Official Title of Study:

A Randomized Phase 3 Study of Nivolumab plus Ipilimumab or Nivolumab Combined with Fluorouracil plus Cisplatin versus Fluorouracil plus Cisplatin in Subjects with Unresectable Advanced, Recurrent or Metastatic Previously Untreated Esophageal Squamous Cell Carcinoma

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Clinical Protocol CA209648

A Randomized Phase 3 Study of Nivolumab plus Ipilimumab or Nivolumab Combined with Fluorouracil plus Cisplatin versus Fluorouracil plus Cisplatin in Subjects with Unresectable Advanced, Recurrent or Metastatic Previously Untreated Esophageal Squamous Cell Carcinoma

(CheckMate 648: CHECKpoint pathway and nivoluMab clinical Trial Evaluation 648)

Revised Protocol Number: 05

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 05	29-Oct-2020	This revised protocol allows for the final PFS analysis to be triggered when 136 PFS events per BICR are observed among the PD-L1 expressing subjects in the chemotherapy arm or when at least 12 months minimum follow up is reached, if the target number of PFS events is unlikely to be reached.
Revised Protocol 04	12-Sep-2018	This revised protocol restricts study entry to participants of previous nivolumab clinical studies where overall survival was listed as a primary or co-primary endpoint. Live /attenuated vaccines were prohibited and the inclusion criterion related to the assessment of renal function was expanded to allow the consideration of measured creatinine clearance. Cisplatin infusion times longer than 120 minutes were allowed if deemed necessary by investigator per local standard of care/local label. PFS2/TSST was added as an exploratory endpoint. The section on biomarker assessments was revised. Program updates were added and internal inconsistencies were corrected.
Revised Protocol 03	02-Feb-2018	This revised protocol removed the procedures for the reinitiation of nivolumab ± ipilimumab treatment after disease progression for up to 1 additional year. In addition, it added clarification to the treatment beyond progression procedures to limit treatment to a maximum duration of 24 months.
Revised Protocol 02	25-Oct-2017	To align the protocol with the latest SmPC, simplify procedures, and provide clarifications in the protocol.
Revised Protocol 01	21-Dec-2016	Incorporates Amendment(s) 02
Amendment 02	21-Dec-2016	Expansion of the esophageal cohort into a 3-arm randomized Phase 3 study in first line squamous esophageal cancer. The study now includes a nivolumab plus chemotherapy arm (fluorouracil and cisplatin) and a chemotherapy alone arm in addition to the existing nivolumab and ipilimumab arm. The gastric cohort was removed.
Administrative Letter 01	30-Mar-2017	To correct typographical errors to Study Drug Table in Synopsis, and Table 4.5.1.1-1 and Table 5.1-2, and Section 4.5.1.1.
Original Protocol	01-Jun-2016	Not applicable

OVERALL RATIONALE FOR THE REVISED PROTOCOL 05

Per protocol, the planned interim analysis (PFS final analysis and OS interim analysis) will be triggered when 136 PFS events per blinded independent central reviewer (BICR) are observed among subjects expressing at least 1% tumor PD-L1 in the chemotherapy arm (Arm C). PFS event tracking is conducted by an independent external statistical group (Axio, Inc), which supports statistical analyses and generates reports for review by an independent Data Monitoring Committee. BMS remains blinded to the number of PFS events in arm A and arm B. Event tracking commenced in July 2020. PFS events are observed to be tracking at a much slower rate than projected per protocol. This is largely due to censoring due to start of subsequent therapy or withdrawal of consent prior to progression, the extent of which was unforeseen when this protocol was developed.

This protocol amendment adds another trigger for the interim analysis (Final PFS/Interim OS) in the event that the target number of PFS events is not reached. The revised protocol allows for the final PFS analysis to be triggered when 136 PFS events are observed among the PD-L1 expressing subjects in the chemotherapy arm, or when at least 12 months minimum follow up (defined as the time from the date of the last patient was randomized to the clinical cutoff date) is reached. In the eventuality that the target number of PFS events is not reached, the 12 months minimum follow-up ensures adequate follow-up for PFS in this patient population.

As per original design, OS IA will be conducted at the same time as PFS final analysis (FA) and the alpha allocation will be calculated per the specified method (see section 7.5 of SAP).

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis, Section 8.1: Sample Size Determination	Amended trigger for the IA	Added provision for triggering the planned IA when at least 12 months minimum follow-up is reached, in the eventuality that the planned 136 PFS events per BICR among the PD L1 expressing subjects in the chemotherapy are unlikely to be reached.

SYNOPSIS

Clinical Protocol CA209648

Protocol Title: A Randomized Phase 3 Study of Nivolumab plus Ipilimumab or Nivolumab Combined with Fluorouracil plus Cisplatin versus Fluorouracil plus Cisplatin in Subjects with Unresectable Advanced, Recurrent or Metastatic Previously Untreated Esophageal Squamous Cell Carcinoma

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

- Nivolumab + Ipilimumab: Nivolumab 3 mg/kg as a 30-minute infusion every 2 weeks and ipilimumab 1 mg/kg as a 30-minute infusion every 6 weeks (Arm A) or
- Nivolumab + Chemotherapy: Nivolumab 240 mg as a 30-minute infusion every 2 weeks (i.e. on Day 1 and Day 15), fluorouracil 800 mg/m²/day as an IV continuous infusion on Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m² as a 30- to 120-minute infusion* on day 1 of 4-week cycle(Arm B) or
- Chemotherapy: fluorouracil 800 mg/m²/day as an IV continuous infusion on Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m²/day as a 30- to 120-minute infusion* on day 1 of 4-week cycle (Arm C).

*Subjects are allowed to receive treatment with cisplatin 80 mg/m² as an IV infusion over a period of longer than 120 min if it is in accordance with local standard of care/local label.

Treatment with nivolumab or nivolumab with ipilimumab (arms A and B) will be given for up to 24 months in the absence of disease progression or unacceptable toxicity. Chemotherapy (Arms B, and C) will be given as per the study dosing schedule until disease progression, unacceptable toxicity or other reasons specified in the protocol.

Study Phase: Phase 3

Research Hypothesis:

- The administration of nivolumab plus ipilimumab will improve overall survival (OS) compared with fluorouracil and cisplatin combination in subjects with unresectable advanced, recurrent or metastatic ESCC with PD-L1 expression ≥ 1%.
- The administration of nivolumab combined with fluorouracil plus cisplatin will improve OS compared with fluorouracil and cisplatin combination alone in subjects with unresectable advanced, recurrent or metastatic ESCC with PD-L1 expression ≥ 1%.
- The administration of nivolumab plus ipilimumab will improve progression free survival (PFS) as assessed by a blinded independent central review committee (BICR) compared with fluorouracil and cisplatin combination in subjects with unresectable advanced, recurrent or metastatic ESCC with PD-L1 expression ≥ 1%.
- The administration of nivolumab combined with fluorouracil plus cisplatin will improve PFS as assessed by a BICR compared with fluorouracil and cisplatin combination alone in subjects with unresectable advanced, recurrent or metastatic ESCC with PD-L1 expression ≥ 1%.

Objectives:

Primary Objectives

- To compare the OS of nivolumab plus ipilimumab (Arm A) to fluorouracil plus cisplatin chemotherapy (Arm C) in subjects with PD-L1 expression ≥ 1%.
- To compare the OS of nivolumab combined with fluorouracil plus cisplatin (Arm B) to fluorouracil plus cisplatin chemotherapy (Arm C) in subjects with PD-L1 expression ≥ 1%.
- To compare the PFS of nivolumab plus ipilimumab (Arm A) to fluorouracil and cisplatin combination (Arm C) as assessed by a BICR in subjects with PD-L1 expression ≥ 1%.

- To compare the PFS of nivolumab combined with fluorouracil plus cisplatin (Arm B) to fluorouracil and cisplatin combination (Arm C) as assessed by a BICR in subjects with PD-L1 expression ≥ 1%.

