Official Title of Study:

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

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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)

Protocol Amendment: 04

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 04	26-Apr-2024	Added the option to conduct a time-driven analysis [redacted]
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. • Added PFS2 to exploratory endpoint and follow-up procedures. • 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 [redacted] • Replaced original sample-size determinations based on co-primary endpoints. • [redacted] • [redacted] • 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. [redacted] • 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 [redacted] • 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. • Clarified that the biomarker assessments during the Follow-Up Phase (Table 5.1-3) only need to be collected upon the first recurrence of disease • [redacted] • Clarified that if the biomarker samples are collected at the scheduled time, but subsequently the dose of study drug is delayed, additional biomarker samples are not required to be collected • 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 • Clarify that subjects will receive their randomized treatment (nivolumab or

Document	Date of Issue	Summary of Change
		placebo) for the duration of the On-Treatment Period • Changed the term BMS and BMS Medical Monitor to Sponsor or designee • Clarified that [redacted] • 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 [redacted] • 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 [redacted] • Specified that [redacted] 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 • Removed PK and immunogenicity sample collections at Follow-Up Visit 1 and 2 • 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 • Added language regarding the planned analysis for the Tumor Samples and Peripheral Blood Marker • 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 • Updated terminology used for the statistical censoring scheme

Document	Date of Issue	Summary of Change
		• 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

OVERALL RATIONALE FOR REVISED PROTOCOL 04

The rationale for the change to the overall survival (OS) final analysis (FA) trigger includes factors observed during the conduct of the trial. The actual OS event accrual in the study has been much slower than projected. Initial projections for the OS FA estimated [redacted] Blinded OS event tracking commenced in 2021 after the first planned interim analysis was completed. While Bristol-Myers Squibb (BMS) remains blinded to the number of OS events by treatment arm, the overall accrual of events has slowed significantly year over year, since tracking began. [redacted]

The treatment landscape has changed markedly since the study was designed. Patients who experience recurrence after adjuvant therapy have increased treatment options and can receive subsequent therapy with immune checkpoint inhibitors (ICI) or a combination of immune checkpoint inhibitors with chemotherapy. A portion of patients may also be cured with treatment. Increased treatment options may reduce disease mortality, therefore impacting the OS event rate.

Protocol Amendment 04 adds the option to conduct a time-driven analysis. [redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04

Section Number & Title	Description of Change	Brief Rationale
Title Page	Updated European Union (EU) Trial Number. Updated Medical Monitor address.	Administrative update.
Synopsis Statistical Considerations	Added the option to conduct overall survival (OS) final analysis (FA) [redacted]	Refer to the overall rationale for revised protocol.
Section 2.1: Good Clinical Practice Section 6.1.1: Serious Adverse Event Collection and Reporting	Replaced Directive 2001/20/EC with European Regulation 536/2014.	To update the legal framework of the trial after transition to EU-CTR.
Section 8.1.4: Timing of the DFS and OS Interim and Final Analyses Section 8.1.5: Potential Adjustment	Added the option to conduct OS FA [redacted]	Refer to the overall rationale for revised protocol.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
of Analysis Timing for DFS and OS		
Throughout	Minor typographical and grammatical errors have been corrected.	For clarity and flow.

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.

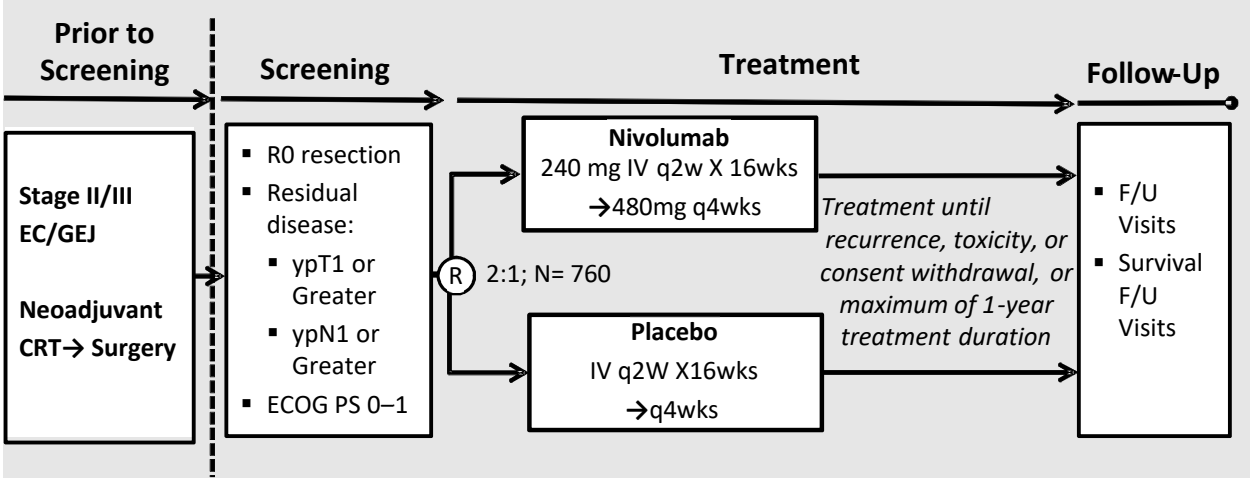
Exploratory objectives:

- To assess the overall safety and tolerability of nivolumab versus placebo in subjects with resected EC or GEJ cancer.

- To evaluate the distant metastasis free survival (DMFS) in subject with resected EC or GEJ cancer.
- To evaluate whether PD-L1 status is a predictive biomarker for DFS and OS in subjects with resected EC or GEJ cancer.
- To evaluate PD-L1 status prior to CRT and at the time of surgery in subjects with resected EC or GEJ cancer
- To explore potential biomarkers associated with clinical efficacy (DFS, and OS) and/or incidence of adverse events of nivolumab by analyzing biomarker measures within the tumor microenvironment and periphery [redacted] in comparison to clinical outcomes.
- [redacted]
- To characterize the pharmacokinetics and explore exposure-response relationships with respect to safety and efficacy
- To characterize the immunogenicity of nivolumab.
- To assess the subject's overall health status using the 3-level version of the EQ-5D (EQ-5D-3L) index and visual analog scale
- To assess the subject's cancer-related quality of life using the Functional Assessment of Cancer Therapy-Esophageal (FACT-E) questionnaire and selected components, including the Esophageal Cancer Subscale (ECS) and 7-item version of the FACT-General (FACT-G7)
- To assess progression-free survival after the next line of the subsequent therapy (PFS2) as assessed by investigators.

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 [redacted] 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 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.
- 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 [redacted]

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 [redacted]

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 [redacted]

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 [redacted]

[redacted]

Overall survival will be [redacted]

[redacted]

Survival rate analysis will be carried out only for those time points which are mature enough by the time of the given database-lock. [redacted]

TABLE OF CONTENTS

1 INTRODUCTION AND STUDY RATIONALE

1.1 Study Rationale

CA209577 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. Over the last 30 years in Western Europe, North America and Australia there has been a dramatic shift in the histological subtypes of EC from squamous cell to adenocarcinoma.[1,2] This has been attributed to a decline in smoking and an increase in adenocarcinoma risk factors including obesity, gastro-esophageal reflux disease (GERD) and Barrett's esophagus. Adenocarcinoma of the lower esophagus or gastroesophageal junction has increased dramatically amongst both men and women in the last 3 decades and its incidence is increasing faster than any other solid tumor in the Western world.[3] CRT followed by surgery (trimodality therapy) is now considered as a standard of care for the local and locoregional EC and GEJ cancers in the US and EU, and also a treatment option in Asia including Japan.[4,5,6] However, only 25-30% of subjects whose tumors have a pathological complete response (pCR) and those subjects have been shown to have a survival benefit with a 50% of 5 year survival rate.[7,8,9,10,11] The remaining 70-75% of subjects whose tumors did not achieve pathological complete response (non-pCR) have a significantly worse survival with a 37% of 5 year survival rate, and much worse for lymph node positive subjects where the median survival is only 9 months and 5 year survival is 17%.[11] There is no established standard of care in the adjuvant setting in subjects who have received CRT followed by surgery and no clinical trials have been performed in this patient population for many years. Thus there is a significant medical need for novel treatment strategies in both EC and GEJ cancers which represents a major health care problem and whose prevalence is increasing rapidly.

Immunotherapeutic approaches recently have demonstrated clinical efficacy in several advanced cancer types, including melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC).[12,13,14,15] In addition to advanced cancers, immunotherapy has also recently demonstrated a clinical benefit in adjuvant setting. Ipilimumab, a fully human monoclonal antibody that blocks CTLA-4 to augment anti-tumor immune responses□□rovided a clinically and statistically significant improvement in recurrence free survival (RFS) compared to placebo in stage III melanoma, and was recently approved by FDA.[16]

The preliminary data from Nivolumab monotherapy in heavily pre-treated GC (Gastric Cancer), GEJ and adenocarcinoma esophageal cancer (AEC) patients showed durable anti-tumor activity with 12 % objective response rate (ORR), and the duration of response (DCR) was 7 months.[17] In addition, in the squamous esophageal cancer (SEC) patients, nivolumab also showed durable anti-tumor activity with 17.2% ORR.[18] These results are promising for the advanced GC and EC patients where there is a paucity of treatment options and, in fact, demonstrate more activity than ramucirumab which has recently been approved for 2L or 3L treatment in advanced GC or GEJ cancer.[19]

An immunotherapy approach is plausible in the adjuvant setting in EC or GEJ cancer, considering the lack of effective treatment options, clinical activity in the adjuvant setting in melanoma as well as several advanced solid tumors, and the promising preliminary results with PD-1/PD-L1 blockade in the advanced GC and EC patients.

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.

1.3.3 Exploratory Objectives

- To assess the overall safety and tolerability of nivolumab versus placebo in subjects with resected EC or GEJ cancer.
- To evaluate the distant metastasis free survival (DMFS) in subject with resected EC or GEJ cancer.
- To evaluate whether PD-L1 status is a predictive biomarker for DFS and OS in subjects with resected EC or GEJ cancer.
- To evaluate PD-L1 status prior to CRT and at the time of surgery in subjects with resected EC or GEJ cancer.
- To explore potential biomarkers associated with clinical efficacy (DFS, and OS) and/or incidence of adverse events of nivolumab by analyzing biomarker measures within the tumor microenvironment and periphery [redacted] in comparison to clinical outcomes.
- [redacted]
- To characterize the pharmacokinetics (PK) and explore exposure-response relationships with respect to safety and efficacy.
- To characterize the immunogenicity of nivolumab.

- To assess the subject's overall health status using the 3-level version of the EQ-5D (EQ-5D-3L) index and visual analog scale.
- To assess the subject's cancer-related quality of life using the Functional Assessment of Cancer Therapy-Esophageal (FACT-E) questionnaire and selected components, including the Esophageal Cancer Subscale (ECS) and 7-item version of the FACT-General (FACT-G7).
- To assess progression-free survival after the next line of the subsequent therapy (PFS2) as assessed by investigators.

1.4 Product Development Background

1.4.1 Nivolumab Mechanism of Action

Immunotherapeutic approaches recently have demonstrated clinical efficacy in several cancer types, including melanoma, NSCLC, and RCC.[20,21,22,23] Tumors may modulate and evade the host immune response through a number of mechanisms, including down regulation of tumor-specific antigen expression and presentation, secretion of anti-inflammatory cytokines, and upregulation of inhibitory ligands. T cell checkpoint regulators such as CTLA-4 and programmed death-1 (PD-1, CD279) are cell surface molecules that, when engaged by their cognate ligands, induce signaling cascades down-regulating T cell activation and proliferation. One proposed model by which therapeutic T cell checkpoint inhibitors derive antitumor activity is through breaking of immune tolerance to tumor cell antigens.

