies must include CT/MRI scan of chest and abdomen.

i) Tumor tissue from the resected site of disease must be provided for biomarker analyses. In order to be randomized, a subject must have a PD-L1 status classification (≥ 1%, < 1% or indeterminate or non-evaluable) as determined by the central lab. If insufficient tumor tissue content is provided for analysis, acquisition of additional archived tumor tissue (block and /or slides) for the biomarker analysis is required.

j) All baseline laboratory requirements will be assessed and should be obtained within 14 days prior to randomization. Screening laboratory values must meet the following criteria (Using CTCAE v4.)

i) WBCs ≥ 2000/μL
ii) Neutrophils ≥ 1500/μL
iii) Platelets ≥ 100 x 10^3/μL
iv) Hemoglobin ≥ 9.0 g/dL

v) Creatinine: Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or creatinine clearance > 50 mL/minute (using Cockcroft/Gault formula)

1) Female CrCl = (140- age in years) x weight in kg x 0.85

2) 72 x serum creatinine in mg/ dL

3) Male CrCl = (140- age in years) x weight in kg x 1.00

4) 72 x serum creatinine in mg/ dL

vi) AST ≤ 3 x ULN

vii) ALT ≤ 3 x ULN

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

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

l) Complete resection must be performed in a window 4-16 weeks prior to randomization

3. Age and Reproductive Status

a) Males and Females, ≥ 18 years of age

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

c) Women must not be breastfeeding

d) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for a period of 30 days (duration of ovulary cycle) plus the time required for the investigational drug to undergo approximately five half-lives. WOCBP receiving nivolumab should use an adequate method to avoid pregnancy for 5 months (30 days plus the time required for nivolumab to undergo approximately five half-lives) after the last dose of investigational product.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for a period of 90 days (duration of sperm turnover) plus the time required for the investigational drug to undergo approximately five half-lives. Males receiving nivolumab who are sexually active with WOCBP must continue contraception for 7 months (90 days plus the time required for nivolumab to undergo approximately five half-lives) after the last dose of investigational drug.) In addition, male subjects must be willing to refrain from sperm donation during this time.

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

Investigators shall counsel WOCBP, and male subjects who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the

use of highly effective methods of contraception. Highly effective methods of contraception (see Appendix 3) have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to the use one highly effective method of contraception. See Appendix 3 for details on highly effective methods of contraception.

3.3.2 Exclusion Criteria

3.3.2.1 Target Disease Exceptions

a) Subjects with cervical esophageal carcinoma. Location of tumor as it relates to eligibility can be discussed with BMS medical monitor.

b) Subjects who do not receive concurrent CRT prior to surgery. Subjects who only receive chemotherapy or only radiation prior to surgery are not eligible.

c) Subjects with Stage IV resectable disease

3.3.2.2 Medical History and Concurrent Diseases

a) Treatment directed against the resected GEJ and esophageal cancer (eg, chemotherapy, targeted agents, radiation, or biologic therapy) that is administered after the complete resection.

b) Subjects with previous malignancies are excluded unless a complete remission was achieved at least 5 years prior to study entry and no additional therapy is required or anticipated to be required during the study period (exceptions include but are not limited to, non-melanoma skin cancers; in situ bladder cancer, or in situ colon cancers; in situ cervical cancers/dysplasia; or breast carcinoma in situ) - **Exclusion Criteria 3.3.2.2b is no longer applicable per Protocol Amendment 05**

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

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

e) Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.

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

g) All toxicities attributed to prior anti-cancer therapy other than nephropathy, neuropathy, hearing loss, 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 peripheral neuropathy after platinum based therapy, are permitted to enroll. Peripheral neuropathy must have resolved to Grade 2 (NCI CTCAE version 4).

h) Any serious or uncontrolled medical disorder or active infection that, in the opinion of the investigator, may increase the risk associated with study participation, study drug administration, or would impair the ability of the subject to receive protocol therapy.

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

j) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.

k) Subjects who have received a live/attenuated vaccine within 30 days of the first treatment.

3.3.2.3 Physical and Laboratory Test Findings

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

3.3.2.4 Allergies and Adverse Drug Reaction

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

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

3.3.2.5 Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

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

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

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, bilateral salpingectomy, or bilateral oophorectomy) and is not postmenopausal. A postmenopause 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.

*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 judgment 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.

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3.6 Post Study Drug, Study Follow-up

In this study, DFS is the primary endpoint. 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 recurrence (till distant recurrence) and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study. The importance of follow up should be clearly communicated to study subjects.

BMS may request that survival data be collected on all randomized subjects outside of the protocol defined window (per Table 5.1-3). 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.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject

specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

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

Table 4-1: Study Drugs for CA209577

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	100 mg (10 mg/mL)	IMP	Blinded	10 mL Vial/Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect from light and freezing
Placebo	N/A	IMP	Blinded	10 mL Vial/Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect from light and freezing

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.

In this protocol, investigational products are: nivolumab and placebo for nivolumab.

4.2 Non-investigational Product

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

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

4.3 Storage and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately. Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Storage facilities for controlled substances must be securely locked and substantially constructed, with restricted access to prevent theft or diversion, as applicable by local regulations.

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

For study drug, please refer to the current version of the Investigator Brochures and/or drug preparation manual for complete storage, handling, dispensing, and infusion information. For diluents, please refer to the package insert, summary of product characteristics, or equivalent documentation.

Study drug is to be administered as an approximately 30-minute IV infusion. At the end of the infusion, flush the line with a sufficient quantity of normal saline or dextrose solution in an identical fashion as nivolumab in order to maintain the blind.

4.4 Method of Assigning Subject Identification

After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by entering information into IWRS to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IWRS. Specific instructions for using IWRS will be provided to the investigational site in a separate document. The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

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

Once enrolled in IWRS, enrolled subjects that have met all eligibility criteria (the required tumor tissue received and result obtained by the central laboratory and the pathology report approved by the investigator) will be ready to be randomized through the IWRS. The following information is required for subject randomization:

- Subject number
- Date of birth
- PD-L1 status (Note that the result of PD-L1 expression ≥ 1%, or PD-L1 expression < 1% or indeterminate or non-evaluable is entered by the central laboratory vendor into IWRS and both the site and the BMS study team remain blinded to the result)
- Pathologic evidence of disease in lymph nodes (ypN0 vs. ≥ ypN1)
- Histology (Squamous vs. adenocarcinoma)

Subjects meeting all eligibility criteria will be randomized in a 2:1 ratio to Arm A nivolumab or Arm B placebo stratified by the following factors:

- PD-L1 status (≥ 1% vs. < 1% or indeterminate or non-evaluable)
- Pathologic evidence of disease in lymph nodes (ypN0 vs. ≥ ypN1)
- Histology (Squamous cell type vs. adenocarcinoma)

The exact procedures for using the IWRS will be detailed in the IWRS manual.