Secondary Objectives

- To compare the OS of nivolumab plus ipilimumab (Arm A) and nivolumab combined with fluorouracil plus cisplatin (Arm B) to fluorouracil and cisplatin combination (Arm C) in all randomized subjects.
- To compare the PFS of nivolumab plus ipilimumab (Arm A) and nivolumab combined with fluorouracil plus cisplatin (Arm B) to fluorouracil and cisplatin combination (Arm C) as assessed by a BICR in all randomized subjects.
- To compare the objective response rate (ORR) of nivolumab plus ipilimumab (Arm A) and nivolumab combined with fluorouracil plus cisplatin (Arm B) to fluorouracil and cisplatin combination (Arm C) as assessed by a BICR in subjects with PD-L1 expression ≥ 1%.
- To compare the ORR of nivolumab plus ipilimumab (Arm A) and nivolumab combined with fluorouracil plus cisplatin (Arm B) to fluorouracil and cisplatin combination (Arm C) as assessed by a BICR in all randomized subjects.

Exploratory Objectives

Exploratory objectives are listed in Section 1.3.3 of the protocol

Study Design: This is a randomized Phase 3 study of nivolumab plus ipilimumab or nivolumab combined with fluorouracil plus cisplatin compared with fluorouracil in combination with cisplatin in adult (≥ 18 years) male and female subjects with unresectable, advanced, recurrent or metastatic, previously untreated ESCC. The total number of subjects to be randomized is approximately 939 subjects.

After signing the informed consent form, and upon confirmation of the subject's eligibility, subjects with unresectable, advanced, recurrent or metastatic ESCC will be randomized in a 1:1:1 ratio to one of the following open-label treatments (Arms A, B and C):

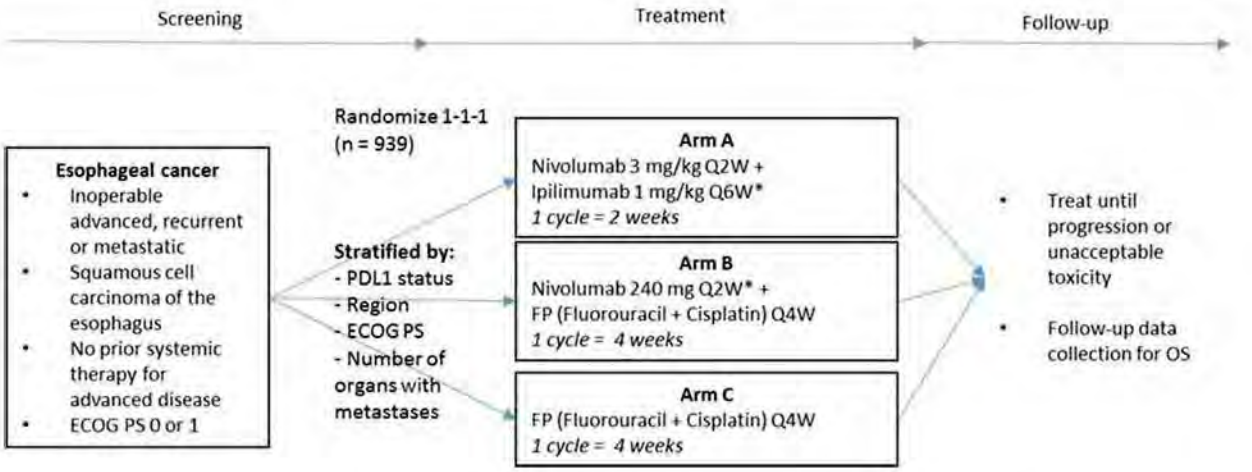
- Arm A: Subjects will receive treatment with nivolumab 3 mg/kg as a 30-minute infusion every 2 weeks and ipilimumab 1 mg/kg as a 30-minute infusion every 6 weeks.
- Arm B: Subjects will receive treatment with nivolumab 240 mg as a 30-minute infusion on Day 1 and Day 15, fluorouracil 800 mg/m²/day as an IV continuous infusion from Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m² as a 30- to 120-minute infusion* on day 1 of each 4-week cycle.
- Arm C: Subjects will receive treatment with fluorouracil 800 mg/m²/day as an IV continuous infusion on Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m² as a 30- to 120-minute infusion* on day 1 of each 4-week cycle.

*Subjects are allowed to receive treatment with cisplatin 80 mg/m² as an IV infusion over a period of longer than 120 min if it is in accordance with local standard of care/local label.

Stratification factors:

1. PD-L1 status (≥ 1% vs < 1% [including indeterminate])*
2. Region (East Asia (Japan, Korea, Taiwan) vs Rest of Asia vs Rest of world)
3. Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1).
4. Number of organs with metastases (≤1 vs. ≥2)

*The proportions of subjects with or without PD-L1 tumor expression will be monitored and reassessed as needed to ensure that the sample size of randomized subjects with PD-L1 tumor expression ≥ 1% is adequate for analysis (ie, approximately 50% of all comers).



*Treatment with nivolumab or nivolumab + ipilimumab will be limited to 2 year maximum duration

Study Population: Subjects must meet all eligibility criteria specified in Section 3.3 of the protocol. The key inclusion and exclusion criteria are as follows.

Key Inclusion Criteria:

a) Subjects must have histologically confirmed squamous cell carcinoma or adenosquamous cell carcinoma (predominant squamous differentiation) of esophagus (per AJCC 7th edition, see Appendix 4).

b) Subjects must have unresectable advanced, recurrent or metastatic ESCC (per AJCC 7th edition, see Appendix 4).

c) Subjects must not be amenable to curative approaches such as definitive chemoradiation and/or surgery

d) No prior systemic anticancer therapy given as primary therapy for advanced or metastatic disease.

i .Prior adjuvant, neoadjuvant, or definitive, chemotherapy/radiotherapy/chemoradiotherapy for ESCC is permitted if given as part of curative intent regimen and completed before enrollment. A recurrence-free period is required for 24 weeks after completion of neoadjuvant or adjuvant chemotherapies, or after completion of multimodal therapies (chemotherapies and chemoradiotherapies) for locally advanced diseases

e) ECOG Performance Status of 0 or 1, see Appendix 3

f) Subjects must have at least one measurable lesion by CT or MRI per RECIST 1.1 criteria; radiographic tumor assessment must be performed within 28 days prior to randomization.

g) Tumor tissue must be provided for biomarker analyses. Either 1 formalin fixed paraffin embedded (FFPE) tumor tissue block or 15 unstained tumor tissue slides, with an associated pathology report if available, must be submitted for biomarker evaluation prior to study drug administration. The tumor tissue sample may be fresh or archival if obtained within 6 months prior to randomization, and there can have been no systemic therapy (eg, adjuvant) given after the sample was obtained. Tissue must be a core needle biopsy, excisional or incisional biopsy. Fine needle biopsies or drainage of pleural effusions with cytospins are not considered adequate for biomarker review and randomization. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable.

h) In order to be randomized, a subject must have an evaluable PD-L1 expression classification $\geq 1\%$ or $< 1\%$, or indeterminate) as determined by the central lab.

   a. Subjects with non-evaluable results will not be allowed to be randomized.

Key Exclusion Criteria:

a) Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before randomization.

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

c) Subjects with active, known, or suspected autoimmune disease. Subjects with Type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll. For any cases of uncertainty, it is recommended that a BMS medical monitor be consulted prior to signing informed consent.

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

e) 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.

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

Study Drug for CA209648		
Medication	**Potency**	**IP/Non-IP**
Nivolumab	10 mg/mL	IP
Ipilimumab	5 mg/mL	IP
Fluorouracil	1 g/vial (50 mg/ mL)	IP
Cisplatin	100 mg (1 mg/mL)	IP

Study Assessments: Subjects will be assessed for response by CT or MRI. Radiologic assessments will be performed at baseline (within 28 days prior to randomization), then every 6 weeks (± 7 days) up to and including Week 48, and then every 12 weeks (± 7 days) thereafter, regardless of treatment schedule, until disease progression (unless treatment beyond progression is permitted) or the subject discontinues the study, whichever comes first. Subjects who discontinue study drug for reasons other than PD and who continue in the follow-up phase of the study will continue to have tumor assessments as indicated above. All radiologic images from the study will be submitted to a central imaging core lab for analysis by a BICR. The BICR will review tumor images in all randomized subjects to determine RECIST 1.1 response for the analyses of PFS and ORR.