Nivolumab (BMS-936558) is a fully human, IgG4 (kappa) isotype mAb that binds PD-1 on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273), thereby abrogating inhibitory signals and augmenting the host antitumor response. Nivolumab has demonstrated activity in several tumor types, including melanoma, renal cell cancer (RCC), and NSCLC.[24] Nivolumab (Opdivo®) is approved in multiple countries including the US for treatment of previously treated, unresectable or metastatic melanoma and previously treated, metastatic squamous NSCLC, and non-squamous NSCLC and RCC.[25]

1.4.2 Gastric, Gastroesophageal Junction and Esophageal Cancer Background

Esophageal cancer causes over 400,000 deaths worldwide each year.[3] The principle histologic types of esophageal cancer are esophageal squamous cell carcinoma (ESC) and esophageal adenocarcinoma (EAC). The relative frequency of histologic subtypes differs greatly by geographical location. Over the last 30 years in Western Europe, North America and Australia there has been a dramatic shift in the histological subtypes from squamous cell to adenocarcinoma, mainly located in the distal esophagus.[1] This has been attributed to a decline in smoking and an increase in adenocarcinoma risk factors including obesity, gastro-esophageal reflux disease (GERD) and possibly with falling incidence of helicobacter pylori infection and an increase in the incidence of Barrett's esophagus.[3] In contrast to the Western population, in Asia, squamous cell carcinoma predominates. ESC is mainly located in the upper or middle esophagus; smoking and

alcohol intake are considered the main contribution factors however other lifestyle choices such as methods of food preparation have been implicated.[26] GEJ tumors which are predominantly adenocarcinoma type were treated historically either like EC or GC depending on the design of prior studies.[7,27,28,29,30] The classification of GEJ has however changed from GC to EC in the United States and Europe and the NCCN esophageal guidelines now place GEJ with EC instead of GC.[4] In Asia, however, physicians treat GEJ like GC.[6]

1.4.3 Local and Locoregional Esophageal, and Gastroesophageal Junction Cancer Background

Approximately 50% of esophageal cancers will be locally or locoregionally advanced at diagnosis and thus amenable to potentially curative locoregional therapy. Five-year survival rates for all patients with EC have shown modest improvements over the past 35 years from 5% in 1975 to approximately 20% for patients diagnosed in 2004.[3] Five year survival rates for loco-regionally advanced disease treated with surgery alone has been consistently poor ranging from 6% to 26% in published series.[10,31,32]

The high incidence of recurrence, both local and distant, after ostensibly curative surgery has provided the impetus for many studies of multimodality therapy incorporating radiation and/or chemotherapy primarily in the neoadjuvant setting aimed at reducing the overall risk of relapse and death. The appropriate management of locally advanced disease has been contentious for a number of years and no standard of care has been clearly defined that has been accepted worldwide. For patients with adenocarcinoma there is clinical trial data supporting the various approaches of induction concurrent chemo-radiation (CRT), chemotherapy, peri-operative chemotherapy, or resection following by adjuvant CRT or chemotherapy. Recent data suggests that preoperative CRT is superior to surgery alone and this approach is now regarded as standard of care in the United States and Europe countries.[7]

Peri-operative chemotherapy

Multiple studies have evaluated the role of neo-adjuvant chemotherapy prior to definitive surgery for esophageal cancer.[33,34,35] Cisplatin-based combinations result in 50% or greater regression of tumor, in half of patients however a pathological complete response (pCR) occurs in only 2-6% of all patients.[33,34,35] A large US Intergroup study and several other smaller studies conducted in Europe showed no survival benefit to preoperative chemotherapy followed by surgery when compared with surgery alone.[36] Conflicting data arose from the MRC – OEO2 study conducted in the United Kingdom which reported a 5 year survival advantage of 6% for neoadjuvant chemotherapy when compared with surgery alone.[34] Similarly a Japanese study comparing preoperative chemotherapy with postoperative chemotherapy in patients with ESC suggested a survival advantage for preoperative therapy of 12% at 5 years.[37] Of note this study did not have a surgery only control arm.

Several phase III studies of peri-operative chemotherapy primarily looking at gastric cancer have enrolled subpopulations of lower esophageal or GEJ adenocarcinoma patients. The MAGIC study

conducted in the United Kingdom included 26% of patients with lower esophageal or GEJ adenocarcinoma.[27] This study demonstrated a 13% improvement in 5 year survival for patients who received multiagent ECF (epirubicin, cisplatin, fluorouracil) chemotherapy for 3 cycles preoperatively followed by a further 3 cycles postoperatively. Subgroup analyses suggested that the trend for improved survival was preserved in the group of patients with lower esophageal or GEJ tumors. A French study by Ychou et al randomized 224 adenocarcinoma patients (72% esophageal or GEJ tumors) to 2 or 3 cycles of preoperative cisplatin/5-flourouracil followed by 3 or 4 cycles of postoperative therapy, of note only 50% of patients who received at least one cycle of preoperative chemotherapy actually received postoperative therapy.[35] Despite closing early due to poor recruitment this study showed a significant survival advantage at 5 years of 14% in favor of the chemotherapy group over surgery alone. In 2011 a meta-analysis of preoperative chemotherapy suggested a hazard ratio (HR) for all-cause mortality of 0.87 (95% confidence interval [CI] 0.79 – 0.96) in favor of chemotherapy compared with surgery alone which translated to a 2 year absolute survival advantage of 5%.[38] Analysis by histology suggested a significant benefit to neoadjuvant chemotherapy for adenocarcinoma, HR 0.83 (0.71 – 0.95; p = 0.01), however the benefit for squamous tumors did not reach significance, HR 0.92 (0.81 – 1.04; p = 0.18). At present some consider peri-operative chemotherapy in tumors of the GEJ that are classified as Siewert stage 3 and where a gastric origin is favored. Neoadjuvant chemoradiation is however the treatment of choice in patients with operable esophageal or gastroesophageal junction carcinomas.

Preoperative chemo-radiotherapy

Many trials have been conducted to address the potential benefit of preoperative concurrent chemo-radiation using either surgery alone or preoperative radiation followed by surgery as a control arm. In general, these trials report a pCR in 25% to 30% of patients with associated long-term survival for this subset.[10,39,40]Approximately two thirds of patients are down-staged after preoperative CRT. Median survival rates with trimodality therapy (chemo-radiation followed by surgery) in recent studies exceed 2 years, and 3-year and 5-year survival rates are in the 30% to 40% range in US and European studies. These outcomes compare favorably with historic series of surgery alone which demonstrated 5-year survival rates of 15% to 20%. The first randomized study to show a survival advantage for trimodality therapy was published in 1996, however it was criticized for non-uniform staging of patients and the poor survival rate of the surgery only control patients.[41] Nevertheless this study encouraged the adoption of trimodality therapy as a standard of care in the United States.

Several other studies published during the 2000's failed to support a survival advantage for the trimodality approach.[9,42,43] Many of these studies were flawed, including utilizing suboptimal chemotherapy and radiation schedules, being statistically underpowered or adopting lower radiation dosing. Importantly these studies did suggest that achieving pCR was prognostically important after preoperative therapy with a significant improvement in overall survival for those achieving pCR.[44]

The Dutch CROSS study, published in 2012, has confirmed the benefits of tri-modality treatment in esophageal cancer.[7] This large, well conducted study examined weekly, low dose, radio-sensitizing carboplatin (AUC 2)/paclitaxel (50 mg/m^2) chemotherapy for 5 weeks concurrent with a standard radiation schedule followed by surgery compared with surgery alone. The majority of patients had adenocarcinoma (74.7%) with 24% having tumors of the GEJ. Multimodality treatment was well tolerated with over 90% of patients receiving all scheduled chemotherapy and radiation. R0 resections were significantly more frequent after preoperative therapy (92% vs. 69% for surgery alone, $p < 0.001$), lymph node positivity at resection was markedly reduced by preoperative therapy (31% vs. 75%, $p < 0.001$ for surgery alone) and there was no increase in postoperative morbidity or mortality. In the CROSS study with long-term follow-up, median overall survival was more than doubled for patients who received multimodality therapy (49.4 months vs. 24 months for surgery alone, $p = 0.011$) and the benefit of multimodality therapy appeared to be preserved across tumor histological subtypes and all other stratified variables. Interestingly in this study while there was a higher rate of pCR with preoperative therapy for squamous (49%) compared with adenocarcinomas (23%) this translated into better outcomes for patients with squamous histology with 81.6 months compared with adenocarcinoma type with 43.2 months.[45] The survival in patients with pCR after neoadjuvant CRT followed by surgery is much better than non-PCR patients some reported even doubled survival outcome across the histological types.[11,46] There is concern however that the chemotherapy used in the CROSS regimen is using radiation sensitizing doses of chemotherapy rather than full systemic doses. Adjuvant chemotherapy has been proposed after trimodality therapy but widespread consensus is that additional chemotherapy may not add significant benefits.[47]

Post-operative therapy

Postoperative chemotherapy and CRT have also been investigated. .CRT demonstrated a survival benefit of 36 months compared to 27 months seen with surgery alone in resectable adenocarcinoma GC and GEJ patients who did not receive neoadjuvant chemotherapy in the INT-0116 study.[48] However, the regimen (bolus fluorouracil and leucovorin before and after chemoradiation with the same combination) used in INT-0116 study is associated high rates of Grade 3 or 4 hematologic and gastrointestinal (GI) toxicities and is therefore no longer widely used. Recently, alternative postoperative CRT regimens have been investigated, but those did not improve survival compared to 0116 study.[49]

Postoperative chemotherapy in GC is the standard of care in Asia supported by the ACTS-GC and CLASSIC studies. These two large trials demonstrated improved survival compared to surgery with 5 year survival rates of 71.7% vs. 61.1% and 78% vs. 69%, respectively.[50,51]

The survival of local and locoregional GEJ cancer patients in Asia is much higher than the US and Europe, where 5 year survival has not exceeded 50% across preoperative, perioperative and post-operative approaches.[7,27,28] Differences in biology, screening and diagnosis, and surgical techniques are some of the factors thought to contribute to the survival differences between Asia and the US and Europe.

As described before, treatment of local and locoregional GEJ tumors include preoperative, perioperative and post-operative approaches. Despite these improvements compared to surgery alone, there still exists a substantial unmet medical need in the US and Europe.[7,27,28] Recent data suggests that the survival of preoperative CRT is numerically better than other approaches, and this approach is now regarded as standard of care in the US and Europe.[7] For patients who complete preoperative CRT but do not have pCR of their tumors, no accepted adjuvant therapy exists and mOS is less than 2 years.[52] This population continues to have a high unmet medical need.

1.4.4 Rationale for the Blockage of PD-1/PD-L1 in Gastric and Esophageal Cancer

PD-1 is a 55 kD type I transmembrane protein primarily expressed on activated T cells, B cells, myeloid cells, and antigen-presenting cells (APCs).[53] Binding of PD-1 to PD-L1 and PD-L2 has been shown to down-regulate T-cell activation in both murine and human systems.[54,55,56,57]

PD-L1 or PD-L2 expressing tumors have been reported in around 40% of patients in GC and EC respectively. PD-L1 expression was associated with depth of muscle invasion, tumor size, and lymph node metastasis. The overall survival of patients with PD-L1 or PD-L2–positive tumors was significantly worse than those with of PD-L1 non expressing tumors.[58,59] Thus, blockage of PD-1/PD-L1/PD-L2 might improve the survival of this population.

Pembrolizumab, a PD-1 inhibitor, reported anti-tumor activity in both advanced GC and EC tumor types who had PD-L1 expressing tumors recently. PD-L1 expression tumor (cut off 1%) was reported in 40% of GC patients as well as EC patients which is consistent with previous reports. The ORR in patients with PD-L1 expressing tumors was around 33% (13/39) and 30.4% (7/23) in GC and EC, respectively.[60,61]

1.4.5 Previous Studies of Nivolumab in Esophageal and Gastric Cancer

Nivolumab monotherapy was investigated in subjects with advanced GC including EAC and GEJ cancer in a phase 1/2 study CA209032. A total of 59 subjects received nivolumab 3 mg/kg every 2 weeks, approximately 70% of the subjects were GEJ and AEC. The preliminary data showed a durable anti-tumor activity with ORR 12%, and the duration of response was 7 months. The response was confirmed in both PD-L1 expressing and non-expressing tumors.[17] Thus, this study will not limit to subjects with PD-L1 expressing tumor only, but stratify by PD-L1 status. Preliminary data from an ongoing phase 2 study in subjects with heavily pre-treated ESC, also suggested a durable antitumor activity in nivolumab monotherapy with ORR 17.2%.[18]

These internal and external promising data of PD-1 inhibitors support us to investigate nivolumab in the EC as well as GEJ. A clinical benefit has been demonstrated in adjuvant setting in melanoma and research efforts are ongoing in other tumors. It is hoped that a similar OS benefit can be seen in the adjuvant setting in the EC/GEJ post trimodality therapy in patients who have failed to achieve a complete pathological response.