4.5 Selection and Timing of Dose for Each Subject

Table 4.5-1: Nivolumab (or placebo) dosing

Drug	Dose	Frequency of administration	Route of administration	Duration
Nivolumab (or placebo)	240 mg (or placebo) [Cycles 1-8]	Every 2 weeks, for 8 doses	Intravenous (IV) infusion	Until recurrence or discontinuation from study for a maximum of 1 year
	480 mg (or placebo) [Cycles 9-17]	Every 4 weeks starting at Cycle 9		

Subjects will receive treatment with nivolumab (BMS-936558) or placebo monotherapy. Subjects randomized to nivolumab will receive 240 mg nivolumab administered as an IV infusion over 30 minutes every 2 weeks for 16 weeks (8 doses) followed by 480 mg nivolumab administered as an IV infusion over 30 minutes every 4 weeks beginning at Week 17 (2 weeks after the 8th dose). Subjects randomized to placebo will receive placebo administered as an IV infusion over 30 minutes every 2 weeks for 16 weeks (8 doses) followed by placebo as an IV infusion over 30 minutes every 4 weeks beginning at Week 17 (2 weeks after the 8th dose). Treatment will be given until disease recurrence, unacceptable toxicity, or subject withdrawal of consent with a maximum of 1-year total duration of study medication.

First dose must be administered within 3 calendar days following randomization. There are no pre-medications recommended on the first cycle. If an acute infusion reaction is noted, subjects should be managed according to Section 4.5.6. At the end of the infusion, flush the line with a sufficient quantity of diluent. Refer to drug preparation manual for more detail.

Dosing modifications:

There will be no dose modifications allowed for the management of toxicities of individual subjects. 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.

Dosing window:

For Cycles 1-8, subjects may have study drug administered up to 2 days before or 3 days after the scheduled dosing date. Subjects may be dosed no less than 12 days from the previous dose. For Cycles 9-17, subjects may be dosed within a +/- 3 day window. A maximum delay of 6 weeks (42 days) between doses of nivolumab (or placebo) during Cycles 1-8 or a maximum delay of 10 weeks (70 days) between doses of nivolumab (or placebo) during Cycles 9-17 are allowed.

4.5.1 Antiemetic Premedications

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

4.5.2 Dose Delay Criteria

Dose delay criteria apply for all drug-related adverse events. Treatment delays up to 6 weeks (42 days) from the last dose of nivolumab (or placebo) during Cycles 1-8 or up to 10 weeks (70 days) from the last dose of nivolumab (or placebo) during Cycles 9-17 are allowed.

Nivolumab (or placebo) administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue does not require a treatment delay
- Grade 2 drug-related creatinine, AST, ALT or Total Bilirubin abnormalities
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality (excluding AST, ALT or Total Bilirubin), with the following exceptions for lymphopenia, and asymptomatic amylase or lipase:
  - Grade 3 lymphopenia does not require dose delay
  - Any Grade ≥ 3 drug-related amylase or lipase abnormalities that is not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay.
- 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.

Note: per BMS standards, the term “interruption” is reserved for interruption of the actual IV infusion during administration. The terms omission and interruption should not be used synonymously when completing the CRF forms.

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4.5.3 Dose Modifications

Dose reductions for the management of toxicities of individual subjects or dose escalations are not permitted. All dose modifications rules apply to both arms given the blinded nature of this study

4.5.4 Criteria to Resume Treatment

All criteria to resume treatment apply to both arms given the blinded nature of this study. Subjects may resume treatment with study drug when the treatment-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- For subjects with Grade 2 AST, ALT, or TBILI elevations, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.5.5) should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed. 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 BMS Medical Monitor
- Grade 2 or 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor, except for Grade 3 adrenal insufficiency which requires permanent discontinuation as described in Section 4.5.5

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time point per protocol.

However, if the treatment is withheld past the window period of the next scheduled time point per protocol to ensure adequate recovery from the adverse event or tapering of immunosuppression, the dosing should start as soon as possible once it is safe to do so (ie, no need to wait until the

subsequent scheduled time point to resume dosing). If treatment is delayed > 6 weeks (42 days) from the last dose of nivolumab (or placebo) during Cycles 1-8 or > 10 weeks (70 days) from the last dose of nivolumab (or placebo) during Cycles 9-17, the subject must be permanently discontinued from study therapy, except as specified in Section 4.5.5.

4.5.5 Discontinuation of Subjects from Treatment:

All discontinuation criteria for nivolumab also apply for the placebo, given the blinded nature of this study.

Treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, myocarditis, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation, except for Grade 3 adrenal insufficiency which requires permanent discontinuation as described in Section 4.5.5
  - 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 drug-related AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any drug-related Grade 4 endocrinopathy and Grade 3 adrenal insufficiency requires discontinuation
- 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
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical squeal and are corrected with supplementation/appropriate management within 72 hours of their onset
- Dosing that is withheld > 6 weeks (42 days) from the last dose of nivolumab (or placebo) during Cycles 1-8 or > 10 weeks (70 days) from the last dose of nivolumab (or placebo) during Cycles 9-17, with the following exceptions:

- Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
- Dosing delays lasting > 6 weeks or > 10 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 (42 days) from the last dose of nivolumab (or placebo) during Cycles 1-8 or > 10 weeks (70 days) from the last dose of nivolumab (or placebo) during Cycles 9-17, 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 under current illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

Post treatment study follow-up is critically important and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment will continue to be followed for collection of tumor surveillance assessments, safety, QoL questionnaires and biomarker sampling as per protocol.

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

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

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

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

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

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

4.6 Blinding/Unblinding

The Sponsor, subjects, investigator and site staff will be blinded to the study therapy administered.

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the investigator. The subject’s safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual subject's treatment, the investigator should determine that the unblinded information is necessary, ie, that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not related to the investigational product, the problem may be properly managed by assuming that the subject is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The Principal Investigator should only call in for emergency unblinding AFTER the decision to discontinue the subject has been made.

For this study, the method of unblinding for emergency purposes is through the IWRS. For information on how to unblind for emergency, please consult the IWRS manual.

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to preserve the blind. Any request to unblind a subject for non-emergency purposes should be discussed with the Medical Monitor.

In addition, designated staff of Bristol-Myers Squibb Research & Development may be unblinded prior to database lock to facilitate the bioanalytical analysis of pharmacokinetic samples and immunogenicity. A bioanalytical scientist in the Bioanalytical Sciences department of Bristol-Myers Squibb Research & Development (or a designee in the external central bioanalytical laboratory) will be unblinded to the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples.

To further minimize bias, the sponsor central study team and the investigative clinical site staff are blinded to results from PD-L1 analysis.