Statistical Considerations:

Sample size: The sample size is based on the primary objectives, ie, on the comparisons of the PFS/OS distributions of subjects with PD-L1 expressing tumors between those who were randomized to receive nivolumab plus ipilimumab vs those randomized to receive chemotherapy, and between those who were randomized to receive nivolumab plus chemotherapy vs those randomized to receive chemotherapy.

Sample size calculations assume that the prevalence of subjects with PD-L1 tumor expression level ≥ 1% is approximately 50%. (During enrollment, the proportion of subjects with or without PD-L1 tumor expression will be monitored, and may be re-assessed in case it does not reflect study assumptions.)

Piecewise mixture cure rate model was used for the design setup, assuming for both experimental arms the same OS distributions and the same PFS distributions. As a result, for each of the nivolumab plus ipilimumab vs chemotherapy and nivolumab plus chemotherapy vs chemotherapy comparisons:

- 250 PFS events in approximately 313 subjects with PD-L1 expressing tumors will provide approximately 90% power to detect an average HR of 0.62 with a Type I error of 1.5% (two-sided)
- 250 OS events in approximately 313 subjects with PD-L1 expressing tumors will provide approximately 90% power to detect an average HR of 0.6 with a Type I error of 1% (two-sided).

To have approximately 313 randomized subjects with PD-L1 expressing tumors for each comparison, approximately 470 subjects with PD-L1 expressing tumors need to be randomized in a 1:1:1 ratio in the 3 arms. Which therefore translates to a total of approximately 939 subjects (with any PD-L1 result) to be randomized in a 1:1:1 ratio to the nivolumab plus ipilimumab or nivolumab plus chemotherapy or chemotherapy arms. Assuming a piecewise constant accrual rate, it is estimated that these 939 subjects will be accrued within 29 months.

Although for the comparison of both experimental arms with the control arm, the same treatment effect is assumed, observed treatment effects may vary. Therefore, the events of interest (OS, PFS) observed in the chemotherapy arm *only* will be used for determining the timing of the interim and final efficacy analyses. Final PFS analysis is planned when 136 PFS events per BICR are observed among the PD-L1 expressing subjects in the chemotherapy arm. This is expected to be reached after approximately 33 months. If the planned number of PFS events is unlikely to be reached for any unforeseen reasons, the final PFS analysis may occur when at least 12 months minimum follow-up (defined as the time from the date when the last patient was randomized to the clinical cutoff date) is reached. Should this scenario occur, corresponding to PFS events of 110 and 121, the power would be 80% and 85%, respectively (details of this scenario are discussed in Appendix 7 of the SAP). Final OS analysis is planned when 140 events are observed among the PD-L1 expressing subjects in the chemotherapy arm. This is expected to be reached after approximately 49 months.

Simulations were conducted in R-v3.1.3.

Endpoints:

Primary Endpoint

Overall survival (OS) in subjects with PD-L1 expressing tumors. OS is defined as the 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.

Progression-free Survival (PFS) (as assessed by BICR) in subjects with PD-L1 expressing tumors. PFS is defined as the time from randomization to the date of the first documented PD per BICR or death due to any cause. Subjects who die without a reported prior PD per BICR (and die without start of subsequent therapy) will be considered to have progressed on the date of death. Subjects who did not have documented PD per BICR per RECIST1.1 criteria and who did not die, will be censored at the date of the last evaluable tumor assessment on or prior to initiation of the subsequent anti-cancer therapy. Subjects who did not have any on-study tumor assessments and did not die (or died after initiation of the subsequent anti-cancer therapy) will be censored at the randomization date. Subjects who started any subsequent anti-cancer therapy without a prior reported PD per BICR will be censored at the last tumor assessment on or prior to initiation of the subsequent anti-cancer therapy.

Secondary Endpoints

Overall survival (OS) in All Randomized subjects. OS is defined the same way as for the primary endpoint (for subjects with PD-L1 expressing tumors).

Progression-free Survival (PFS) (as assessed by BICR) in All Randomized subjects. PFS is defined the same way as for the primary endpoint (for subjects with PD-L1 expressing tumors).

Objective Response Rate (ORR) (as assessed by BICR) in subjects with PD-L1 expressing tumors and All Randomized subjects. It is defined as the number of subjects with a best overall response (BOR) of CR or PR divided by the number of randomized subjects in the population for each treatment group. BOR is defined as the best response designation as determined by BICR, recorded between the date of randomization and the date of objectively documented progression (per RECIST 1.1 as determined by BICR) or the date of subsequent anti-cancer therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first. For subjects without documented progression or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination.

Analyses:

Primary Endpoint

Progression free survival in subjects with PD-L1 expressing tumors will be compared

- between nivolumab plus ipilimumab vs chemotherapy using a two-sided log rank test and an endpoint-specific (i.e. initially allocated) significance level of 1.5%; and
- between nivolumab plus chemotherapy vs chemotherapy using a two-sided log rank test and an endpoint-specific significance level of 1.5%.

Overall survival in subjects with PD-L1 expressing tumors will be compared

- between nivolumab plus ipilimumab vs chemotherapy using a two-sided log rank test and an endpoint-specific overall significance level of 1% defined for the groups sequential testing procedure;
- between nivolumab plus chemotherapy vs chemotherapy using a two-sided log rank test and an endpoint-specific overall significance level of 1% defined for the groups sequential testing procedure.

All tests will be stratified by region (East Asia [Japan, Korea, Taiwan] vs Rest of Asia vs RoW), ECOG status (0 vs 1), and number of organs with metastases (≤ 1 vs ≥ 2) as recorded in the IRT. Endpoint-specific significance levels are split based on the conservative Bonferroni method and may be updated through graphical approach where the family-wise error rate will be protected in the strong sense. Rules for updating endpoint-specific significance levels following the Bonferroni-based graphical approach by Maurer and Bretz (2013) will be detailed in the statistical analysis plan (SAP).

For each comparison, the HR with its associated two-sided 100*(1 - adjusted α)% confidence intervals (CI) will be estimated via a stratified Cox model with treatment arm as the only covariate in the model. Both PFS and OS for each treatment arm will be estimated and plotted using the Kaplan-Meier (KM) product-limit method. Median survival time along with 95% CI will be constructed based on a log-log transformed CI for the survival function.

Secondary Endpoints

Time-to-event endpoints (OS and PFS as assessed by BICR in all randomized subjects) will be estimated and plotted using the KM product-limit method for each treatment arm. Median survival time along with 95% CI will be constructed based on a log-log transformed CI for the survival function. The HR with its associated two-sided 95% CI will be estimated via a stratified Cox model with treatment arm as the only covariate in the model.

Overall Survival and PFS in all randomized subjects will be tested only if significance level is passed on them. Rules for passing on significance levels will be defined together with the graphical approach in the SAP. Comparisons will use a two-sided log rank test, stratified by the same stratification factors as the primary endpoint and by PD-L1 status ($\geq 1\%$ vs $< 1\%$ [including indeterminate]) as recorded in IRT.

ORR as assessed by BICR and by investigator in subjects with PD-L1 expressing tumors and in all randomized subjects will be computed in each treatment group along with the exact 95% CI using Clopper-Pearson method. An estimate of the difference in ORRs, and corresponding 95% CI will be calculated using Cochran-Mantel-Haenszel (CMH) methodology and adjusted by the randomization stratification factors. The stratified odds ratios (Mantel-Haenszel estimator) between the treatments will be provided along with the 95% CI.

ORR as assessed by BICR in subjects with PD-L1 expressing tumors and in all randomized subjects will be tested only if significance level is passed on them. Rules for passing on significance levels will be defined together with the graphical approach in the SAP. Comparisons will use a two-sided CMH test.

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1 INTRODUCTION AND STUDY RATIONALE

Esophageal cancer (EC) is a worldwide health problem. EC is the 8th most common cancer and the 6th leading cause of cancer death worldwide.[1] The 5-year survival for patients with esophageal cancer improved only modestly over the last 50 years to 17% during the period 1996 to 2003.[2,3] The majority of EC patients require palliative treatment at some point in the course of their disease. Cytotoxic chemotherapy can provide symptom palliation, improve quality of life, and prolong survival in patients with advanced EC. In the current EC standard treatments, platinum-based combination chemotherapy regimens provide higher response rates than do single agents. However, this translates into only modestly longer duration of disease control and survival and the therapeutic efficacy of platinum-based chemotherapy has reached a plateau. Therefore, new, more effective therapies are urgently needed.