1.4.6 Summary of Nivolumab Monotherapy Safety

In clinical trials, Nivolumab has demonstrated an acceptable benefit-risk across multiple tumor types, including advanced melanoma, RCC, NSCLC, and liver cancer.

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

A total of 39 and 306 subjects with selected recurrent or treatment-refractory malignancies have been treated in a completed Phase 1 single-dose study (CA209001) and an ongoing Phase 1 multidose study (CA209003), respectively. As the safety profile from CA209003 to date is consistent with that observed for CA209001, only data from the larger and more recent study, CA209003, is presented below.

In CA209003 (n=306, including 129 subjects with NSCLC), as of the 05-Mar-2013 data base lock, drug related AEs of any grade occurred in 75% of subjects. The most frequent drug-related AEs occurring in > 5% of subjects included fatigue (28%), rash (15%), diarrhea (13%), pruritus (11%), nausea (9%), decreased appetite (9%), hemoglobin decreased (6%) and pyrexia (6%). The majority of events were low grade, with grade 3/4 drug-related AEs observed in 17% of patients. The most common Grade 3/4 drug-related AEs occurring in > 1% of subjects were fatigue (2%), pneumonitis (1%), diarrhea (1%), abdominal pain (1%), hypophosphatemia (1%), and lymphopenia (1%). Drug-related serious AEs (SAEs) occurred in 14% of patients; 8% were of Grade 3/4 including pneumonitis (1%) and diarrhea (1%). The spectrum, frequency, and severity of drug-related AEs were generally similar across the dose levels tested. A review of the safety data by tumor type (RCC, NSCLC, mCRPC, CRC, and melanoma) also did not show any clinically meaningful differences in the proportion of subjects with AEs noted across tumor type.

Select adverse events with potential immune-related causality, previously termed “immune related adverse events” or “adverse events of special interest” were also analyzed taking into account multiple events, with rates adjusted for treatment duration. Most events occurred within the first 6 months of therapy; cumulative or novel toxicities were not observed with prolonged drug exposure. Nineteen of 306 patients (6%) experienced grade 3-4 treatment related select adverse events. Fifty-two of 230 patients (23%) with drug-related adverse events required management with systemic glucocorticoids and/or other immunosuppressive agents. Twenty-one of 52 (40%) resumed nivolumab therapy after toxicity resolved, while others discontinued therapy.

Although tumor progression was the most common cause of mortality, there were 3 drug-related deaths associated with grade 3-4 pneumonitis. Pneumonitis (any grade) occurred in 12 of 306 patients (4%), and grade 3-4 pneumonitis occurred in 4 patients (1%), with clinical presentations ranging from asymptomatic radiographic abnormalities to progressive, diffuse pulmonary infiltrates associated with cough, fever, and/or dyspnea. No clear relationship between

the occurrence of pneumonitis and tumor type, dose level, or treatment duration was noted. In 9 of 12 patients, pneumonitis was reversible with treatment discontinuation and/or immunusuppression (glucocorticoids, infliximab, mycophenolate). There were no pneumonitis associated deaths between November 2011 and March 2013, the point of data analysis, while 79 patients continued to receive nivolumab during this time (median 29 weeks, range 2-69 weeks).

In CA209032 study, Nivolumab monotherapy has been administrated to subjects with heavily pre-treated advanced GC, GEJ and EAC. As of Nov 2015, 59 subjects received nivolumab 3 mg/kg every 2 weeks. Nivolumab related AEs of any grade occurred in 70% of subjects (41/59), most of them were grade 1 and 2. Grade 3 - 4 drug related AEs were observed in 17% of subjects (10/59), and no grade 5 drug related events. The safety profile in patients with advanced GC including GEJ and EAC is considered tolerable and manageable similar with other tumor types.[17]

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

1.4.7 Rationale for CA209577 Study Design

1.4.7.1 Rationale for DFS Being the Single Primary Endpoint and OS Being the First Secondary Endpoint to Be Tested in a Hierarchical Way

Disease-free survival is considered a meaningful measurement of clinical benefit in the adjuvant setting:

- Disease-free survival directly measures disease recurrence that is confirmed by imaging/cytology/pathology. Disease-free survival can be used to evaluate whether adjuvant immunotherapy after complete resection prevents or delays recurrence in subjects who have not obtained a pathological complete response following trimodal therapy.[62]
- Disease-free survival is not impacted by effects introduced by subsequent therapies. Though OS is considered a golden standard endpoint in oncology studies, it does reflect a combined treatment effect of the adjuvant setting and therapies administrated in subsequent lines. [redacted]

Disease-free survival is expected to have a strong correlation with OS in this study population:

- In the adjuvant treatment of gastric cancer, DFS has been demonstrated to be an acceptable surrogate for OS in meta-analyses comparing adjuvant chemotherapy versus surgery alone in curatively resected gastric cancer.[63] In this publication, the author concluded that the analysis showed both very tight individual-level association between DFS and OS and very high trial-level association between the effects of adjuvant chemotherapy on DFS and the treatment effects on OS. Though CA209577 studies adjuvant nivolumab administrated in subjects with resected esophageal or gastroesophageal junction cancer, the similar correlation as seen in gastric cancer between DFS and OS is also expected in this study.
- [redacted]

1.4.7.2 Rationale for Flat Dosing of Nivolumab Monotherapy

The nivolumab dose of 240 mg every 2 weeks (Q2W) was selected based on clinical data and modeling and simulation approaches using population PK (PPK) and exposure-response analyses of data from studies in multiple tumor types (melanoma, non-small-cell lung cancer [NSCLC], and renal cell carcinoma [RCC]) where body weight normalized dosing (mg/kg) has been used.

At 4 months after initiation of treatment, subjects will be switched from nivolumab 240 mg every 2 weeks to nivolumab 480 mg every 4 weeks (Q4W), which provides a more convenient dosing regimen for subjects.

1.4.7.3 Rationale for 30 minutes Infusion Times

Long infusion times place a burden on patients and treatment centers. Establishing that nivolumab can be safely administered using shorter infusion times of 30 minutes duration in subjects will diminish the burden provided no change in safety profile. Previous clinical studies show that nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg over long treatment duration. In Study CA209010, (a Phase 2, randomized, double blinded, dose-ranging study of nivolumab in subjects with advanced/metastatic clear cell RCC) a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). All the events were Grade 1 - 2 and were manageable. An infusion duration of 30 minutes for 240 mg or 480 mg nivolumab (~ 60% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60-minute duration. Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab clinical studies. A change in safety profile is not anticipated with 30-minute infusion of nivolumab.

1.4.7.4 Rationale for Placebo as the Comparator and Blinding

There are no standards of treatment for patients with EC and GEJ who received CRT followed by surgery and achieved complete resection (R0). Perioperative chemotherapy and post-operative (adjuvant) CRT or chemotherapy attempted to improve the survival, however, a meta-analysis found no relevant differences for postoperative morbidity/mortality compared to surgery alone.[66] But poor compliances of post-operative chemotherapy were reported with only 20-40% of planned doses due to the higher toxicity.[27,67,68,69] At the present time, the standard of care is for patients to go on surveillance imaging after trimodality therapy. Taken together, placebo is considered to be acceptable comparator for this population.

The subjects will be randomized into a 2:1 ratio of nivolumab to placebo, this will allow more subjects access to the active drug. The study will be double-blinded in order to minimize the bias arising from placebo, which might affect treatment duration between the arms and have an impact on the primary endpoint of disease-free survival. In addition, blinding will reduce bias in reporting, classification, and management of adverse events.

1.4.7.5 Rationale for Treating for 1 Year Total Duration

The optimal treatment duration for patients in the adjuvant setting for EC, GEJ and GC is not known. S1 monotherapy for one year treatment in the adjuvant setting is a standard treatment practice for GC in Japan based on the data from ACTS-GC. This regimen was very tolerable with 22.8% grade 3 or 4 AEs.[29] Capecitabine in combination with oxaliplatin for 6 months is also a SOC in GC adjuvant setting in Asia. However, this combination regimen has a toxicity concern with 56% Grade 3 or 4 AEs, which prevents physicians from selecting the combination regimen as the first choice in the adjuvant setting.[51]

Throughout the nivolumab development program, most protocols have dosed until progression, unacceptable toxicity, or withdrawal of consent. In the absence of dose-limiting toxicity, the treatment duration for many prior Nivolumab trials was usually not restricted.

Based on the data from S1 monotherapy for 1 year treatment, which provides promising survival benefit and tolerated safety profile in GC including GEJ, and the well tolerated safety profile of Nivolumab monotherapy, one year treatment duration is considered a reasonable duration of drug administration.

1.4.7.6 Rationale for Evaluation of PD-L1 Expression as a Predictive Biomarker of Efficacy

PD-L1 is expressed by many tumor types and its expression has been noted to correlate with decreased immune system function and worse clinical prognosis. It is hypothesized that PD-L1 expression within the tumor microenvironment, either on tumor cells, macrophages or lymphocytes is a means of evading immune system detection and destruction. Still others postulate that PD-L1 expression on tumor cells is a surrogate for interferon-gamma release from neighboring activated T cells and thus portends a good prognosis for immunotherapy agents, and in particular, agents targeting the PD-1/PD-L1 axis.

In the study CA209057 nivolumab versus docetaxel in previously treated non-squamous NSCLC, nivolumab demonstrated superior OS (HR=0.73; 96% CI: 0.59-0.89; P = 0.00155) and improved ORR (19.2% vs 12.4%; P = 0.0235). In subjects with PD-L1 expressing tumors, Nivolumab significantly improved ORR vs docetaxel (P=0.0246), with ORR as high as 36%, OS approximately doubled with nivolumab vs docetaxel across the PD-L1 expression continuum (The detail HRs at different PD-L1 cut off refer Table 1.4.7.6-1). In contrast, no difference in OS was seen between nivolumab and docetaxel when PD-L1 was not expressed in the tumor.[70]

Table 1.4.7.6-1: PD-L1 Quantifiable patients

PD-L1 expression	Nivolumab, n (N = 231)	Docetaxel n (N = 224)	OS HR (95% CI)
< 1%	108	101	0.9 (0.66, 1.24)
≥ 1%	123	123	0.59 (0.43, 0.81)
< 5%	136	138	1.01 (0.76, 1.33)
≥ 5%	95	86	0.43 (0.3, 0.63)
< 10%	145	145	1.00 (0.76, 1.31)
≥ 10%	86	79	0.4 (0.27, 0.59)

Approximately 40% of EC and GC patients reported have PD-L1 expressing tumors, which are associated with depth of muscle invasion, tumor size, lymph node metastasis and poor survival.[58,59]Recently, Pembrolizumab has demonstrated to have significant anti-tumor activity in PD-L1 expressing upper GI tumors (cut off ≥ 1%) with 30% ORR in the heavily pre-treated metastatic EC and GC in phase 1/2 studies.[60,61] In the nivolumab CA209032 study, the ORR of Nivolumab monotherapy seems better in subjects with PD-L1 expressing tumors (1% cut off) with 27% than subjects with PD-L1 non expressing tumors with 12%.[17] As the signal of anti-tumor activity also found in PD-L1 non-expressing tumors, stratifying PD-L1 status will help understand whether PD-L1 expression will be a potential predictive biomarker for DFS and OS or not. Patients will not be selected for inclusion based on PD-L1 status.

1.4.7.7 Rationale for the Stratification Factors

The stratification factors in this study are PD-L1 status (≥ 1% vs. < 1% or indeterminate or non-evaluable), pathological lymph node (positive ≥ ypN1 vs. negative ypN0) and histology (adenocarcinoma vs. squamous).

The rational of PD-L1 status as the stratification factor described in previous Section 1.4.7.6.