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 of Study Drug

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

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

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

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

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

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

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

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.9 Return of Study Drug

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

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (CA209577)

Procedure	Screening Visit (Day - 49 till Day - 1 prior to Randomization)	Notes
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed during screening and confirmed prior to randomization.
Medical History	X	
Review of pathology report	X	The pathology report must be reviewed, signed and dated by the investigator prior to randomization.
Tumor Tissue Samples	X	Sufficient tumor tissue from the resected site of the disease (either a formalin-fixed, paraffin-embedded [FFPE] tissue block or minimum 20 slides[a]) must be available within 16 weeks prior to randomization, and sent to a central laboratory for biomarker analysis. PD-L1 status will be assessed prior to randomization. Archive tumor tissues at pre-neoadjuvant chemoradiotherapy (ie, the initial diagnosis biopsy) for PD-L1 status biomarker analysis is optional. If this optional sample is provided, please send either a formalin-fixed, paraffin-embedded [FFPE] tissue block or 5 slides. Tissue must be a core needle biopsy, excisional biopsy, or incisional biopsy. Needle biopsies are not considered adequate for biomarker review.
Safety Assessments		
Physical Examination	X	Within 14 days prior to randomization
Physical Measurements	X	Include Height and Weight Within 14 days prior to randomization
Vital Signs	X	Including BP, HR, temperature, Obtain vital signs at the screening visit and within 72 hours prior to first dose
Performance Status (ECOG)	X	Within 14 days prior to randomization

Table 5.1-1: Screening Procedural Outline (CA209577)		
Procedure	**Screening Visit (Day - 49 till Day - 1 prior to Randomization)**	**Notes**
Assessment of Signs and Symptoms	X	Within 14 days prior to randomization
Serious Adverse Event (SAE) Assessment	X	After informed consent is signed.
[redacted]	[redacted]	[redacted]
Electrocardiogram (ECG)	X	Within 14 days prior to randomization
Laboratory Tests	X	On site/local complete blood count (CBC) w/differential, Chemistry panel including: LDH, AST, ALT, ALP, T-Bil, blood urea nitrogen (BUN) or serum urea level, creatinine, Na, K, Cl, total protein, glucose, albumin, amylase, lipase within 14 days prior to randomization. Urinalysis as clinically indicated within 14 days prior to randomization. Endocrine panel (TSH, Free T4, Free T3. Total T3/T4 are acceptable if free T3/T4 are not available), Hep B/C (HBV sAG, HCV antibody or HCV RNA), HIV (when required by local regulations), within 28 days prior to randomization.
Pregnancy Test (WOCBP only)	X	Serum or urine to be done at screening visit and repeated within 24 hours of first dose of study therapy
Efficacy assessment		
Baseline Tumor Imaging Assessment	X	See Section 5.4 After complete resection and within 28 days prior to randomization. Disease-free status should be documented.
IWRS		
IWRS entry	X	IWRS entries must be made 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)

[a] If, despite best efforts, a minimum 20 slides are not obtainable, discuss with Sponsor.

Table 5.1-2: On-Treatment Procedural Outline (CA209577)			
Procedure	**Cycle 1 Day 1 (C1D1)**	**Each cycle on Day 1 (up to 2 days prior to dosing, unless indicated otherwise in the Notes)**	**Notes** ***Each cycle duration is 2 weeks until 8 doses of nivo/placebo are complete. Remaining subsequent cycles are 4 weeks in duration*** ***Treatment is until recurrence or discontinuation from study for maximum treatment duration of 1 year***
Safety Assessments			
Targeted Physical Examination	X	X	To be performed within 72 hours prior to dosing
Vital Signs	X	X	Including BP, HR, temperature, Obtain vital signs within 72 hours prior to first dose.
Weight and ECOG Performance Status	X	X	Within 72 hours prior to dosing See **Appendix 1** for ECOG Performance Status scale
Adverse Events Assessment	Continuously		Assessed using NCI CTCAE v. 4.0.
[redacted]	[redacted]	[redacted]	
Laboratory Tests	X	X	Within 72 hours prior to each dose. Include CBC w/differential, LFT's, BUN or serum urea level, creatinine, Na, K, Cl, LDH, Glucose, amylase, lipase, TSH (with reflexive Free T4 and Free T3. Total T3/T4 are acceptable if free T3/T4 are not available.)[a] Note: Laboratory tests do not need to be repeated if performed within 14 days prior to first dose
Pregnancy Test (WOCBP only)	X	See Note	Serum or urine within 24 hours prior to the initial administration of study drug, then every 4 weeks (± 1 week) regardless of dosing schedule
[redacted]			
[redacted]	[redacted]		
[redacted]	[redacted]		

Table 5.1-2: On-Treatment Procedural Outline (CA209577)			
Procedure	**Cycle 1 Day 1 (C1D1)**	**Each cycle on Day 1 (up to 2 days prior to dosing, unless indicated otherwise in the Notes)**	**Notes** ***Each cycle duration is 2 weeks until 8 doses of nivo/placebo are complete. Remaining subsequent cycles are 4 weeks in duration*** ***Treatment is until recurrence or discontinuation from study for maximum treatment duration of 1 year***
Efficacy Assessments			
Tumor Imaging Assessment	See Section 5.4. Every 12 weeks (± 7 days) from first dose of study treatment through 12 months or distant recurrence whichever comes first		
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Table 5.1-2: On-Treatment Procedural Outline (CA209577)

Procedure	Cycle 1 Day 1 (C1D1)	Each cycle on Day 1 (up to 2 days prior to dosing, unless indicated otherwise in the Notes)	Notes ***Each cycle duration is 2 weeks until 8 doses of nivo/placebo are complete. Remaining subsequent cycles are 4 weeks in duration*** ***Treatment is until recurrence or discontinuation from study for maximum treatment duration of 1 year***
Dispense Study Treatment (Active drug or placebo - blinded)	X	X	First dose to be administered within 3 calendar days of randomization, then every 2 weeks for 8 doses and every 4 weeks beginning at week 17 (2 weeks after the 8th dose). See Section 4.5. For Cycles 1-8, subjects may have study drug administered up to 2 days before or 3 days after the scheduled dosing date. Subjects may be dosed no less than 12 days from the previous dose. For Cycles 9-17, subjects may be dosed within a +/- 3 day window.