Cancer immunotherapy such as a checkpoint inhibitor has recently demonstrated clinical activities and survival benefits as a monotherapy and in combination with other immunotherapies or conventional chemotherapies in multiple cancer types. Nivolumab (Opdivo®) monotherapy or nivolumab combined with ipilimumab (Yervoy®) has been approved in multiple countries including the US for treatment of metastatic melanoma, non-small cell lung cancer (NSCLC), and advanced renal cell carcinoma (RCC). Nivolumab combined with platinum-doublet chemotherapy is under investigation in a Phase 3 NSCLC trial.

CA209648 is a randomized, global Phase 3 study of nivolumab plus ipilimumab or nivolumab in combination with fluorouracil plus cisplatin versus fluorouracil and cisplatin chemotherapy as first line-therapy in unresectable, advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC). This study will determine if nivolumab plus ipilimumab and nivolumab combined with fluorouracil plus cisplatin improve overall survival (OS) and/or progression free survival (PFS) over fluorouracil and cisplatin standard of care chemotherapy in subjects with ESCC whose tumors express PD-L1. Additional objectives include further characterization of the efficacy, adverse event profile, pharmacokinetics, patient reported outcomes and potential predictive biomarkers of nivolumab in combination with ipilimumab or nivolumab in combination with fluorouracil and cisplatin in subjects with ESCC.

1.1 Study Rationale

1.1.1 Disease Background

1.1.1.1 Unresectable Advanced, Recurrent or Metastatic Esophageal Cancer

Although the principal histologic types of esophageal cancer are ESCC and esophageal adenocarcinoma (EAC), ESCC is the predominant histologic type of esophageal cancer worldwide. 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 carcinoma to adenocarcinoma.[4] This has been attributed to a decline in smoking and an increase in adenocarcinoma risk factors including obesity, GERD and Barrett's esophagus. In contrast, the incidence of ESCC is increasing in Asian countries probably due to increased tobacco and alcohol consumption.[5]

Approximately 50% of esophageal cancers will be localized or loco-regionally advanced at diagnosis and thus amenable to potentially curative loco-regional treatment. However, the majority of patients with esophageal cancer will require palliative treatment at some point in the course of their disease. Unresectable advanced, recurrent or metastatic EC is not a curable condition, and thus requires treatment with systemic cytotoxic chemotherapy for palliation of symptoms and prolongation of survival. Five-year survival rates for all patients with esophageal cancer have shown modest improvements over the past 35 years from 5% in 1975 to approximately 20% for patients diagnosed in 2004.[6] The prognosis of patients with metastatic EC is poor with a 5-year survival rate of 4%.[7]

Because of the histological and anatomical distribution, the majority of clinical trials conducted since the mid-1990s have included gastric, esophageal, and GEJ cancer, regardless of histology.[8,9] However, squamous cell carcinoma (SCC) and adenocarcinoma are now being considered separate diseases as differences in genomic alternations in biologic pathways between SCC and adenocarcinoma are beginning to be elucidated.[10,11] Worldwide platinum-based combination chemotherapy is the most commonly used regimen to treat recurrent or metastatic EC. However, adding another cytotoxic agent to platinum has not dramatically improved clinical activity and survival over the past few decades. Therefore, more effective new therapies using a histology specific approach are urgently required.

1.1.1.2 The First Line Treatment in ESCC

Despite a large number of randomized trials, there is no consensus as to the best regimen for initial chemotherapy of advanced esophageal cancer and notably there is almost complete lack of recent randomized control trial data in this disease setting for ESCC. The majority of clinical trials conducted since the mid-1990s in gastric, esophageal, and GEJ cancer, regardless of histology; current NCCN guidelines,[12] ESMO guidelines,[13] and Japan Esophageal Cancer guidelines recommend platinum-based chemotherapy regimens as first line treatment in unresectable advanced, recurrent or metastatic ESCC and EAC.

In general, combination chemotherapy regimens provide higher response rates than do single agents, and two-drug cytotoxic regimens are preferred because of lower toxicity compared to three-drug cytotoxic regimens.[12] The combination of cisplatin and 5-fluorouracil (5-FU) is one of the most commonly used regimens due to its activity and well-established toxicity profile and has been approved worldwide by health authorities for the first line treatment of ESCC. Yet the response rates with this combination are still not regarded as sufficient (15% - 45%) and median survival is less than 10.4 months.[14,15,16,17]

Oxaliplatin based regimens are also commonly used mainly in the US and EU. Oxaliplatin is considered less toxic compared to cisplatin, therefore oxaliplatin regimens tend to be used in older patients or those with poor performance status. However, oxaliplatin is not approved for esophageal cancer treatment in some Asian countries including Japan. In randomized trials, the ECF (epirubicin, cisplatin, 5-FU) and DCF (docetaxel, cisplatin, 5-FU) combinations have also evolved as potential first-line treatment options in medically fit patients. Largely based upon the

results of the REAL2 trial, epirubicin, oxaliplatin, and capecitabine (EOX) could also be used as first-line regimen for patients who are able to tolerate combination chemotherapy.

The outcome for patients with unresectable advanced, recurrent or metastatic esophageal cancer has not improved over a couple of decades as the therapeutic efficacy of platinum-based chemotherapy has reached a plateau. Thus, there is a high unmet medical need for more effective new therapies in first line EC patients.

1.1.2 Rationale for the Blockade of PD-1/PD-L1 in ESCC

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).[18] 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, leading to suppression of immune surveillance and permission of neoplastic growth.[19,20,21,22]

PD-L1 or PD-L2 expressing tumor was reported in 44 - 54% of ESCC patients.[23,24] It has also been demonstrated that PD-L1 expression is associated with worse OS outcomes hence supporting the rationale that PD-L1 blockade might improve survival in ESCC.[24]

Anti PD-L1 inhibitors have been investigated in EC treatment demonstrating anti-tumor activity. In KEYNOTE-028, pembrolizumab monotherapy demonstrated promising antitumor activity and manageable safety profile in heavily treated EC patients with PD-L1 ≥ 1% (N = 23). The ORR was 30.4%, and the stable disease rate was 13.0% with a median duration of response of 40.0 weeks. Six-month and 12-month PFS rates were 30.4% and 21.7%, respectively. The ORR in ESCC (N = 17) was 29.4%.[25]

ONO-4538-07 demonstrated that nivolumab monotherapy in Japanese patients with ESCC was effective in a patient population refractory or intolerant to standard treatments (median number of prior regimens was 3). The ORR by Central Review was 17.2% and the responses were durable. Nivolumab had a tolerable safety profile in pre-treated ESCC patients and there were no treatment-related deaths.[26]

These promising data support further investigation of the use of immunotherapy in the treatment of ESCC.

1.1.3 Previous Studies of Nivolumab in Esophageal Cancer

ONO-4538-07, a Phase 2, multi-center, open-label, single-arm study of nivolumab monotherapy 3 mg/kg IV every 2 weeks (Q2W) was conducted in subjects with esophageal cancer refractory or intolerant to standard therapies. The primary endpoint was ORR (immune-related response criteria (IRRC) assessed according to response evaluation criteria in solid tumors RECIST 1.1). Other secondary endpoints were ORR (investigator's assessment), OS, PFS, DCR, time to progression (TTP), time to response (TTR), best overall response (BOR), immune-related ORR (ir-ORR), ir-PFS, ir-DCR, duration of response (DOR), percent change from baseline in the sum of tumor diameters, and response of the primary esophageal lesion. The data included in this document is as of 17-May-2015; OS data as of 17-Nov-2015. This trial is being conducted at investigational sites in Japan.

A total of 65 subjects were enrolled and treated with nivolumab monotherapy. The median age was 62 years and around 70% of the subjects had 3 or more prior treatment regimens such as fluoropyrimidine, platinum, and taxanes (docetaxel or paclitaxel). Histological tumor type in all the subjects was squamous cell carcinoma. 54% of patients (21/37) expressed PD-L1 above the expression level of 1%.