AJCC stage II and III are the initial clinical diagnostic stages to determine eligibility however the subjects will be randomized after CRT and surgery in this study. Patient outcome might correlate with the initial diagnosis stage, but the best correlation with survival is associated with surgical pathology staging. Pathological lymph node positive status is reported to result in worse survival

in patients with gastroesophageal cancer after trimodality therapy.[7,11] Thus, the pathological lymph status is a better stratification factor at randomization than the initial diagnostic AJCC stage.

Squamous histology showed a higher pCR rate and survival compared to adenocarcinoma in the CROSS study.[7] The HR of mOS for patients with squamous cell type was 0.48 (mOS 81.6 months vs. 21.1 months in CRT/surgery vs. surgery alone), however, the HR for patients with adenocarcinomas was 0.73 (mOS 43·2 months vs. 27·1 months in CRT/surgery vs. surgery alone). The higher pCR rate might contribute to improved survival in squamous histology compared to adenocarcinomas (49% vs. 23%). On the other hand, a meta-analysis of 12 randomized studies comparing neoadjuvant CRT versus surgery alone (n = 1854), shows the survival benefits for neoadjuvant CRT were similar in both subgroups: squamous-cell carcinoma (HR 0.80, 95% CI 0.68–0.93; p = 0.004) and adenocarcinoma (0.75, 95% CI 0.59–0.95; p = 0.02).[71] Patients with non-pCR tumors (the target population for this study) were reported to have a worse survival compared to the population achieving a pCR tumors across both histologic subtypes.[11,46] However, there are no reports to compare directly the survival or DFS between squamous and adenocarcinoma types in tumors with non-pCR. Therefore, the potential risk of unbalance in the two treatment arms by the different survival outcome of the two histology types might be mitigated by stratifying for histology.

1.5 Overall Risk/Benefit Assessment

Patients with EC including GEJ whose tumor did not achieve pCR after CRT followed surgery have a significant unmet medical need. Approximately 70-75% of patients have non-PCR tumors after neoadjuvant CRT at the time of surgery. This population has a significantly worse survival with a 37% 5 year survival rate, and even worse for lymph node positive patients where the median survival is only 9 months and 5 year survival is 17%.[11] There is no established standard of care in the adjuvant setting in patients who have received trimodality therapy for esophageal cancer and no clinical trials have been performed in this patient population for many years.

Nivolumab monotherapy has demonstrated clinical activity across several tumor types, including Melanoma, NSCLC, RCC as well as advanced/metastatic GC and EC. Nivolumab has been approved for sever tumor types in multi countries and region including the US, EU and Japan.

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 8,600 subjects treated to date. The AE profile has been consistent across multiple tumor types including GC and EC, with no maximum tolerated dose reached at any nivolumab monotherapy dose up to 10 mg/kg. Treatment related AEs have included pulmonary toxicity, renal toxicity (including acute renal failure), endocrine abnormalities, GI toxicity, dermatologic toxicity (including rash), and hepatotoxicity. In most cases, these AEs have been managed successfully with supportive care and, in more severe cases, a combination of dose delay, permanent discontinuation, and/or initiation of systemic corticosteroids.

The robust clinical activity demonstrated by nivolumab in several tumor types including advanced/metastatic EC and GC, the manageable safety profile, and the lack of standard of care

for subjects with EC including GEJ whose tumors with non-pCR after CRT following surgery supports the further development of nivolumab in this population.

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 Regulation 536/2014 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.

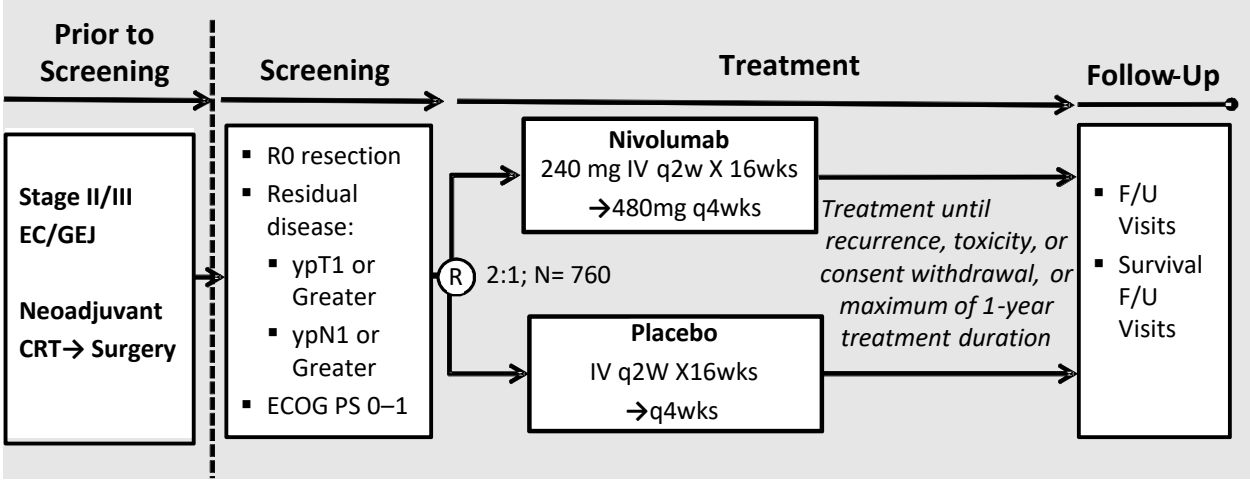
The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

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 [redacted]
- 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 [redacted] to randomization but after completion of CRT treatment, and there can have been no systemic therapy (eg, adjuvant) given after the sample was obtained. [redacted] 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. [redacted]
- Pharmacokinetic and immunogenicity sampling will be collected [redacted]

- The Outcomes Research Assessments and Health Care Resource Utilization data will be completed prior to the first dose and as described in Table 5.1-2 and Table 5.1-3, and in Section 5.7.
- 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), [redacted]
  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
- The Outcomes Research Assessments, Health Care Resource Utilization data collection, and biomarker sampling will continue as detailed in Table 5.1-3

[redacted]

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 [redacted]

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)

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

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

vi) AST ≤ 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.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the treatment and follow-up phases (before recurrence) of the study (unless utilized to treat a drug-related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 3.4.2)
- Any concurrent anti-neoplastic therapy (including, but not limited to chemotherapy, hormonal therapy, immunotherapy, radiation therapy, or standard or investigational agents for treatment of esophageal or GEJ cancer.
- Any live/attenuated vaccine (eg varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 100 days post the last dose.

3.4.2 Permitted Therapy

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

3.5 Discontinuation of Subjects following any Treatment with Study Drug

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

- Subject's request to stop study treatment
- Recurrence (local, regional or distant)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)

- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Unblinding a subject for any reason (emergency or non-emergency)
- Additional protocol specified reasons for discontinuation (see Section 4.5.5)

This is a survival study; therefore subjects discontinuing study treatment will remain on study for documentation of progression and death.

In the case of pregnancy, the investigator must immediately notify the Sponsor or designee of this event. In most cases, the blinded study drug will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of blinded study drug(s), a discussion between the investigator and the Sponsor or designee must occur.

All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

Subjects must be followed for safety for at least 100 days after the last dose of study therapy. Follow-up (FU1) occurs approximately 30 days (+/- 7 days) after last dose or coinciding with the date of discontinuation (+/- 7 days) if the date of discontinuation is greater than 35 days after the last dose. Follow up visit #2 (FU2) occurs approximately 84 days (+/- 7 days) after FU1. These follow-up visits #1 and #2 should occur in person. [redacted]

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.

4.5.2.1 Adverse Event Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with adverse events that can differ in severity and duration than adverse events caused by other therapeutic classes. Nivolumab is considered immuno-oncology agent in this protocol. Early recognition and management of adverse events associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of adverse events:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathies

- Skin
- Neurological

In order to standardize the management of adverse events for all subjects, treatment management algorithms recommended for utilization in this study are from the current IB and included in the Appendix 2 of this protocol. Adverse event treatment management algorithms included in the current IB might be considered for individual cases.

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an adverse event, consider recommendations provided in the current IB.

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 [redacted]) must be available [redacted] 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 [redacted] slides. [redacted]
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.
Concomitant Medication Collection	X	Within 14 days prior to first dose
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)

[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*
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.
Review of concomitant medications	X	X	
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
PK and Immunogenicity Assessments			
PK samples	[redacted]		
Immunogenicity blood sample			

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		
Exploratory Biomarker Assessments			
[redacted]			
Outcomes Research Assessments			
FACT-E	X	See Note	Assessed following drug vial assignment and preferably prior to procedures at Cycles 1, 3, 5, 7, 9, 10, 11, 12, 13, 14, 15, 16, and 17 (± 2 days).
EQ-5D	X	See Note	
Health Care Resource Utilization	X	See Note	
Study Drug			
IWRS Drug Vial Assignment	X	X	Vials may be assigned up to 3 days prior to first dose date

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] [redacted] 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	
Review of Concomitant Medications	X		
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] [redacted] from FU2 (± 14 days)	Notes
Outcomes Research Assessments			
EQ-5D	X	X	Prior to any assessments at FU1 and 2. [redacted] (± 14 days) after FU2, [redacted] up to 2 years from last dose
FACT-E	X		Prior to any assessments at FU1 and 2.
ECS		X	[redacted] (± 14 days) after FU2, [redacted] up to 2 years from last dose.
FACT-G7		X	
Health Care Resource Utilization	X		
Exploratory Biomarker Assessments			
[redacted]			
Subject Status			
Survival Status	X	X	[redacted] (± 14 days) or more frequently as needed after FU2, [redacted] 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] [redacted]

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.

[redacted]

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.
- [redacted]

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.

5.5 Pharmacokinetic Assessments

Samples for pharmacokinetic and immunogenicity assessment will be collected for subjects assigned to both arms [redacted]

Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual.

5.6 Biomarker Assessments

Samples for biomarker assessment will be collected for subjects assigned

[redacted]

5.6.1 Tumor Samples

Tumor specimens will be obtained from consenting subjects prior to treatment to characterize immune cell populations and expression of selected tumor markers. Tumor tissue (block or slides) must be available for submission prior to randomization.

5.6.1.1 In situ Hybridization EBV RNA (EBER) of FFPE Sections

[redacted]

5.6.1.2 Microsatellite Instability Testing

A MSI-H (Microsatellite Instability-High) in tumors refers to changes in 2 or more of the 5 National Cancer Institute-recommended panels of microsatellite markers in tumor tissue compared to a reference whole blood sample (baseline SNP collection). [redacted]

[redacted]

MSI testing will only be performed centrally if the test was not performed locally by the site.

5.6.1.3 HER2

HER2 status, as determined by FISH or IHC and measured locally by the site should be provided if known. In cases in which HER2 is unknown, central testing of tumor tissue may be performed using these platforms.

5.6.1.4 Characterization of Tumor Infiltrating Lymphocytes (TILs) and Tumor Antigens

Immunohistochemistry (IHC) will be used to assess the number and composition of immune infiltrates in order to define the immune cell subsets present within formalin-fixed, paraffin-embedded (FFPE) tumor tissue before and after exposure to therapy. [redacted]

5.6.1.5 Characterization of T Cell Repertoire

DNA sequencing may be performed on pre-and post-treatment tumor tissue to assess the composition of the T cell repertoire. [redacted]

5.6.1.6 Gene Expression Profiling

Tumor tissue [redacted]

5.6.1.7 Tumor Genotyping, Mutational Analysis, and Tumor Antigen Profiling

RNA and DNA from tumor samples will be analyzed [redacted]

5.6.2 Peripheral Blood Markers

A variety of factors that may impact the immunomodulatory properties and efficacy of nivolumab will be investigated in peripheral blood specimens [redacted]

5.6.2.1 Soluble Biomarkers

Soluble factors, [redacted] will be characterized and quantified by immunoassays in serum. [redacted]

5.6.2.2 Immunophenotyping

The proportion of specific lymphocyte subsets and expression levels of T cell co-stimulatory markers in peripheral blood mononuclear cell (PBMC) preparations will be quantified by flow cytometry. [redacted]

5.6.2.3 T Cell Repertoire Analysis

[redacted]

5.6.2.4 Whole Blood for Germline DNA

Whole blood will be collected from all subjects prior to treatment to [redacted]

5.6.2.5 Peripheral Blood Mononuclear Cells (PBMCs)

Peripheral blood samples will be taken [redacted]

[redacted]

5.7 Outcomes Research Assessments

Subjects will be asked to complete the EQ-5D-3L and FACT-E before any clinical activities are performed during on-study clinic visits and at follow up visits 1 and 2. At designated visits during the survival follow up phase, subjects will be asked to complete the EQ-5D-3L, ECS, and FACT-G7. The questionnaires will be provided in the subject's preferred language, when available, and may be administered by telephone during the survival follow-up phase. A standardized script will be used to facilitate telephone administration of the EQ-5D. Similar scripts do not exist for the ECS or FACT-G7, though subjects will be provided with hard copies of these questionnaires to take home and use as visual aids during telephone interviews.