[a] TSH, Free T3, Free T4 (Total T3/T4 are acceptable if free T3/T4 are not available) should be performed prior to dosing at Cycles 1, 4, 7, 10, 12, 14, and 16

Table 5.1-3: Follow-Up Procedural Outline (CA209-577)			
Procedure	**Follow-up, Visits 1 and 2[a] FU1: 30 days (± 7 days) FU 2: 84 days (± 7 days)**	**Survival Follow-Up Visits[b] every 3 months from FU2 (± 14 days)**	**Notes**
Safety Assessments			
Targeted Physical Examination	X		
Adverse Events Assessment	X		Assessed using NCI CTCAE v. 4.0. See Sections 6.1.1 and 6.2.1.
Review of Subsequent Cancer Therapy	X	X	
[redacted]	[redacted]		
Laboratory Tests	X		Include CBC w/differential, LFT's, BUN or serum urea level, creatinine, Na, K, Cl, LDH, Glucose, amylase, lipase, TSH (with reflexive Free T4 and Free T3. Total T3/T4 are acceptable if free T3/T4 are not available.) Urinalysis as clinically indicated To be done at FU1. To be repeated at FU2 if study related toxicity persists.
Pregnancy Test (WOCBP only)	X		Serum or urine pregnancy testing is only required at FU1 and FU2, unless increased frequency and duration is required per local regulations.
Efficacy Assessments			
Tumor Imaging Assessment	Every 12 weeks (± 7 days) ≤ 12 months Every 12 weeks (± 14 days) > 12 months through 24 months After that follow local standard in the range 6-12 months between year 3 and year 5 with the last assessment at year 5. Until distant recurrence. All time points are relative to the first dose of study treatment		See Section 5.4.

Table 5.1-3: Follow-Up Procedural Outline (CA209-577)

Procedure	Follow-up, Visits 1 and 2[a] FU1: 30 days (± 7 days) FU 2: 84 days (± 7 days)	Survival Follow-Up Visits[b] every 3 months from FU2 (± 14 days)	Notes
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	
[redacted]	[redacted]		
[redacted]			
[redacted]		[redacted]	
[redacted]		[redacted]	
[redacted]		[redacted]	
[redacted]		[redacted]	
Subject Status			
Survival Status	X	X	Every 3 months (± 14 days) or more frequently as needed after FU2, may be accomplished by in-person visit or phone contact, to include subsequent anticancer therapy.
Progression-free survival after the next line of subsequent therapy (PFS2)	X	X	Following first progression, subjects will continue to be followed during the safety and survival follow-up visits. Timing of second progression per investigator's assessments will be documented.

[a] Follow-up visit 1 (FU1) = 30 days (± 7 days) from the last dose, Follow-up visit 2 (FU2) = 84 days (± 7 days) from follow-up visit 1. These follow-up visits should occur in person.

[b] Survival visits may be may be accomplished by in-person visit or phone contact. Survival visits may continue for up to 5 years from the last patient last treatment.

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

- NCI CTCAE Version 4.0
- Nivolumab Investigator Brochure
- Pharmacy Binder
- Laboratory Manuals for collection and handling of blood samples (including biomarker and immunogenicity samples) and tissue specimens
- Site manual for operation of IWRS,
- Manual for entry of local laboratory data
- Pregnancy Surveillance Forms
- Subject Questionnaires: FACT-E (ECS, FACT-G7), EQ-5D
- AJCC Cancer Staging Manual for Esophageal Cancers
- NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers
- ESMO Clinical Practice Guidelines for Oesophageal Cancer
- Image Acquisition Guideline
- Imaging Site Operations Manual

5.3 Safety Assessments

5.3.1 Screening Safety Assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include weight, height, ECOG performance status, BP, HR, temperature, electrocardiogram (as noted in Table 5.1-1). A pathology report to determine the subject's current disease status must be reviewed, signed and dated by the investigator prior to randomization. Baseline signs and symptoms are those that are assessed within 14 days prior to first dose of study drug. Concomitant medications including steroid doses will be collected within 14 days prior to first dose of study drug through the study treatment period.

Baseline local laboratory assessments that should be done within 14 days prior to randomization include: CBC with differential, Chemistry panel including: LDH, AST, ALT, ALP, T-Bil, blood

urea nitrogen (BUN) or serum urea level, creatinine, Na, K, Cl, total protein, glucose, albumin, amylase, lipase, and urinalysis (as clinically indicated).

Laboratory assessments that should be done within 28 days prior to randomization include: endocrine panel (TSH, Free T4, Free T3; Total T3/T4 are acceptable if free T3/T4 are not available), Hepatitis B and C (HBV sAG, HCV antibody or HCV RNA), HIV (when required by local regulations (see Table 5.1-1).

Pregnancy testing for WOCBP should be done at screening, within 24 hours prior to first dose.

Serious AEs are to be collected as soon as the informed consent form is signed.

5.3.2 On-Treatment Safety Assessments

Subjects will be evaluated for safety if they have received any study drug. Adverse event assessments will be continuous during the treatment phase. 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.

On study local laboratory assessments should be done within 72 hours prior to dosing (laboratory tests should not be repeated if performed within 14 days prior to the first dose) to include; CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Na, K, Cl, LDH, glucose, amylase, and lipase prior to each dose. TSH with reflexive Free T4, Free T3 (Total T3/T4 are acceptable if free T3/T4 are not available), can be performed at Cycles 1, 4, 7, 10, 12, 14, and 16 (Table 5.1-2). Additional measures including non-study required laboratory tests should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme elevations) 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.

Pregnancy testing for WOCBP should be done every 4 weeks relative to dosing on Day 1 of Cycle 1 regardless of dosing schedule.

On-treatment targeted physical examination, weight, ECOG performance status, BP, HR, temperature (Table 5.1-2) should be performed within 72 hours prior to dosing. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse events page.

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

Some of the previously referred to assessments 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.

5.3.3 Follow-Up Safety Assessments

Adverse events will be assessed, concomitant medication, and subsequent cancer therapy will be reviewed as described in Table 5.1-3. A physical examination will be performed at follow-up visits FU1 and FU2. Laboratory and pregnancy tests will be performed as described in Table 5.1-3.

5.3.4 Imaging Assessment for the Study

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

5.4 Efficacy Assessments

Study evaluations will take place in accordance with the flow charts in Section 5.1.

Baseline assessments of the chest and abdomen should be performed within 28 days prior to randomization utilizing CT or MRI. Subsequent assessments should include chest and abdomen and any clinically indicated sites. Subjects will be evaluated for disease recurrence every 12 weeks from the date of first treatment (+/- 7 days) for the first 12 months, then every 12 weeks (+/- 14 days) between months 12 and 24, and then according to local standards with a minimum of one scan every 6-12 months between years 3-5.

Disease assessment with contrast-enhanced computed tomography (CT) scans acquired on dedicated CT equipment is preferred for this study. Should a subject have contraindication for CT intravenous contrast, a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen, should be obtained. A contrast-enhanced MRI of the chest is also acceptable instead of a non-contrast CT of the chest. The same imaging method as was used at baseline.

At the sponsor's discretion, scans may be collected centrally for a blinded independent central review (BICR) during the study or at a later date.

Refer to CA209577 imaging Site Operations Manual and/or Image Acquisition Guidelines for more specific details.