Preliminary safety data demonstrated that the majority of subjects (84.6%) experienced an AE but most were Grade 1/2. Grade 3/4 AEs/SAEs occurred in 19% of patients and included: diarrhea, dysphagia, fatigue, liver function abnormal, lung infection, pneumonia and decreased appetite. The most frequent drug-related SAEs were lung infection (3.1%), dehydration (3.1%) and interstitial lung disease (3.1%). Most of the AEs were manageable and there were no treatment-related deaths reported during the study. Additional details are provided in the investigator brochure.

Preliminary data of clinical activity are summarized in Table 1.1.3-1. Nivolumab demonstrates single-agent activity in subjects with esophageal cancer (N = 64). Ten subjects had a partial response, 1 had a complete response, and 16 had stable disease under central review (Table 1.1.3-1). The ORR by central review was 17.2% and the mDOR was durable. The mOS was 10.78 months (95% CI: 7.39, 13.34) and the median PFS was 1.51 months (95% CI: 1.41, 2.83) in 64 evaluable subjects.[23]

Table 1.1.3-1: Summary of Clinical Activity - ONO-4538-07

BOR/ORR	Investigator		Central Review	
Response	**N**	**% (95% CI)**	**N**	**% (95% CI)**
Complete Response (CR)	2	3.1 (0.9, 10.7)	1	1.6 (0.3, 8.3)
Partial Response (PR)	12	18.8 (11.1, 30.0)	10	15.6 (8.7, 26.4)
Stable Disease (SD)	20	31.3 (21.2, 43.4)	16	25.0 (16.0, 36.8)
Progressive Disease (PD)	29	45.3	29	45.3
NE	1	1.6	8	12.5
ORR (CR+PR)	14	21.9 (13.5, 33.4)	11	17.2 (9.9, 28.2)

Source: Preliminary data from Study ONO-4538-07, as of 17-May-2015.

1.1.4 Rationale for Nivolumab plus Ipilimumab in First-line ESCC Subjects

The combination of nivolumab and ipilimumab was evaluated in CA209004 (MDX1106-04), a Phase 1b multiple ascending dose study in subjects with treatment-naive and previously treated advanced melanoma. Results showed promising activity with higher, but tolerable toxicity than ipilimumab alone.[27] Based on these data, CA209069, a Phase 2 study, compared the combination to ipilimumab alone in treatment-naïve patients with advanced melanoma: nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks x4 followed by nivolumab 3 mg/kg every 2 weeks versus ipilimumab 3 mg/kg every 3 weeks x 4.[28]

In patients with BRAF wild type tumors, the ORR was 61% (44/72), including 22% (16/72) complete responses (CR) in the group treated with the combination, compared to 11% (4/37) with 0 CRs in those treated with ipilimumab alone. The median PFS was not reached in the combination versus 4.4 months for ipilimumab alone (HR = 0.4). It should be noted that in the combination group, the ORR was independent of PD-L1 expression. In this group, ORR was 58% among patients with PD-L1 expressing tumors and 55% among those with PD-L1 non-expressing tumors. In contrast, in the ipilimumab alone group, the ORR was numerically higher among patients with PD-L1 expressing tumors (18%) compared to those with PD-L1 non- expressing tumors (4%). Grade 3 - 4 treatment-related AEs were reported in 54% of patients receiving the combination compared to 24% for ipilimumab alone.

Based on the initial data in melanoma, and the activity observed with nivolumab and ipilimumab in lung cancer, the nivolumab plus ipilimumab combination has been also evaluated as first-line therapy in patients with advanced NSCLC. In CA209012, early combination cohorts evaluated the 2 dosing schedules that were studied in the CA209004 Study in melanoma. However, these regimens resulted in significant toxicity, with 39% of patients discontinuing treatment due to a treatment-related adverse event. Thus, additional combination cohorts were initiated (nivolumab 1 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four cycles, nivolumab 1 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks, and nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 12 weeks or 6 weeks), using lower doses of both nivolumab and ipilimumab, or the approved dose of nivolumab with less frequent dosing of ipilimumab. These regimens were better tolerated, although clinical activity was suboptimal when nivolumab was given at the lower dose (1 mg/kg). Therefore the regimens which were considered potentially suitable for further clinical development were nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg given either every 12 weeks or every 6 weeks. Each study arm included 15 - 18 % squamous cell carcinoma patients and the safety data are not dissimilar to what has been observed in the nivolumab monotherapy cohort (Arm F in CA209012). (See Table 1.1.4-1).

Table 1.1.4-1: Treatment-related Adverse Events from Selected Cohorts in CA209012 (1L NSCLC)

Arm[a]	No. Subjects/ Arm	Follow-up time (Median, months)	No. Subjects still On-treatment	No. Subjects with Drug-related AEs	No. Subjects with Grade 3 - 4 Drug-related AEs	No. Subjects d/c due to Drug-related AEs (All Grades)
P[b]	38	12.8	9 (24%)	31 (82%)	14 (37%)	4 (11%)
Q[b]	39	11.8	7 (18%)	28 (72%)	13 (33%)	5 (13%)
F[c]	52	14.2	5 (10%)	37 (71%)	10 (19%)	5 (10%)

[a] P: nivolumab 3 mg/kg every 2 weeks plus ipilimumab every 12 weeks; Q: nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks; F: nivolumab 3 mg/kg every 2 weeks.

[b] Based on March 2015 database lock

[c] Based on Jan 2016 database lock

A numerically highest response rate was observed with the arm of nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q12W (Table 1.1.4-2). It would be expected that the ipilimumab every 6-week schedule would be more active in the absence of safety issues, which were not observed in CA209012. However as these cohorts have small numbers of subjects it is difficult to draw any firm conclusions.[29] Currently the combination of nivolumab 3 mg/kg Q2W plus ipilimumab 1 mg/kg Q6W combination regimen in being further evaluated in the Phase 3 CA209227 in previously untreated advanced NSCLC as the Q6W ipilimumab schedule was chosen to avoid any potential loss of efficacy with less frequent dosing.

Table 1.1.4-2: Efficacy of First-line Treatment of Nivolumab/Ipilimumab Combination in NSCLC

	Nivo 3 Q2W + Ipi 1 Q12W (n = 38)	Nivo 3 Q2W+ Ipi 1 Q6W (n = 39)
Confirmed ORR, % (95% CI)	47% (31 - 64)	(38% [23 - 55])
PFS rate at 24 wks (95% CI)	68% (50 - 80)	47% (31 - 62))
mPFS, mos (95% CI)	8.1 (5·6 - 13·6)	3.9 (2·6 - 13·2)
1 year overall survival	NC	69% (52 - 81)
Median length of follow-up, months	12.8	11.8

Based on Ja2016 database lock.

NC = Not calculated (when more than 25% of patients were censored)

Given the similarity of the patient profiles in CA209012 with ESCC (the CA209012 study population included 15 - 18% squamous cell carcinoma patients), nivolumab at a dose of 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks (ie, a dose and frequency of ipilimumab

that improves tolerability to the combination with nivolumab) will be evaluated in first-line ESCC subjects.

1.1.5 Rationale for Nivolumab plus Fluorouracil and Cisplatin Combination in First-line ESCC Subjects

Cancer therapeutics such as chemotherapy may modulate tumor/immune-system interactions in favor of the immune system. Chemotherapy can result in tumor cell death with a resultant increase in tumor antigen delivery to antigen-presenting cells. Tumor cell death may also lead to a reduction in soluble and membrane-bound factors inhibiting tumor-infiltrating T-cells. Chemotherapy may also disrupt immune system regulatory networks by decreasing numbers of T-regulatory cells.

Nivolumab added to chemotherapy has been evaluated in several cohorts of chemotherapy-naive subjects with advanced NSCLC (squamous 29% and non-squamous 71%) in Study CA209012. Nivolumab 10 mg/kg was combined with gemcitabine + cisplatin and pemetrexed + cisplatin. Nivolumab 10 mg/kg, and 5 mg/kg, was combined with paclitaxel and carboplatin.