Subjects' reports of general health status will be measured using the EQ-5D. The EQ-5D is a standardized instrument used to measure self-reports of health status and functioning. The instrument's descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels, reflecting "no health problems," "moderate health problems," and "extreme health problems." A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 3. Thus, the vectors 11111 and 33333 represent the best health state and the worst health state, respectively, described by the EQ-5D. Altogether, the instrument describes $3^5 = 243$ health states. Empirically derived weights can be applied to an individual's responses to the EQ-5D descriptive system to generate an index measuring the value to society of his or her current health. Such preference-weighting systems have been developed for Japan, UK, US, Spain, Germany, and numerous other populations. In addition, the EQ-5D includes a visual analog scale that allows respondents to rate their own current health on a 101-point scale ranging from "best imaginable" to "worst imaginable" health.

The FACT-E questionnaire and selected components, including the FACT-G7 and ECS, will be used to assess the effects of underlying disease and its treatment on health-related quality of life (HRQL). As a generic cancer-related core, the FACT-E includes the 27-item FACT-General (FACT-G) to assess symptoms and treatment-related effects impacting physical well-being (PWB; seven items), social/family well-being (SWB; seven items), emotional well-being (EWB; six items), and functional well-being (FWB; seven items). Seven of these items comprise the FACT-G7, an abbreviated version of the FACT-G that provides a rapid assessment of general HRQL in cancer patients. In addition, the FACT-E includes a 17-item disease-specific ECS that assesses concerns related to swallowing, vocalization, breathing, dry mouth, eating, disrupted sleep due to coughing, stomach pain, and weight loss. Each FACT-E item is rated on a five-point

scale ranging from 0 (not at all) to 4 (very much). Scores for the PWB, FWB, SWB, and EWB subscales can be combined to produce a FACT-G total score, which provides an overall indicant of generic HRQL, while the FACT-G and ECS scores can be combined to produce a total score for the FACT-E, which provides a composite measure of general and targeted HRQL. Higher scores indicate better HRQL. The full FACT-E will be administered to subjects during the on-treatment phase and at follow up visits 1 and 2. To minimize subject response and administrative burden, only the FACT-G7 and ECS will be administered during the survival phase after FU2 for up to 2 years after the last dose.

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

5.8 Other Assessments

5.8.1 Immunogenicity Assessments

Blood samples for immunogenicity analysis will be collected according to the schedule given in [redacted] Only samples collected from subjects receiving nivolumab will be evaluated for development of Anti-Drug Antibody (ADA) by a validated electrochemiluminescent (ECL) immunoassay.

Samples may also be analyzed for neutralizing antibodies and PK samples may be used for ADA analysis in the event of insufficient volume, to complete immunogenicity assessment, or to follow up on suspected immunogenicity-related AEs.

Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual.

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 Regulation 536/2014 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.

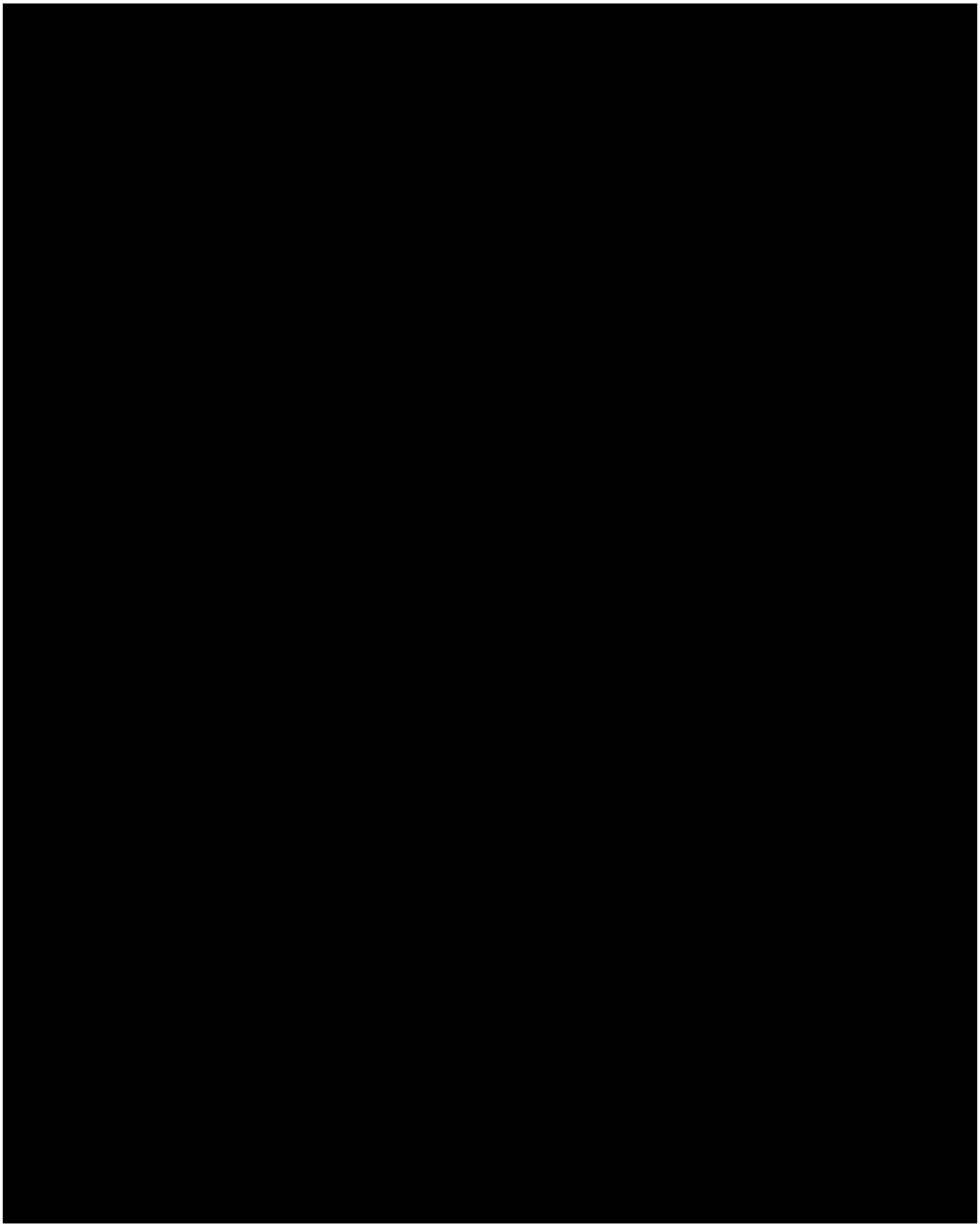
8 STATISTICAL CONSIDERATIONS

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

[redacted]



[redacted]

8.1.2 Assumptions of the Treatment Effect

[redacted]

[redacted]

8.1.3 Sample Size and Power

According to [redacted]

[redacted]

[redacted]

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 [redacted]

8.1.4 Timing of the DFS and OS Interim and Final Analyses

Timing of the Interim and Final DFS Analyses

[redacted]

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. [redacted]

[redacted] final OS analyses will be derived based on the exact number of deaths observed [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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. [redacted]

[redacted]

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.
- PK Subjects: Subjects with available serum time-concentration data from randomized subjects dosed with nivolumab.
- Outcome Research subjects: randomized subjects who have an assessment at screening/baseline and at least 1 follow-up assessment
- Immunogenicity subjects: nivolumab treated subjects who have an assessment at screening/baseline and at least 1 follow-up assessment

- Biomarker subjects: All randomized subjects with available biomarker data (PD-L1 status and other assays).

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.

8.3.3 Exploratory Endpoint(s)

- Safety and tolerability objective will be measured by the incidence of adverse events (AEs), serious adverse events (SAEs), deaths, and laboratory abnormalities.
- DMFS is defined as the time between the date of randomization and the date of first distant recurrence or date of death (whatever the cause), whichever occurs first. For subjects who remain alive and distant recurrence-free, DMFS will be censored on the date of last disease assessment.
- The objective to evaluate PD-L1 status as a predictive biomarker will be measured by the primary endpoint of DFS and the secondary endpoint of OS based on PD-L1 status level.
- The objective to evaluate PD-L1 status prior to CRT and at the time of surgery will be measured by the mean change in PD-L1 status level and by the proportion of PD-L1 positive and negative subjects.
- Pharmacokinetics will be measured using serum concentration-time data.
- PFS2 is defined as the time from randomization to the date of investigator-defined documented objective disease progression on the subsequent next-line therapy or start of second subsequent next-line therapy or death due to any cause, whichever comes first. Details for censoring will be provided in the SAP.

Assessments for other exploratory endpoints including biomarker analysis, immunogenicity, and outcomes research are discussed in Sections 5.6 and 5.8, respectively. Corresponding endpoints will be detailed in the SAP(s).

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 [redacted]

[redacted]

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 [redacted]

8.4.2.3 Secondary Efficacy Endpoints

Overall survival will be [redacted]

Survival rate analysis will be carried out only for those time points which are mature enough by the time of the given database-lock. [redacted] No formal statistical comparison between the 2 arms will be performed on the survival rate.

8.4.2.4 Exploratory Efficacy Endpoints

The HR for DMFS and PFS2 [redacted] via a Cox model with treatment arm as the only covariate in the model. [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.

8.4.4 Pharmacokinetic Analyses

The concentration vs. time data obtained in this study may be combined with data from other studies in the clinical development program to develop population PK models. These models may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab and to determine measures of individual exposure (such as steady state peak, trough and time averaged concentration). Model determined exposures may be used for exposure response analyses of selected efficacy and safety endpoints. If the analyses are conducted, the results of population PK and exposure response analyses will be reported separately.

8.4.5 Biomarker Analyses

To evaluate PD-L1 status as a predictive biomarker, a Cox proportional hazards model will be used to test the interaction between PD-L1 status (positive vs negative) and treatment arm for the OS and DFS endpoints. Additionally, OS and DFS will be analyzed within each PD-L1 expression subgroup (positive and negative) including log-rank tests and HRs with corresponding CIs. OS and DFS curves and medians will be estimated using KM methodology. These analyses will be descriptive and not adjusted for multiplicity.

Methodology for further exploratory biomarker analyses will be described in the SAP.

8.4.6 Outcomes Research Analyses

The analysis of EQ-5D and FACT-E (including FACT-G, FACT-G7, and ECS) data will be performed in all randomized subjects who have an assessment at baseline (Day 1, assessment prior to administration of drug on day of first dose) and at least 1 subsequent assessment while on treatment. Questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number, will be calculated and summarized at each assessment point.

- EQ-5D data will be described by treatment group as randomized in the following ways:
- EQ-5D index scores will be summarized at each assessment time point using descriptive statistics (ie, N, mean with SD and 95% CI, median, first and third quartiles, minimum, maximum). The UK scoring algorithm will be applied as a reference case.
- EQ-VAS scores will be summarized at each assessment time point using descriptive statistics (ie, N, mean with SD and 95% CI, median, first and third quartiles, minimum, maximum).
- The proportion (N) of subjects reporting no, moderate, or extreme problems will be presented for each of the 5 EQ-5D dimensions at each assessment time point. Subjects with missing data will be excluded from the analysis.
- A by-subject listing of the level of problems in each dimension, corresponding EQ-5D health state (ie, 5-digit vector), EQ-5D index score, and EQ-VAS score will be provided.