5.4.1 Definitions of Recurrence

Recurrence is defined as the appearance of one or more new lesions, which can be local, regional, or distant in location from the primary resected site (confirmed by imaging or cytology/pathology).

Local or regional recurrence: Any anastomotic recurrence or/and occurring either in the mediastinum or upper abdomen at the site of previous esophageal resection and nodal clearance or in the cervical area where no lymphadenectomy had been performed.

Distant metastasis: Any recurrence occurring in distant organs, pleura and peritoneum. If both loco-regional recurrence and distant metastases occurred, the case was considered as distant metastases.

Diagnosis of recurrence should be unequivocal. If a new lesion is equivocal, for example because of its small size or ambiguous etiology, the suspected lesion should be confirmed with cytology or histopathology. If biopsy is not possible, the subject should continue therapy, and a follow-up

imaging evaluation (in no less than 4 weeks) should be performed. If repeat scans or cytology/histology confirm recurrence, then recurrence should be declared using the date of the initial scan. For clinically clear recurrence case, the diagnosis can be done by imaging only.

Criteria used to determine CT lymph node metastases were a lymph node diameter at least 1 cm in short axis. The appearance of new malignant lesions denotes disease recurrence. The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor. 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 recurrence, unless found to be secondary or concurrent malignancy which is non-esophageal or non-gastro-esophageal junction-originated malignancy. An example of this is the subject who has CT or MRI brain scan ordered in the on treatment phase which reveals metastases. The subject's brain metastases are considered to be evidence of recurrence even if he/she did not have brain imaging at baseline.

5.4.2 Methods of Measurement

- CT and MRI are an essential part of the work-up to establish recurrence. Conventional CT with IV contrast and MRI gadolinium should be performed with contiguous cuts of 10 mm or less slice thickness. Spiral CT should be performed using a 3- or 5-mm contiguous reconstruction algorithm; this specification applies to the tumors of the chest, abdomen and other clinically relevant sites. In each institute the same technique for CT/MRI should be used to characterize each new lesion.
  - For subjects allergic to contrast media, they may have a CT performed without contrast or MRI after consulted with site radiologist.
- PET alone will not be considered for the disease assessment. Complementary CT and/or MRI or biopsy must be performed in such cases.
- Cytology and/or histology are mandatory to confirm recurrence in solitary or in doubtful lesions, cutaneous, subcutaneous or lymph node lesions. Histological or cytological evidence of recurrence should be attempted in all cases except for brain metastases when safe and clinically feasible. An example when obtaining a biopsy to confirm recurrence may not be safe and clinically feasible is brain metastases.
- Clinically detected new lesions:
  - Superficial cutaneous lesions: the neoplastic nature must be confirmed by cytology/histology.
  - Deep subcutaneous lesions and lymph node lesions should be documented by ultrasound and histological/cytological evidence should be attempted. In absence of pathology report, lesion recurrence will be documented with a CT scan/MRI.
- Tumor markers or auto-antibodies alone cannot be used to assess recurrence.
- At the sponsor's discretion, reports from cytology and/or histology may be collected centrally for a blinded independent central review (BICR) during the study or at a later date.

5.4.3 Date of Recurrence

The first date when recurrence was observed is taken into account regardless the method of assessment. Therefore recurrence will be declared for any lesion when:

- Only imaging was performed and recurrence confirmed
- Only pathology was done and malignancy confirmed (in solitary or in doubtful lesions, any new lesions in esophagus and or stomach, lymph node or distant metastasis)
- Both pathology and imaging were done and recurrence/malignancy confirmed. In this case, the date of whichever examination comes first is considered the date of recurrence.
- The first recurrence was noted, and any additional recurrence found within 1 month was considered to have occurred simultaneously, the first confirmed recurrence is considered the date of recurrence.

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6 ADVERSE EVENTS

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

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

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

6.1 Serious Adverse Events

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

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

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

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1-1 and 5.6.1-2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator 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 BMS (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. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

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.

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

Every adverse event must be assessed by the investigator with regard to whether it is considered immune-mediated. Immune-mediated adverse events (IMAEs) 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 that were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the subject's case report form.

6.3 Laboratory Test Result Abnormalities

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

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

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

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during 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).

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

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 subject 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 the information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

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

6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

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.

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 Data Monitoring Committee (DMC) will be established to provide oversight of safety and efficacy considerations in protocol CA209577. Additionally, the DMC will provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of subjects enrolled in the study. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for nivolumab. The DMC will act in an advisory capacity to BMS and will monitor subject safety and evaluate the available efficacy data for the study. The oncology therapeutic area of BMS has primary responsibility for design and conduct of the study.

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

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The sample size determination takes into consideration the comparison of the primary endpoint of DFS and the first secondary endpoint of OS between the 2 treatment arms.

8.1.1 Assumptions of the Control Arm

The assumptions of DFS and OS in the control arm of this study are made using the chemoradiotherapy followed by surgery (CRT + S) arm in the CROSS trial with long-term follow up (CROSS LT).[45]

Assumption for DFS

The DFS in the control arm is assumed to follow a piece-wise exponential distribution with a median of 21 months, as described below:

- The median PFS of the CRT+S arm in the CROSS LT trial was 37.7 months, which was defined from the start of CRT to disease progression.
- Considering the median time from the start of CRT+S to the completion of surgery is approximately 6 months, the median time from the completion of surgery to disease progression (to approximate DFS) is then estimated to be approximately 31 months in the setting of the CROSS LT trial.
- The study population in CA209577 are subjects who have residual pathologic disease, ie, non-pathologic complete response (non-pCR). This population represents a high-risk subgroup in the CROSS LT trial that included 29% subjects who achieved complete pathological response (pCR) after resection and 71% non-pCR subjects. This subgroup of non-pCR subjects have worse clinical outcome compared with pCR subjects.[11] Therefore, the assumed median DFS in CA209577 should be less than 31 months.
- The assumption of 21-months median DFS in the control arm is made in consultation with external experts. Additionally, a single-center study of 518 esophageal adenocarcinoma patients suggested that 85.1% and 94.4% of relapses occurred within 24 and 36 months of surgery, respectively.[73] This also supports the median DFS being less than 24 months in the study population.
- Chemoradiotherapy + surgery has demonstrated long-term survival benefit, as indicated by a long-lasting plateau toward the end of the survival curve in multiple clinical trials.[73,74,75] As such, the distribution of the DFS curve in the control arm of this study is assumed to follow a piece-wise exponential distribution with landmark DFS hazard rates and corresponding landmark DFS rates in Table 8.1.1-1. The shape of the DFS curve in the control arm reflects the shape of the PFS curve in the CRT+S arm of the CROSS LT trial.