The safety profile of nivolumab plus platinum-doublet chemotherapy reflects additive toxicities of the individual agents, which were manageable using established safety guidelines (Appendix 1). 95% of patients (53 of 56 patients) and 45% of patients (25 of 56 patients) experienced any grade and Grade 3 or 4 treatment-related AEs, respectively.[30] The most commonly reported (≥ 30% of patients) treatment-related AEs of any grade were fatigue, nausea, decreased appetite, and alopecia and the most common (≥ 5% of patients) treatment-related Grade 3 or 4 AEs were pneumonitis, fatigue, and acute renal failure. Treatment-related AEs led to discontinuation of all study therapy in 21% of patients (12 of 56 patients). The frequency of most immune-related AEs was higher than what has been observed in nivolumab monotherapy. However, these treatment-related AEs, including pneumonitis, were effectively managed and did not lead to any deaths.

The observed response rates of nivolumab and chemotherapy (Table 1.1.5-1) were similar to that of platinum-doublet chemotherapy alone, though the duration of responses is longer. The median duration of response across all the nivolumab + chemotherapy cohorts was 27.3 weeks. The 1-year survival rate for all cohorts combined is 71%.

Table 1.1.5-1: Efficacy of First-Line Treatment Nivolumab + Chemotherapy in NSCLC

	Nivo/Gem/Cis (n = 12)	Nivo/Pem/Cis (n = 15)	Nivo/Pac/Carbo (n = 29)	Nivo/Chemo (n = 56)
ORR, n (%)	4 (33%)	7 (47%)	13 (45%)	24 (43%)
Median DOR (wks)	45	24.4	27.3	27.3
PFS rate at 24 wks	51%	71%	43%	52%
Median PFS (wks)	24.7	29.7	21.4	24.7
OS rate at 12 mos	50%	87%	72%	71%

Table 1.1.5-1: Efficacy of First-Line Treatment Nivolumab + Chemotherapy in NSCLC

	Nivo/Gem/Cis (n = 12)	Nivo/Pem/Cis (n = 15)	Nivo/Pac/Carbo (n = 29)	Nivo/Chemo (n = 56)
OS rate at 18 mos	33%	60%	62%	55%
Median OS (wks)	50.5	83.4	89.6	83.4

Platinum-based doublet chemotherapy is considered standard of care treatment in first-line ESCC as well as for NSCLC. The combination of 5-FU + and cisplatin is the most commonly used regimen in the first-line ESCC patients due to its activity and well-established toxicity profile.

Since platinum-doublet chemotherapy + nivolumab combination regimens were tested in 1L NSCLC patients (in a patient population which included 29% squamous histology) and demonstrated encouraging clinical activity with acceptable safety profile, the combination of 5-FU and cisplatin (a globally accepted standard therapy in first-line ESCC) plus nivolumab will be evaluated in this trial.

1.1.5.1 Rationale for Fluorouracil (800 mg/m²/day on Days 1 - 5) plus Cisplatin (80 mg/m² on Day 1) Every 4 Weeks Regimen as First-line Standard Chemotherapy

As described in Section 1.1.1.2, over the past two decades, the combination of fluorouracil and cisplatin (FP) has been commonly used as a standard 1L chemotherapy in patients with both metastatic and localized esophageal cancer. The FP regimen which is currently used in clinical practice varies among countries. Current NCCN guidelines[12] recommends fluorouracil (750 - 1000 mg/m² on Days 1 - 4) plus cisplatin (75 - 100 mg/m² on Day 1) every 4 weeks, and Japan Esophageal Cancer Guideline[31] recommends fluorouracil (700 - 1000 mg/m² on Days 1 - 4 or 1 - 5) plus cisplatin (70 - 100 mg/m² on Day 1) every 3 or 4 weeks. ESMO guidelines[13] do not describe any specific dose and schedule of FP regimen to recommend to use as first line treatment in locally advanced unresectable and metastatic ESCC.

At present in Japan, the most commonly used FP regimen is fluorouracil (800 mg/m² on Days 1 - 5) plus cisplatin (80 mg/m² on Day 1) every 4 weeks based on four Phase 2 studies[32,33,34,35] conducted by The Japan Esophageal Oncology Group (JEOG). The same dose and schedule is also used in clinical practice in US and Europe due to the similar safety and efficacy outcomes to other FP regimens.'[36]

Therefore, fluorouracil (800 mg/m² on Days 1 - 5) plus cisplatin (80 mg/m² on Day 1) every 4 weeks was selected to be combined with nivolumab 240 mg every 2 weeks (Arm B) and as the standard chemotherapy in the control arm (Arm C).

1.1.6 Rationale for Dose Selection of Nivolumab in Combination with Ipilimumab (Arm A) and Chemotherapy (Arm B) in First-line ESCC Subjects

As described in Section 1.1.4, it may be beneficial to administer nivolumab in combination with ipilimumab in the treatment of ESCC, as it has demonstrated activity across multiple tumor types, including NSCLC and melanoma. Nivolumab 3 mg/kg Q2W in combination with ipilimumab 1 mg/kg Q6W was selected for Arm A, as it allows the study of clinical benefit of the addition of ipilumumab 1 mg/kg Q6W to nivolumab 3 mg/kg Q2W, which is the dose studied for the treatment of advanced line ESCC (see Section 1.1.3 for ONO-4538-07 results). Further, this nivolumab-ipilimumab combination regimen is being tested in first-line NSCLC subjects (CA209-227, including Squamous and non-Squamous) due to enhanced tolerability versus regimens using ipilimumab Q3W. Finally, weight based dosing is being used in the combination of nivolumab and ipilimumab, to be consistent with nivolumab-ipilimumab combination dosing in other tumor types, e.g. NSCLC.

Nivolumab 240 mg Q2W in combination with FP chemotherapy was selected for Arm B, as it is the flat dose equivalent to 3 mg/kg Q2W dosing that has been studied in advanced line ESCC (ONO-4538-07). Nivolumab 240 mg Q2W was selected based on clinical data and modeling and simulation approaches using population pharmacokinetic (PPK) and exposure-response analyses of data from studies in multiple tumor types (melanoma, NSCLC, and RCC) where body weight normalized dosing (mg/kg) has been used.

PPK analyses have shown that the PK of nivolumab is linear with proportional exposure over a dose range of 0.1 to 10 mg/kg, and no differences in PK across ethnicities and solid tumor types were observed. Nivolumab clearance and volume of distribution were found to increase as the body weight increases, but less than proportionally with increasing weight, indicating that mg/kg dosing represents an over-adjustment for the effect of body weight on nivolumab PK. Using data from 1,544 subjects from 7 studies investigating nivolumab in the treatment of melanoma, NSCLC, and RCC, the median (minimum - maximum) weight was 77 kg (35 kg - 160 kg) and thus, an approximately equivalent dose of 3 mg/kg for an 80 kg subject, nivolumab 240 mg Q2W was selected for future studies. To predict relevant summary exposures of nivolumab 240 mg Q2W, the PPK model was used to simulate nivolumab 3 mg/kg Q2W and 240 mg Q2W. The simulated measure of exposure of interest, time-averaged concentrations (Cavgss) for 240 mg Q2W are predicted to be similar for all subjects in reference to 80 kg subjects receiving 3 mg/kg Q2W. Because no differences in PK were noted across ethnicities and solid tumor types, these simulated melanoma and NSCLC data will be applicable to subjects with other tumor types.

It should be noted that nivolumab 240 mg Q2W is currently approved in US for monotherapy treatment of NSCLC, RCC, melanoma, UC, HCC, and MSI-H/dMMR CRC and is currently under review by other Health Authorities.

1.1.7 Rationale for Shorter Infusion Times for Nivolumab and Ipilimumab

Long infusion times place a burden on patients and treatment centers. Establishing that nivolumab and ipilimumab can be safely administered using shorter infusion times of 30 minutes' duration

will diminish the burden, provided that there is no change in the safety profile. Previous clinical studies of nivolumab and ipilimumab monotherapies and the combination of nivolumab and ipilimumab have used a 60-minute infusion duration for nivolumab and a 90-minute infusion duration for ipilimumab (1 - 3 mg/kg dosing for both). However, both nivolumab and ipilimumab have been administered at up to 10 mg/kg with the same infusion duration (ie, 60 minutes).