From the beginning of the on-treatment phase through follow-up visit 2, data for the FACT-E will be described by assigned treatment group in the following ways:

- ECS, FACT-G7, FACT-G, and FACT-E total scores will be summarized at each assessment time point using descriptive statistics (ie, N, mean with SD and 95% CI, median, first and third quartiles, minimum, maximum).
- Changes from baseline in ECS, FACT-G7, FACT-G, FACT-E total scores will be summarized at each post-baseline assessment time point using descriptive statistics (ie, N, mean with SD and 95% CI, median, first and third quartiles, minimum, maximum).

During the survival follow-up phase, data for the ECS and FACT-G7 will be described by assigned treatment group in the following ways:

- ECS and FACT-G7 scores will be summarized at each assessment time point using descriptive statistics (ie, N, mean with SD and 95% CI, median, first and third quartiles, minimum, maximum).
- Changes from baseline in ECS and FACT-G7 scores will be summarized at each post-baseline assessment time point using descriptive statistics (ie, N, mean with SD and 95% CI, median, first and third quartiles, minimum, maximum).

8.4.7 Other Analyses

Immunogenicity may be reported for ADA positive status (such as persistent positive, only last sample positive, other positive, baseline positive) and ADA negative status, relative to baseline. In addition, presence of neutralizing antibodies may be reported, if applicable. Effect of immunogenicity on safety, efficacy, biomarkers and PK may be explored. Additional details will be described in the SAP.

8.5 Interim Analyses

8.5.1 DFS Analyses

[redacted]

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.

[redacted]

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
[redacted]	[redacted]
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
[redacted]	[redacted]
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

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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

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APPENDIX 2 MANAGEMENT ALGORITHMS

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

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

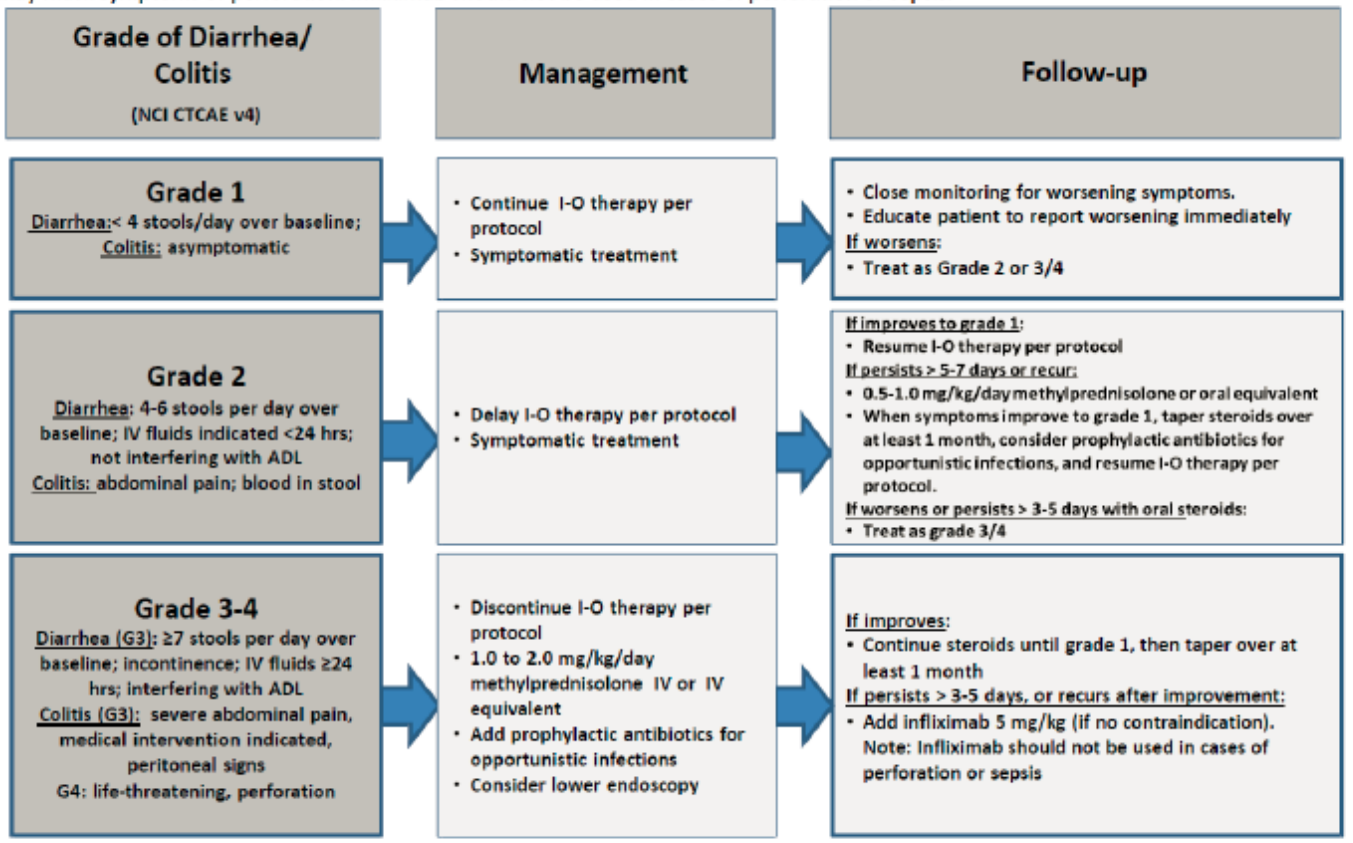
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