Assumption for OS

The OS in the control arm of this study is also assumed to follow a piece-wise exponential distribution with a median of 31 months. The assumption of the median OS is 10 months longer than the assumption of the median DFS in the control arm as described below:

- The median PFS and median OS of the CRT+S arm in the CROSS LT trial were 37.7 months and 48.6 months respectively, which give 11 months difference between median PFS and median OS.
- The differences between median PFS and median OS are all less than 12 months in the meta-analysis of 14 adjuvant gastric cancer studies.[63]

The shape of OS curve in the control arm of this study reflects the observed OS curve in the CRT+S arm of the CROSS LT trial. The assumed landmark OS hazard rates and corresponding landmark OS rates in this study are provided in Table 8.1.1-2.

Table 8.1.1-1: Assumed DFS Hazard Rates, Landmark Rates and Hazard Ratios

By Time	DFS Hazard Rate/DFS Rate (%) in the Control Arm	DFS Hazard Rate/DFS Rate (%) in the Nivolumab Arm	Hazard Ratio
3 months	0.035/90.0	0.035/90.0	1
1 year	0.035/65.7	0.023/73.0	0.667
2.5 years	0.03/38.3	0.02/50.9	0.667
5 years	0.02/21.0	0.013/34.1	0.667
10 years	0.003/17.5	0.002/29.5	0.8

Table 8.1.1-2: Assumed OS Hazard Rates, Landmark Rates and Hazard Ratios

By Time	OS Hazard Rate/OS Rate (%) in the Control Arm	OS Hazard Rate/OS Rate (%) in the Nivolumab Arm	Hazard Ratio
4 months	0.026/90.1	0.026/90.1	1
1 year	0.026/73.2	0.018/78.2	0.685
2.5 years	0.0205/50.6	0.014/60.7	0.685
6 years	0.018/23.8	0.012/36.2	0.685
12 years	0.002/20.5	0.002/32.2	0.8

8.1.2 Assumptions of the Treatment Effect

Assumption for DFS

An average HR of 0.72 is assumed for DFS between nivolumab and placebo in CA209577 at the final DFS analysis, which accounts for the piece-wise HRs summarized in Table 8.1.1-1. This translates to a median DFS of 31 months in the nivolumab arm.

In many trials studying immunotherapies, the PFS and OS curves in the immunotherapy-treated arms tend to have a delayed separation from the control arms across tumor indications;[76] therefore, the treatment effect for DFS is assumed to have a delayed separation with an HR of 1 for the first 3 months and a larger treatment effect after delayed separation with an HR of 0.667. After 5 years, the treatment effect for DFS is assumed to decrease slightly with an HR of 0.8. This takes into consideration that patients who have not had disease recurrence within 5 years of surgery are generally cured from the disease and the treatment effect is more reflective of the survival benefit.

Assumption for OS

The average HR of 0.73 is assumed for OS between nivolumab and placebo in CA209577 at the final OS analysis, which accounts for the piece-wise HRs summarized in Table 8.1.1-2. This translates to median OS of 44 months in the nivolumab arm.

The assumption of the OS treatment effect between the 2 arms follows the same thought process as the assumption of the DFS treatment effect. The treatment effect for OS is assumed to have a delayed separation with HR of 1 for the first 4 months, and a larger treatment effect after delayed separation with an HR of 0.685. After 6 years, the treatment effect for OS is assumed to decrease slightly with an HR of 0.8. This takes into consideration the combined effect of potential for more subsequent immunotherapies in the control arm and other effective subsequent therapies in both arms for long-term survivors.

8.1.3 Sample Size and Power

According to the assumptions for DFS described in Sections 8.1.1 and 8.1.2, the study will require approximately 760 subjects to be randomized at a 2:1 ratio to nivolumab and placebo and observations of at least 440 DFS events in order to achieve approximately 91% power to detect an average HR of 0.72 at a 2-sided alpha of 0.05.

The sample-size determination accounts for 1 DFS interim analysis. Details of the DFS analysis timing are provided in Section 8.1.4.

It is estimated that these 760 subjects will be accrued and randomized within approximately 36 months from the first-patient first-visit (FPFV).

Overall survival will be tested following the overall hierarchical testing procedure[64] upon demonstration of superiority in DFS at either interim or final analyses for all randomized subjects.

With the sample size of 760, it is required to observe at least 460 OS events at the final OS analysis in order to achieve approximately 90% power to detect an average HR of 0.73 at a 2-sided alpha of 0.05. The power of the OS final analysis accounts for 2 OS interim analyses that occur at the same time as the DFS interim and DFS final analyses, respectively. Details of the OS analysis timing are provided in Section 8.1.4.

8.1.4 Timing of the DFS and OS Interim and Final Analyses

Timing of the Interim and Final DFS Analyses

Considering the potential plateau of the DFS curve after 3 years,[45] the study is designed with 1 interim DFS analysis when at least 85% of all 440 DFS events (374 DFS events) are observed. Based on the current assumptions, it is projected to occur approximately 12 months after the last patient being randomized. The final DFS analysis will be triggered when at least 440 DFS events have been observed. The final DFS analysis is projected to occur approximately 22 months after the last patient being randomized. The stopping boundaries at the interim and final DFS analyses will be derived based on the exact number of DFS events observed using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries.

Timing of the Interim and Final OS Analyses

Based on the current design, the first interim OS analysis is planned at the time of the DFS interim analysis, and the second interim OS analysis is planned at the time of the DFS final analysis. It is expected to have approximately 65% and 80% of OS events at the time of the interim DFS and final DFS analysis respectively. This formal comparison of OS will allow for early stopping for

superiority. The stopping boundaries at the interim and final OS analyses will be derived based on the exact number of deaths observed using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries.

The final OS analysis will be triggered when at least 460 OS events have been observed and is projected to occur approximately 41 months after the last patient being randomized.

The timing and power of the interim and final DFS and OS analyses are summarized in Table 8.1.4-1.

The statistical software East version 6.3 (Cytel, Inc 2010) was used for study design calculations.

Table 8.1.4-1: Timing and Power of Interim and Final DFS and OS Analyses

	DFS	OS
Interim Analysis (IA) for DFS/IA 1 for OS		
Projected time from 1st patient randomized	48 months	48 months
Number of events	374 (85% of all DFS events)	299 (65% of all OS events)[a]
Significance level	0.03	0.01
Probability of crossing boundary	81%	45%
Final Analysis (FA) for DFS/IA 2 for OS		
Projected time from 1st patient randomized	58 months	58 months
Number of events	440	368 (80% of all events)[b]
Significance level	0.042	0.022
Cumulative Probability of crossing boundary	91%	70%
FA for OS		
Projected time from 1st patient randomized	NA	77 months
Number of events		460
Significance level		0.042
Cumulative Probability of crossing boundary		90%

[a] IA 1 for OS is at the time of DFS interim analysis. The actual number of OS events may be different.