Establishing that nivolumab can be safely administered using a shorter infusion time (30 minutes) is under investigation. Previous clinical studies of nivolumab monotherapy have used a 60-minute infusion duration wherein, nivolumab has been safely administered up to 10 mg/kg over long treatment periods. Infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab clinical program. In CA209010, 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 3 mg/kg nivolumab (30% 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. The safety of nivolumab 3 mg/kg administered as a 30-min infusion was assessed in CA209153 in patients (n = 322) with previously treated advanced NSCLC. Overall, there were no clinically meaningful differences in the frequency of hypersensitivity/infusion-related reactions (of any cause or treatment-related) in patients administered nivolumab over a 30-minute infusion compared with that reported for patients with the 60-minute infusion. Thus, it was shown that nivolumab can be safely infused over 30 minutes.

Similarly, ipilimumab at 10 mg/kg has been safely administered over 90 minutes. In subjects with advanced Stage II or Stage IV melanoma (CA184022 Study), where ipilimumab was administered up to a dose of 10 mg/kg, on-study drug related hypersensitivity events (Grade 1/2) were reported in 1 subject (1.4%) in the 0.3 mg/kg and in 2 subjects (2.8%) in the 10 mg/kg group. There were no drug-related hypersensitivity events reported in the 3 mg/kg group. Across the 3 treatment groups, no Grade 3/4 drug-related hypersensitivity events were reported and there were no reports of infusion reactions. Ipilimumab 10 mg/kg monotherapy has also been safely administered as a 90-minute infusion in a large Phase 3 study in prostate cancer (CA184043) and as adjuvant therapy for Stage III melanoma (CA184029), with infusion reactions occurring in subjects. Administering 3 mg/kg of ipilimumab represents approximately one-third of the 10 mg/kg dose.

Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across clinical studies of nivolumab, ipilimumab, and nivolumab/ipilimumab combinations. Furthermore, a 30-minute break after the first infusion for the combination cohort will ensure the appropriate safety monitoring before the start of the second infusion. Overall, a change in safety profile is not anticipated with 30-minute infusions of nivolumab, ipilimumab or combination.

1.1.8 Rationale for Including Subjects with PD-L1 and Non PD-L1 Expressing Tumors and Stratification by PD-L1 Expression

In ESCC cancer, PD-L1 expression has been suggested as a prognostic marker[24] as it is has been shown to be associated with adverse survival. In ONO-4538-07 responses were observed irrespective of PD-L1 status although numerically higher ORR was seen in subjects expressing

PD-L1 ≥ 1% [ORR 23.8 (5/21)] compared to those with PD-L1 <1% 12.5% (2/16). OS was survival was 11.33 months in subjects with PD-L1 ≥ 1% vs 6.24 months in those with PD-L1 < 1%.[23]

In study CA209012, 56 subjects with NSCLC received nivolumab and platinum based chemotherapy. Activity was also evaluated by PD-L1 expression and was observed in subjects with both PD-L1 expressing and non-expressing tumors although some enrichment for response was seen by PD-L1 status (see Table 1.1.8-1). At the 1% expression level, the response rate was 48% and 43% for PD-L1 ≥ 1% and all comers population respectively, which compared favorably to the responses observed with nivolumab monotherapy (28% and 23% for PD-L1 ≥ 1% and all comers, respectively). Similarly, for the combination of nivolumab with ipilimumab at the 1% expression level, the response rate was 57% and 43% for PD-L1 ≥ 1% and all comers population.

Table 1.1.8-1: Efficacy of Nivolumab and Platinum-based Chemotherapy, Nivolumab plus Ipilimumab and Nivolumab Monotherapy in NSCLC

	Nivo + Chemo[a] (n = 56)	Nivo + Ipi[b] (n = 77)	Nivo 3 Q2W (n = 52)
ORR, % (n/N)			
All comers ≥ 1% PD-L1	43 48 (11/23)	43 57 (26/46)	23 28 (9/32)
mPFS, mo			
All comers ≥ 1% PD-L1	5.7 6	8.0 12.7	3.6 3.5
1-year OS Rate			
All comers ≥ 1% PD-L1	71 70	76 87	73 69

[a] Pulled analysis of Nivo/Gem/Cis (n = 12), Nivo/Pem/Cis (n = 15), Nivo/Pac/Carbo (n = 29) cohorts.

[b] Pulled analysis of Nivo 3 Q2W + Ipi Q12W (n = 38) and Nivo 3 Q2W + Ipi 1 Q6W (n = 39).

Nivo + Ipi combination data based on September 2016 database lock; Nivo monotherapy data based on a March 2015 database lock except for OS data which are based on August 2015 database lock.

Thus for these reasons, in study CA209648 subjects will be enrolled into the study regardless of PD-L1 tumor expression with stratification by PD-L1 at the expression level of 1% and the primary analysis of PFS/OS will be conducted in subjects with PD-L1 expressing tumor.

1.1.9 Rationale for Two-Year Duration of Treatment

The optimal duration of immunotherapy is currently unknown. However, because immunotherapy engages the immune system to control the tumor, continuous treatment as is required with targeted agents or cytotoxic therapy may not be necessary. Accumulating evidence from different clinical

trials in different tumors types with nivolumab or nivolumab combined to ipilimumab indicates that most of the responses are generally occurring early, with a median time to response of 2 - 4 months including in patients with NSCLC,[46,47,48] and a recent analysis in a melanoma study suggests the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment.[37] Furthermore, a limited duration of ipilimumab including only 4 induction doses resulted in long term survival in patients with metastatic melanoma, with a sustained plateau in survival starting at around Year 3.[22]

For these reasons, in study CA209648, treatment with nivolumab or nivolumab with ipilimumab will be given for up to 24 months in the absence of disease progression or inacceptable toxicity. Chemotherapy will be given as per the study dosing schedule until disease progression or unacceptable toxicity.

1.2 Research Hypothesis

- The administration of nivolumab plus ipilimumab will improve overall survival (OS) compared with fluorouracil and cisplatin combination in subjects with unresectable advanced, recurrent or metastatic ESCC with PD-L1 expression ≥ 1%.
- The administration of nivolumab combined with fluorouracil plus cisplatin will improve OS compared with fluorouracil and cisplatin combination alone in subjects with unresectable advanced, recurrent or metastatic ESCC with PD-L1 expression ≥ 1%.
- The administration of nivolumab plus ipilimumab will improve progression free survival (PFS) as assessed by a blinded independent central review committee (BICR) compared with fluorouracil and cisplatin combination in subjects with unresectable advanced, recurrent or metastatic ESCC with PD-L1 expression ≥ 1%.
- The administration of nivolumab combined with fluorouracil plus cisplatin will improve PFS as assessed by a BICR compared with fluorouracil and cisplatin combination alone in subjects with unresectable advanced, recurrent or metastatic ESCC with PD-L1 expression ≥ 1%.

1.3 Objectives(s)

1.3.1 Primary Objectives

- To compare the OS of nivolumab plus ipilimumab (Arm A) to fluorouracil and cisplatin combination (Arm C) in subjects with PD-L1 expression ≥ 1%.
- To compare the OS of nivolumab combined with fluorouracil plus cisplatin (Arm B) to fluorouracil and cisplatin combination (Arm C) in subjects with PD-L1 expression ≥ 1%.
- To compare the PFS of nivolumab plus ipilimumab (Arm A) to fluorouracil and cisplatin combination (Arm C) as assessed by a BICR in subjects with PD-L1 expression ≥ 1%.
- To compare the PFS of nivolumab combined with fluorouracil plus cisplatin (Arm B) to fluorouracil and cisplatin combination (Arm C) as assessed by a BICR in subjects with PD-L1 expression ≥ 1%.