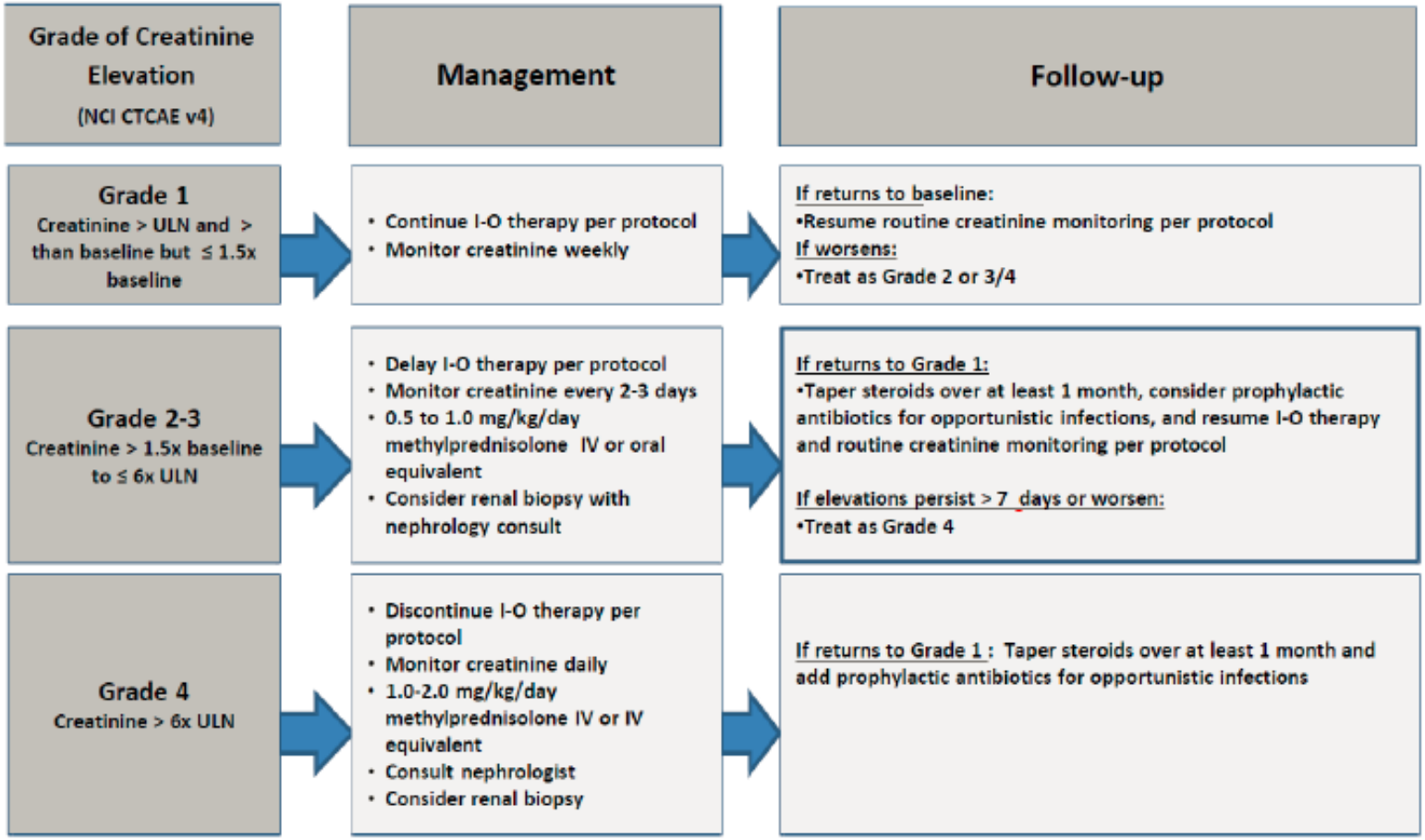


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2018

Renal Adverse Event Management Algorithm

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

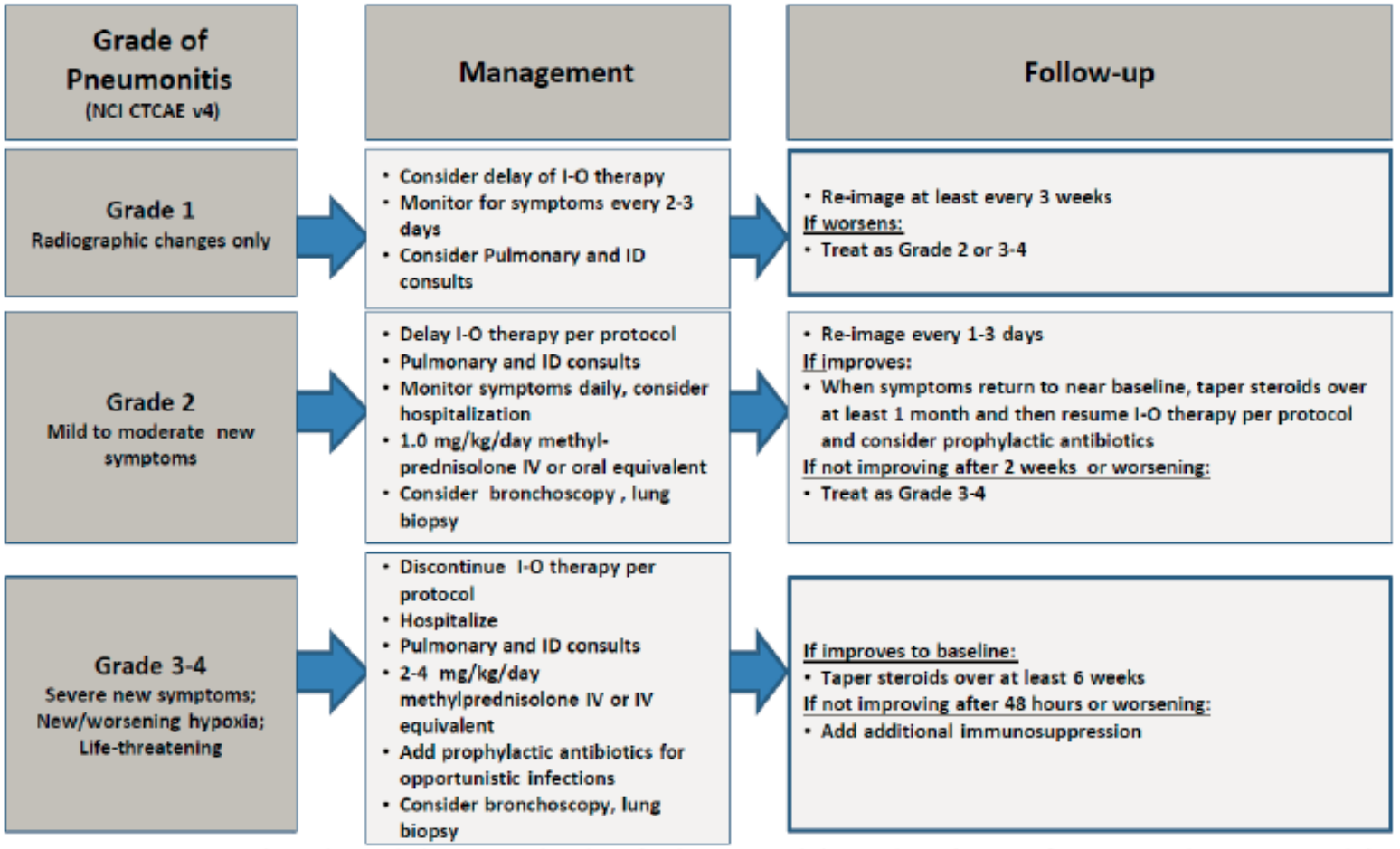


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2018

Pulmonary Adverse Event Management Algorithm

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

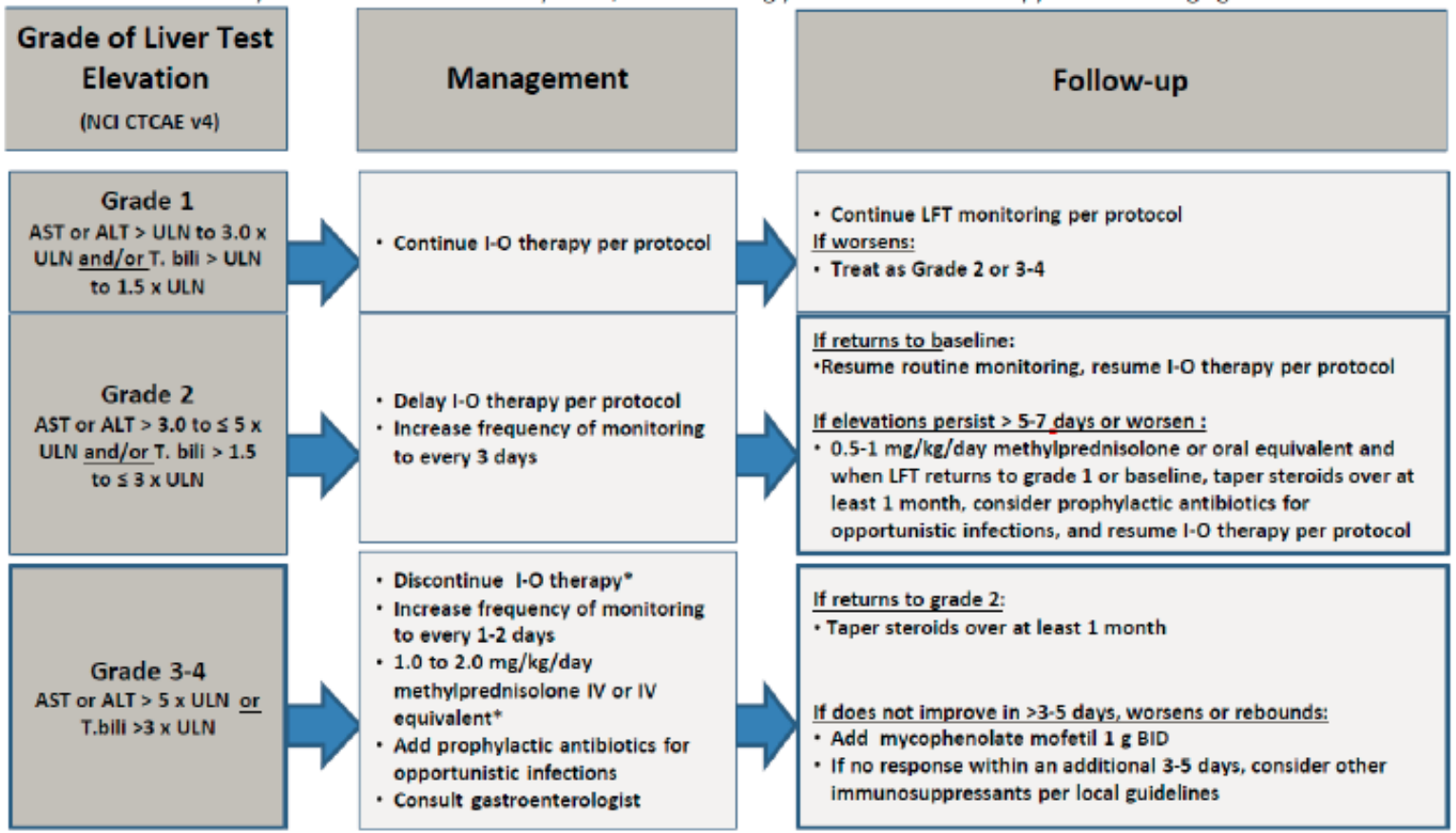


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2018

Hepatic Adverse Event Management Algorithm

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



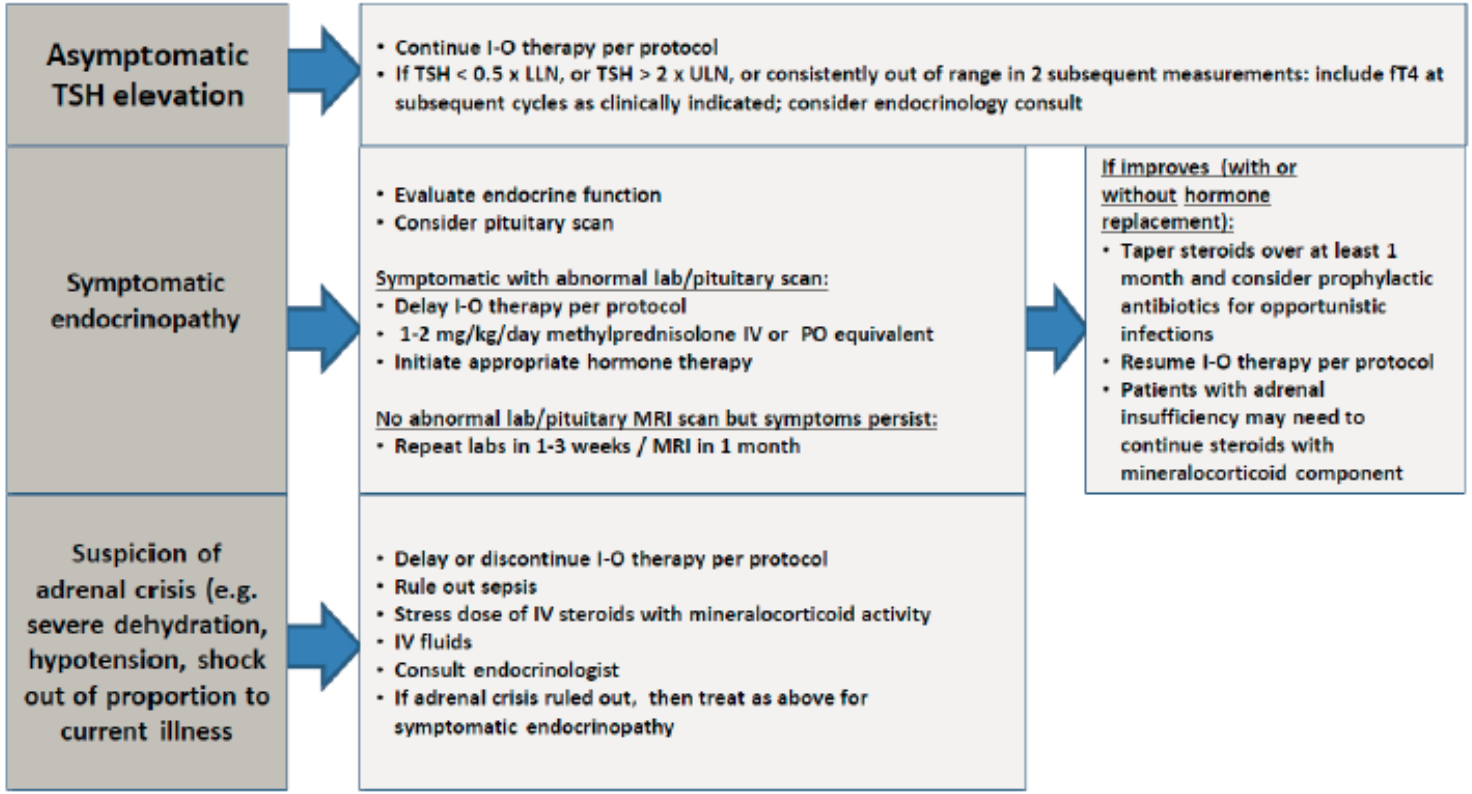
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