[b] IA 2 for OS is at the time of DFS final analysis. The actual number of OS events may be different.

8.1.5 Potential Adjustment of Analysis Timing for DFS and OS

As discussed in the Section 8.1.1, there was no historical trial with the exact same population studied in this trial. As such, the assumptions made for the DFS and OS in the control arm might be very different from the actual rates. Since the events rates will impact the data maturity and

timing of DFS and OS analyses, BMS will conduct periodic monitoring of the DFS and OS events rates in a pooled, blinded fashion under the assumed HR of DFS and OS once a majority of the subjects are randomized. Should such monitoring suggests a big variability of the assumptions made for DFS and OS in the control arm, the impact on the data maturity and timing of analyses for DFS and OS will be evaluated and the trigger for the timing of the DFS and OS analyses may be adjusted accordingly. To maintain a strong control of type I error of the study, the significance level at interim and final analyses for DFS and OS will be adjusted based on actual events observed. The statistical analysis plan (SAP) will be used to document such changes prior to the first DFS interim analysis. Two potential scenarios are discussed below:

Scenario 1: Blinded monitoring suggests that the DFS event rate in the control arm is higher than assumed. To ensure the data maturity, a minimum follow-up time of 12 months may be added as a condition to trigger the interim DFS analyses. The minimum follow-up of 12 months ensures that all randomized subjects in the study have completed the treatment period at the time of the interim DFS analysis. In this case, all the DFS events observed will be used in the primary analysis. If the projection suggested that by the time of 12 months minimum follow-up, the number of DFS events is close to the final 440 DFS events, the DFS final analysis may be adjusted accordingly.

Scenario 2: Blinded monitoring suggests that the DFS event rate in the control arm is lower than assumed (eg, a high 'cure rate' after 2 years from surgery). In order to not significantly delay the DFS interim and final analyses, the DFS interim analysis may be triggered with less than the 85% of DFS events after a minimum follow-up time of 12 months. If the projection suggested a significant delay of the final DFS analysis timing, the final DFS may be triggered when a minimum 24 months of follow up achieved.

8.2 Populations for Analyses

- All Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IWRS.
- All Randomized Subjects: All subjects who were randomized to any treatment arm in the study. This is the primary dataset for analyses of study conduct, study population, and efficacy.
- All Treated Subjects: All randomized subjects who received at least one dose of nivolumab or placebo during the study. This is the primary dataset for analyses of exposure and safety.
- [redacted]

8.3 Endpoints

8.3.1 Primary Endpoint

Disease-free survival is the primary endpoint of this study. Disease-free survival is the time between randomization date and first date of recurrence or death, whichever occurs first. Recurrence is defined as the appearance of one or more new lesions, which can be local, regional, or distant in location from the primary resected site (by imaging or pathology). DFS will be programmatically determined based on the disease recurrence date provided by the investigator. All deaths without prior recurrence will be included as DFS event - regardless of cause or of how long it has been since the last known disease evaluation. For subjects who remain alive and without recurrence, DFS will be censored on the date of last evaluable disease assessment.

Detailed censoring rules for the primary definition of DFS are presented in Table 8.3.1-1. (Sensitivity analyses of DFS will be described in the Statistical Analysis Plan [SAP]).

Table 8.3.1-1: Censoring Scheme Used in the Primary Definition of DFS

Situation	Date of Event or Censoring	Outcome
Recurrence[a,c]	Date of first recurrence	Event
Death[b,c] without recurrence	Date of death	Event
No baseline disease assessment	Date of randomization	Censored
No on-study disease assessments and no death	Date of randomization	Censored
No recurrence and no death	Date of last evaluable disease assessment	Censored
New anticancer therapy, tumor-directed radiotherapy, or tumor-directed surgery received without recurrence reported prior to or on the same day of disease assessment	Date of last evaluable disease assessment prior to or on the same date of initiation of subsequent therapy	Censored
Second non-esophageal and non-GEJ primary cancer reported prior to or on the same day of disease assessment	Date of last evaluable disease assessment prior to or on the same date of diagnosis of second non-esophageal and non-GEJ primary cancer	Censored

[a] recurrence = appearance of one or more new lesions, which can be local, regional, or distant in location from the primary resected site

[b] All deaths will be included as DFS event - regardless of cause or of how long it has been since the last known disease evaluation.

[c] Without receiving preceding new anticancer therapy, tumor-directed radiotherapy, or tumor-directed surgery

8.3.2 Secondary Endpoint(s)

8.3.2.1 Overall Survival

Overall survival is the time between the date of randomization and the date of death. For subjects without documentation of death, OS will be censored to the last date the subject was known to be alive.

8.3.2.2 Overall Survival Rate

The overall survival rate at 1, 2, and 3 years is defined as the probability that a subject is alive at 1, 2, and 3 years, respectively, following randomization.

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment arm as randomized using descriptive statistics for all randomized subjects.

8.4.2 Efficacy Analyses

8.4.2.1 Protection of Type-I Error

For the analysis purposes of primary endpoint of DFS and the first secondary endpoint of OS, the overall hierarchical approach[64] will be used to strongly control family-wise error rate of 0.05 across 2 endpoints and repeated DFS and OS analyses at interim and final analyses. Hierarchical

test of OS will be performed following the overall hierarchical testing procedure[64] upon demonstration of superiority in DFS at DFS interim or DFS final analyses for all randomized subjects.

The details will be provided in the statistical analysis plan (SAP).

8.4.2.2 Primary Efficacy Endpoint

DFS will be compared between treatment arms using a 2-sided log rank test, stratified by the 3 randomization stratification factors (defined in Section 3.1) as recorded in IWRS. The HR for DFS with its corresponding 2-sided 100x(1 - adjusted α)% confidence intervals (CI) will be estimated via a stratified Cox model with treatment arm as the only covariate in the model.

DFS for each treatment arm will be estimated and plotted using the Kaplan-Meier (KM) product-limit method. Median survival time will be computed using the KM estimate and a 95% CI for the median will be computed based on a log-log transformation of the survivor function.

8.4.2.3 Secondary Efficacy Endpoints

Overall survival will be estimated and plotted using the KM product-limit method for each treatment arm. Median survival time along with the 95% CI will be constructed based on a log-log transformed CI for the survival function. The HR for OS with its corresponding 2-sided 100x (1 - adjusted α)% CIs will be estimated via a stratified Cox model with treatment arm as the only covariate in the model.

Overall survival will only be tested if superiority has been demonstrated in DFS. Overall survival will be compared between treatment arms using a 2-sided log rank test, stratified by the 3 randomization stratification factors (defined in Section 3.1) as recorded in IWRS.

Survival rate analysis will be carried out only for those time points which are mature enough by the time of the given database-lock. Point estimates will be provided using KM product-limit method. For each survival rate per treatment arm, two-sided 95% CIs using log-log transformation will be computed. No formal statistical comparison between the 2 arms will be performed on the survival rate.

[redacted]

8.4.3 Safety Analyses

Safety analyses will be performed in all treated subjects. Descriptive statistics of safety will be presented using NCI CTCAE version 4.0 by treatment group. All on-study AEs, treatment-related AEs, SAEs, and treatment-related SAEs will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study lab parameters including

hematology, chemistry, liver function, and renal function will be summarized using worst grade NCI CTCAE v 4.0 criteria.

[redacted]

[redacted]

8.5 Interim Analyses

8.5.1 DFS Analyses

There is 1 interim DFS analysis planned when at least 85% of all 440 DFS events (374 DFS events) are observed. Details are specified in Section 8.1.4.

Lan-DeMets alpha spending function with O'Brien-Fleming boundaries will be used to determine the statistical significance boundaries. If the DFS interim analysis is performed exactly at 85% of all 440 DFS events (374 DFS events), the boundary in terms of statistical significance for declaring superiority would be 0.03. The boundary for declaring superiority in terms of statistical significance for the final DFS analysis after 440 DFS events would be 0.042. The significance levels for the final DFS analysis will be adjusted according to the actual alpha spent at the interim analysis and the actual number of DFS events at the interim and final analyses.

8.5.2 OS Analyses

Two OS interim analyses are planned. The first interim OS analysis is planned at the time of the DFS interim analysis, and the second interim OS analysis is planned at the time of the DFS final analysis. Details of the 2 OS interim analyses are specified in Section 8.1.4.

The significance levels for the final OS analysis will be adjusted according to the actual alpha spent at interim analysis 1 and interim analysis 2 and the actual number of OS events at OS interim analysis 1, interim analysis 2, and final analysis. Details of the type I error control across 2 endpoints and repeated DFS and OS analyses at interim and final analyses are in Section 8.1.4.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

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

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

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

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

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

9.1.2 Monitoring

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

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the

facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents.

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

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

9.1.2.1 Source Documentation

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

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

9.1.3 Investigational Site Training

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

9.2 Records

9.2.1 Records Retention

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

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

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

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include investigational product. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

9.2.3 Case Report Forms

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

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively.

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

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

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and

approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

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

9.3 Clinical Study Report and Publications

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

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

1) External Principal Investigator designated at protocol development
2) National Coordinating Investigator
3) Subject recruitment (eg, among the top quartile of enrollers)
4) Involvement in trial design
5) Regional representation (eg, among top quartile of enrollers from a specified region or country)
6) Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing participation in the study. These requirements include, but are not limited to, submitting proposed publications to BMS 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

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

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
AEC	Adenocarcinoma Esophageal cancer
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
AST	aspartate aminotransferase
AT	Aminotransaminases
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
A-V	Atrioventricular
β-HCG	beta-human chorionic gonadotrophin
BICR	blinded independent central review
BID, bid	bis in die, twice daily
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
C12	concentration at 12 hours
C24	concentration at 24 hours
Ca++	Calcium
Cavg	average concentration
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
C1-	Chloride

Term	Definition
CLcr	creatinine clearance
cm	Centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CNS	Central nervous system
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
CRT	Chemoradiotherapy
Ct	Expected concentration at a certain time, usually at the end of an expected future dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
Ctau	Concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Trough observed plasma concentration
CV	coefficient of variation
CYP	cytochrome p-450
D/C	Discontinue
dL	Deciliter
DFS	Disease Free Survival
DMFS	distant metastasis free survival
EC	Esophageal Cancer
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
ECS	Esophageal Cancer Subscale
EDC	Electronic Data Capture
EEG	electroencephalogram
eg	exempli gratia (for example)
EQ-5D-3L	EuroQol questionnaire comprising 5 dimensions, with each dimension having 3 levels
FACT-E	Functional Assessment of Cancer Therapy-Esophageal
FACT-G7	7-item version of FACT-General

Term	Definition
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FSH	follicle stimulating hormone
g	Gram
GC	Gastric Cancer
GCP	Good Clinical Practice
G criteria	adjusted R2 value of terminal elimination phase
GEJ	GastroEsophageal Junction
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
h	Hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO3-	Bicarbonate
HIV	Human Immunodeficiency Virus
HNPCC	hereditary nonpolyposis colorectal cancer
HR	heart rate or hazard ratio
HRT	hormone replacement therapy
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
IV	Intravenous
IWRS	Interactive Web Response System
K	slope of the terminal phase of the log concentration-time curve
K+	Potassium

Term	Definition
kg	Kilogram
KM	Kaplan-Meier
λz	terminal disposition rate constant
L	Liter
LDH	lactate dehydrogenase
mg	Milligram
Mg++	Magnesium
min	Minute
mL	Milliliter
mmHg	millimeters of mercury
MSI	Microsatellite Instability
MSI-H	Microsatellite Instability - High
MSI-L	Microsatellite Instability - Low
MSI-S	Microsatellite Instability - Stable
MTD	maximum tolerated dose
μg	Microgram
N	number of subjects or observations
Na+	Sodium
N/A	not applicable
ng	Nanogram
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
pCR	pathological complete response
PCR	polymerase chain reaction
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamics
PD-1/PD-L1/PD-L2	programmed cell death protein 1/programmed cell death ligand 1 or 2
PFS2	Progression-free survival after the next line of the subsequent therapy

Term	Definition
PK	pharmacokinetics
QC	quality control
QD, qd	quaque die, once daily
R0	complete resection
R2	coefficient of determination
RBC	red blood cell
RCC	Renal Cell Cancer
SAE	serious adverse event
SD	standard deviation
SNP	single nucleotide polymorphism
SOP	Standard Operating Procedures
Subj	Subject
SUSAR	Suspected, Unexpected Serious Adverse Reaction
TAO	Trial Access Online, the BMS implementation of an EDC capability
T-HALF	Half life
Tmax, TMAX	time of maximum observed concentration
TR_Cmax	Cmax treatment ratio
TSH	thyroid stimulating hormone
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

APPENDIX 1 ECOG PERFORMANCE STATUS

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

[redacted]

APPENDIX 3 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 • 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 4 COUNTRY SPECIFIC REQUIREMENTS

Argentina, Czech Republic, France, Germany, Italy, Spain, and Any Other Countries Where Exclusion of HIV Positive Participants Is Locally Mandated

	Country-specific language
Section 5 Flow Chart/Time and Events Schedule, Table 5.1-1: Screening Procedural Outline (CA209577), Safety Assessments, Laboratory Tests	Add "HIV" to the list of laboratory tests
Section 3.3.2 Exclusion Criteria, 3.3.2.2 Medical History, Exclusion criterion i	"Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)"to be replaced with "Positive test for HIV".