27-Jun-2018

Endocrinopathy Adverse Event Management Algorithm

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

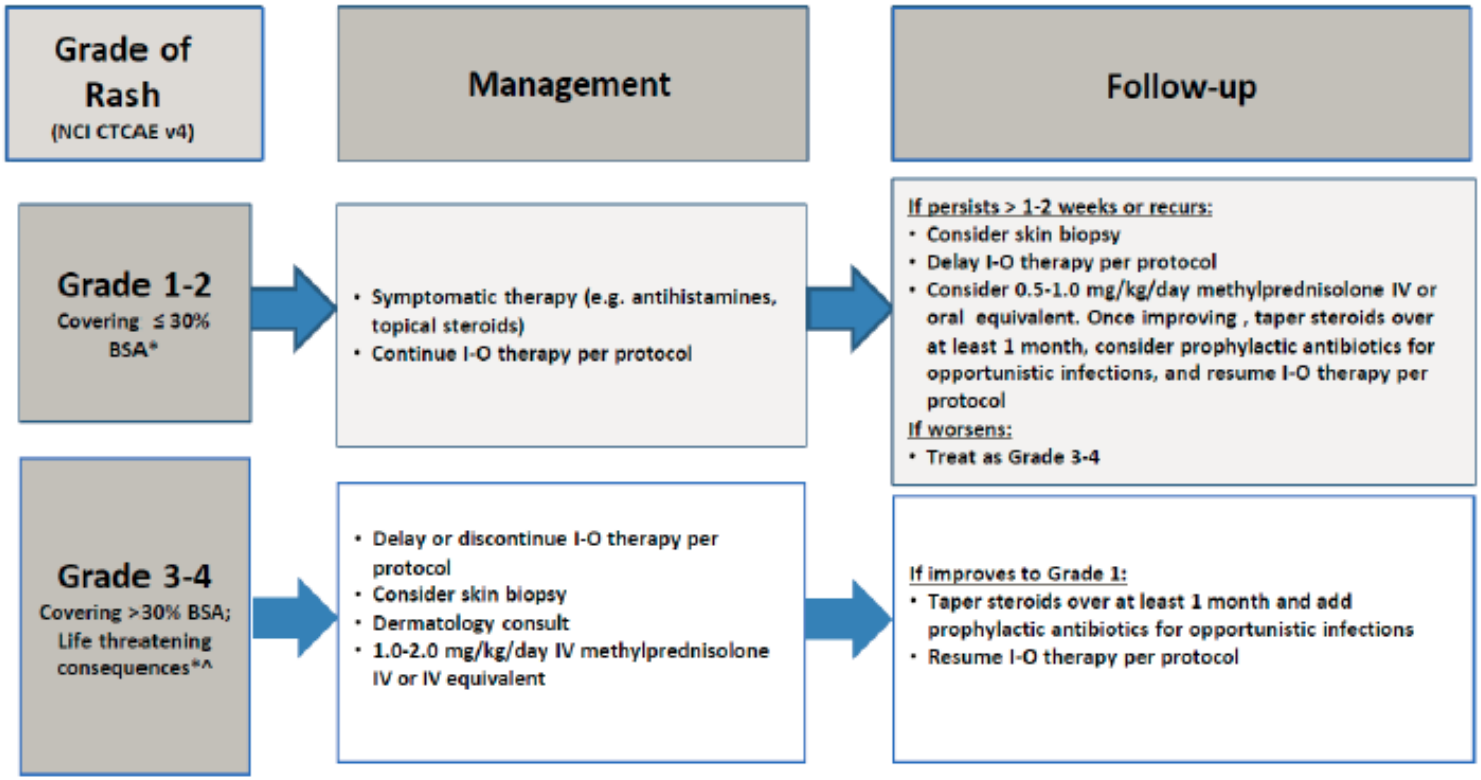


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2018

Skin Adverse Event Management Algorithm

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



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

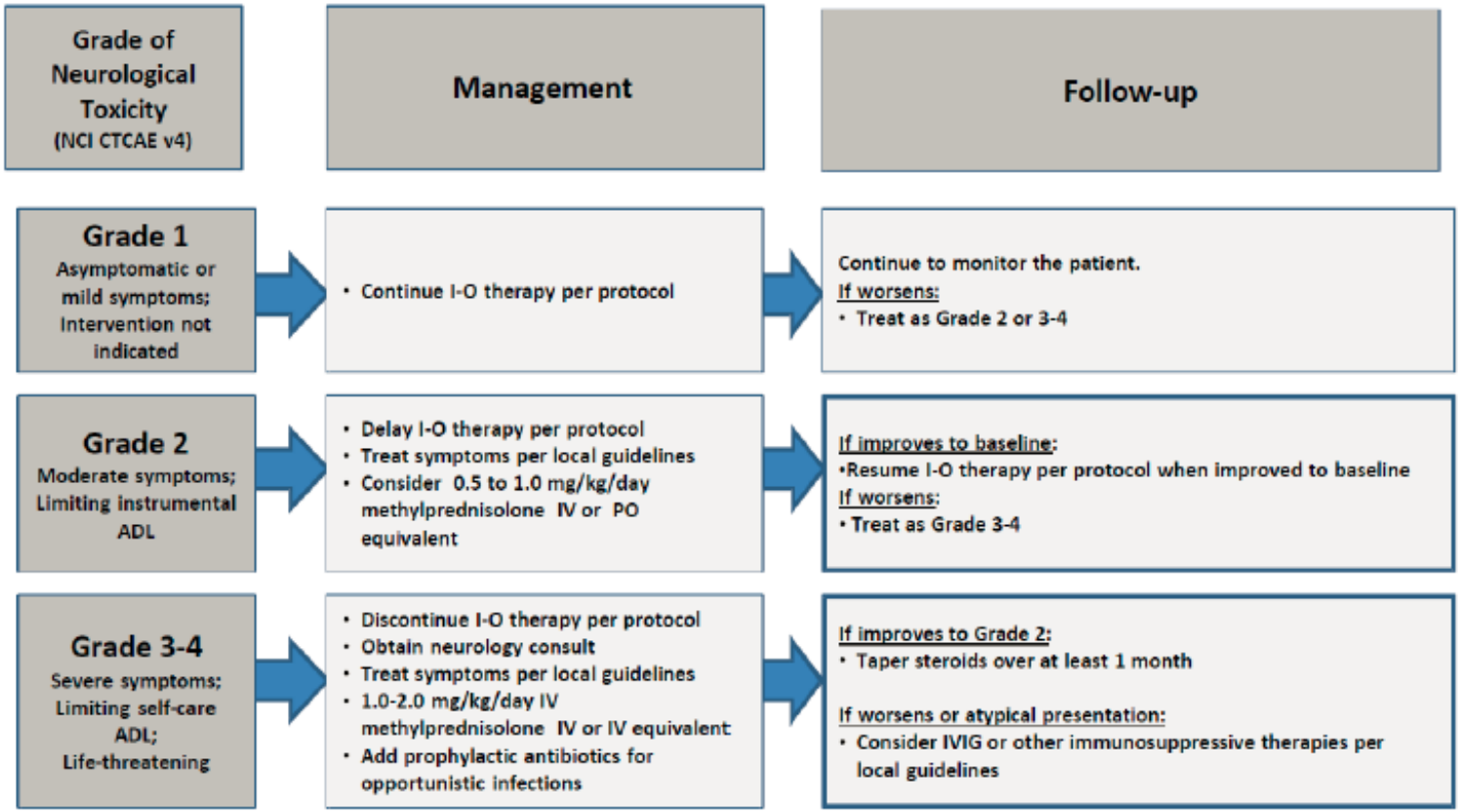
*Refer to NCI CTCAE v4 for term-specific grading criteria.

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

27-Jun-2018

Neurological Adverse Event Management Algorithm

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



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

27-Jun-2018

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".

APPENDIX 5 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

OVERALL RATIONALE FOR REVISED PROTOCOL 03

The rationale for study design changes include factors observed during the conduct of the trial. The actual enrollment in the study has been much slower than initial projections. The enrollment period was re-estimated to be 26 months (versus 15 months in the original protocol) in the Revised Protocol 02 (04-May-2017). More recently it was re-projected to approximately [redacted]

When evaluating the impact of the slow enrollment to the study design and conduct, published external data related to the study population were examined and the impact on study assumptions in the control arm were evaluated. The data from the chemoradiotherapy followed by surgery (CRT + S) arm in the CROSS trial with long-term follow up (CROSS LT) was considered the most relevant data to the study population. In consultation with external clinical experts and using data from the CROSS LT trial, it was concluded that the median disease-free survival (DFS) and overall survival (OS) in the placebo arm should be much longer than the original assumption. [redacted] Therefore, changes in the study design were needed in order to ensure that the study is adequately powered.

Given the above considerations and the rationale in Section 1.4.7.1 of Revised Protocol 03, the following major changes were made:

1) DFS has become the single primary endpoint in the study and OS changed from a co-primary endpoint to the first secondary endpoint to be tested hierarchically.
2) Progression-free survival after the next line of subsequent therapy (PFS2) has been added as an exploratory endpoint to the study per recent EMA guidance. PFS2 has recently been proposed as a surrogate for OS, particularly for trials evaluating maintenance therapy.

[redacted] were held prior to this protocol revision. Revisions apply to future subjects enrolled in the study, and where applicable, to all subjects currently enrolled.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03

Section Number & Title	Description of Change	Brief Rationale
Synopsis 1.3.1, Primary Objectives; 1.3.2, Secondary Objectives	Moved overall survival (OS) from co-primary objective to secondary objective.	See overall rational for the revised protocol above.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis 1.3.3, Exploratory Objectives	Added progression-free survival after the next line of subsequent therapy (PFS2) as an exploratory objective.	See overall rational for the revised protocol above.
1.4.3, Local and Locoregional Esophageal, and Gastroesophageal Junction Cancer Background	Added direct reference to the CROSS study long-term follow-up.	See overall rational for the revised protocol above.
1.4.7.1, Rationale for DFS Being Single Primary Endpoint and OS Being First Secondary Endpoint to Be Tested in a Hierarchical Way	Replaced entire section with robust rationale supporting disease-free survival (DFS) as single primary and OS as first secondary endpoints.	See overall rational for the revised protocol above.
3.1, Study Design and Duration	Changed accrual from [redacted] and removed sentence for total expected duration of study.	See overall rational for the revised protocol above.
3.3.2.2, Medical History and Concurrent Disease; 3.4.1, Prohibited and/or Restricted Treatments	Added exclusion criteria, on-study, and post-study requirements regarding live/attenuated vaccines.	To bring in line with current program standards. The use of vaccines in the study has been guided according to the program-wide recommendation.
3.3.2.3, Physical and Laboratory Test Findings	Updated language for clarity regarding hepatitis B or C virus exclusion criteria.	To bring in line with current program standards.
3.3.3, Women of Childbearing Potential	Updated to be consistent with updated appendix.	To bring in line with current program standards.
3.6, Post Study Drug, Study Follow-up	Removed OS from being included as a co-primary endpoint.	To reflect the design change.
4.5, Selection and Timing of Dose for Each Subject	Added language regarding monitoring for infusion-related reactions.	To bring in line with current program standards.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Added language regarding dose interruptions, delays, and discontinuation.	
4.5.5, Discontinuation of Subjects from Treatment:	Added myocarditis to Grade 3 non-skin drug-related adverse events (AEs).	To bring in line with current program standards.
Table 5.1-3: Follow-up Procedural Outline	Removed AE assessment from survival follow-up visits.	Correction to assessment table, marked in error previously.
Table 5.1-3: Follow-up Procedural Outline	Removed specific instructions from exploratory biomarkers assessments in favor of cross-referencing the full sampling schedule.	Editorial change.
Table 5.1-3: Follow-up Procedural Outline	Added x to show that survival status will be collected at follow-up visits 1 and 2. Added PFS2 assessments at follow-up visits 1 and 2 and survival follow-up visits.	Correction to assessment table To ensure adequate assessments in order to evaluate PFS2.
5.4.1, Definitions of recurrence	Clarified language regarding diagnosis of recurrence.	To bring in line with current standards.
5.4.2, Methods of Measurement	[redacted]	[redacted]
5.7, Outcomes Research Assessments	Clarified that questionnaires will be provided in the subject's preferred language when available.	To bring in line with current program language
6.2.1, Nonserious Adverse Event Collection and	Added clarifying language regarding immune-mediated adverse events.	To bring in line with current program standards.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Reporting		
8.1, Sample Size Determination	Replaced the original sample-size determinations based on co-primary endpoints.	See overall rational for the revised protocol above.
8.1.1, Assumptions of Control Arm	[redacted]	
8.1.2, Assumptions of the Treatment Effect		
Synopsis 8.1.3, Sample Size and Power	Added new section to update sample size and power estimates based on new assumptions provided in Sections 8.1.1 and 8.1.2. Synopsis was revised to reflect the information in these new sections.	To reflect the updated sample size and power based on new assumptions.
8.1.4, Timing of the DFS and OS Interim and Final Analyses	Updated entire section to provide new triggers and timing for the interim and final analyses.	[redacted]
8.1.5, Potential Adjustment of Analysis Timing for DFS and OS	Added new section to explain how timing of DFS/OS analyses will be adjusted to maintain a strong control of type I error.	To add flexibility in the trigger of the DFS/OS analyses should the blinded pooled data suggests variability of the DFS/OS rates in the control arm. The Statistical Analysis Plan will document such change.
Synopsis 8.3, Endpoints; 8.3.1, Primary	Removed OS from being a co-primary endpoint; removed headings for Sections 8.3.1.1 and	See overall rational for the revised protocol above.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Endpoints	8.3.1.2. Synopsis was revised to reflect the information in these new sections.	
Synopsis 8.3.2.1, Overall Survival; 8.3.2.2, Overall Survival Rate	Added new section to define OS and added new section heading to distinguish OS rate. Synopsis was revised to reflect the information in these new sections.	To be consistent with changes in primary and secondary endpoints.
Synopsis 8.3.3, Exploratory Endpoint(s)	Updated PD-L1 status bullet to distinguish DFS as primary and OS as secondary endpoints. Added bullet defining PFS2 as exploratory endpoint. Synopsis was revised to reflect the information in these new sections.	To be consistent with changes in primary and secondary endpoints.
8.4.2.1, Protection 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.	To reflect the design change.
8.4.2.2, Primary Efficacy Endpoint	Moved error-rate discussion to new section and removed mention of OS as a primary endpoint.	To reflect the design change.
8.4.2.3, Secondary Efficacy Endpoint	Added language describing OS analyses as secondary endpoint.	To be consistent with changes in secondary endpoints.
8.4.2.4, Exploratory Efficacy Endpoint	Added PFS2 to exploratory endpoint analyses.	To be consistent with changes in endpoints.
8.5, Interim Analyses; 8.5.1, DFS Analyses; 8.5.2, OS Analyses	Removed text under Interim Analyses and added two separate sections to address each of the DFS and OS analyses.	To be consistent with Section 8.1.4.
12, References	References have been added and	Updated to bring in line with all

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	deleted.	new text revisions.
Appendix 2, Management Algorithms	Updated to reflect current IB.	Updated to bring in line with current program standards.
Appendix 3, Women of Childbearing Potential Definition	Updated to reflect current version of appendix.	Updated to bring in line with current program standards.
Appendix 4, County Specific Requirements	Added	Updated to bring in line with current program standards.
Global	Typographical and grammatical, errors have been corrected.	Minor, therefore have not be summarized.