1.3.2 Secondary Objectives

- To compare the OS of nivolumab plus ipilimumab (Arm A) and nivolumab combined with fluorouracil plus cisplatin (Arm B) to fluorouracil and cisplatin combination (Arm C) in all randomized subjects.
- To compare the PFS of nivolumab plus ipilimumab (Arm A) and nivolumab combined with fluorouracil plus cisplatin (Arm B) to fluorouracil and cisplatin combination (Arm C) as assessed by a BICR in all randomized subjects.
- To compare the objective response rate (ORR) of nivolumab plus ipilimumab (Arm A) and nivolumab combined with fluorouracil plus cisplatin (Arm B) to fluorouracil and cisplatin combination (Arm C) as assessed by a BICR in subjects with PD-L1 expression ≥ 1%.
- To compare the ORR of nivolumab plus ipilimumab (Arm A) and nivolumab combined with fluorouracil plus cisplatin (Arm B) to fluorouracil and cisplatin combination (Arm C) as assessed by a BICR in all randomized subjects.
-

1.3.3 Exploratory Objectives

- To assess PFS of nivolumab plus ipilimumab (Arm A) and nivolumab combined with fluorouracil plus cisplatin (Arm B) vs fluorouracil and cisplatin combination (Arm C) as assessed by investigators in subjects with PD-L1 expression ≥ 1% and in all randomized subjects.
- To assess ORR of nivolumab plus ipilimumab (Arm A) and nivolumab combined with fluorouracil plus cisplatin (Arm B) vs fluorouracil and cisplatin combination (Arm C) as assessed by investigators in subjects with PD-L1 expression ≥ 1% and in all randomized subjects.
- To assess DOR of nivolumab plus ipilimumab (Arm A) or nivolumab combined with fluorouracil plus cisplatin (Arm B) vs fluorouracil and cisplatin combination (Arm C) as assessed by BICR and by investigators in subjects with PD-L1 expression ≥ 1% and in all randomized subjects.
- To assess time from randomization to the date of investigator-defined documented second objective disease progression or start of second subsequent therapy or death due to any cause, whichever comes first (PFS2/TSST) of nivolumab plus ipilimumab (Arm A) or nivolumab combined with fluorouracil plus cisplatin (Arm B) vs fluorouracil and cisplatin combination (Arm C) as assessed by investigators in subjects with PD-L1 expression ≥ 1% and in all randomized subjects.
-
- To assess the overall safety and tolerability of treatment with nivolumab plus ipilimumab (Arm A) or nivolumab combined with fluorouracil plus cisplatin (Arm B) vs fluorouracil and cisplatin combination (Arm C).
- To characterize the PK of nivolumab plus ipilimumab (Arm A) or nivolumab combined with fluorouracil plus cisplatin (Arm B).
- To characterize the immunogenicity of nivolumab plus ipilimumab (Arm A) or nivolumab combined with fluorouracil plus cisplatin (Arm B).

- To characterize immune correlates of nivolumab plus ipilimumab (Arm A), nivolumab combined with fluorouracil plus cisplatin (Arm B), and fluorouracil and cisplatin combination (Arm C).
- To evaluate the pharmacodynamic activity of nivolumab plus ipilimumab (Arm A) or nivolumab combined with fluorouracil plus cisplatin (Arm B) in the peripheral blood.
- To explore potential biomarkers associated with clinical efficacy (OS, PFS, and ORR) and/or with incidence of adverse events of nivolumab plus ipilimumab (Arm A) or nivolumab combined with fluorouracil plus cisplatin (Arm B) by analyzing biomarker measures within the tumor microenvironment and periphery (eg, blood, serum, plasma) in comparison to clinical outcomes. These biomarkers may include, but not necessarily be limited to tumor mutational burden (TMB), tumor infiltrating lymphocytes, inflammatory signatures, microbiome, serum and plasma biomarkers.
- To assess the subject's overall health status using 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).

1.4 Product Development Background

1.4.1 Mechanism of Action

1.4.1.1 Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune response.[38,39,40] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[41] Collectively, these signals govern the balance between T-cell activation and tolerance.[41]

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA 4, ICOS, and BTLA.[42] PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, interferon γ (IFN γ) and Bcl-xL. PD-1 expression also been noted to inhibit T cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[43] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various

host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 < 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a CMV re stimulation assay with human Peripheral Blood Mononuclear cells (PBMC), the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[44]

Immunotherapeutic approaches recently have demonstrated clinical efficacy in several cancer types, including melanoma, and NSCLC, and RCC.[45,46,47,48] Nivolumab (Opdivo®) is approved in multiple countries including the US for treatment of previously treated, unresectable or metastatic melanoma and previously treated, metastatic NSCLC, and advanced RCC.[49]

1.4.1.2 Ipilimumab Mechanism of Action

CTLA-4, an activation-induced T-cell surface molecule, is a member of the CD28:B7 immunoglobulin superfamily that competes with CD28 for B7. CTLA-4 mediated signals are inhibitory and turn off T cell-dependent immune responses.[50,51]

Ipilimumab is a fully human monoclonal IgG1κ that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. The proposed mechanism of action for ipilimumab is interference of the interaction of CTLA-4 with B7 molecules on APCs, with subsequent blockade of the inhibitory modulation of T-cell activation promoted by the CTLA 4/B7 interaction.

1.4.1.3 Nivolumab-plus-Ipilimumab Mechanism of Action

Preclinical and clinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve antitumor activity. In vitro combinations of nivolumab plus ipilimumab increase IFN-γ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4- and PD-1-expressing CD4/CD8 tumor-infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone.[52]

In the Phase 1 dose escalation Study CA209004, the combination of nivolumab and ipilimumab has been studied in subjects with unresectable or metastatic melanoma. In this study, a safe dose level for the combination of ipilimumab and nivolumab was established for the treatment of advanced melanoma. At this dose level, 3 mg/kg ipilimumab plus 1 mg/kg nivolumab, an ORR of

53% was observed. This dose level has been approved in subjects with advanced melanoma in the US based on the Phase 3 Study CA209067.[53]

1.4.2 Summary of Clinical Pharmacology

1.4.2.1 Nivolumab

The pharmacokinetics (PK) of nivolumab was studied in subjects over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. Based on a population pharmacokinetic (PPK) analysis using data from patients with various tumor types, including melanoma, NSCLC, and RCC and a time varying CL model, nivolumab clearance was shown to decrease over time, with a median maximal reduction from baseline values of approximately 25% resulting in a geometric mean steady state clearance (CLss) (% coefficient of variation [CV%]) of 8.2 mL/h [53.9%]. The decrease in CLss is not considered to be clinically relevant. The geometric mean [CV%] volume of distribution at steady state (Vss) is 6.8 L (27.3%), and elimination half-life (t1/2) is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by approximately 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3.7-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The clearance of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1, solid tumor type, baseline tumor size, and hepatic impairment. Although ECOG status, baseline glomerular filtration rate (GFR), albumin, and body weight had an effect on nivolumab CL, the effect was not clinically meaningful. PPK analysis suggested that nivolumab CL in subjects with cHL was approximately 32% lower relative to subjects with NSCLC; however, the lower CL in cHL subjects was not considered to be clinically relevant as nivolumab exposure was not a significant predictor for safety risks for these patients. When nivolumab is administered in combination with ipilimumab, the CL of nivolumab was increased by 24%, whereas there was no effect on the clearance of ipilimumab. Additionally, PPK and exposure response analyses have been performed to support use of 240 mg Q2W dosing in addition to the 3 mg/kg Q2W regimen. Using the PPK model, exposure of nivolumab at 240 mg flat dose was identical to a dose of 3 mg/kg for subjects weighing 80 kg, which was the approximate median body weight in nivolumab clinical trials (see Section 1.1.5). Additional details are provided in the investigator brochure.

1.4.2.2 Ipilimumab

The PPK of ipilimumab was studied in 785 subjects (3,200 serum concentrations) with advanced melanoma in 4 Phase 2 studies (CA184004, CA184007, CA184008, and CA184022),[54] 1 Phase 3 study (CA184024), and 1 Phase 1 study (CA184078). The PPK analysis demonstrated that the PK of ipilimumab is linear, the exposures are dose proportional across the tested dose range of 0.3 to 10 mg/kg, and the model parameters are time-invariant, similar to that determined by noncompartmental analyses.

Upon repeated dosing of ipilimumab, administered Q3W, minimal systemic accumulation was observed by an accumulation index of 1.5-fold or less, and ipilimumab steady-state concentrations

were achieved by the third dose. The ipilimumab CL of 16.8 mL/h from PPK analysis is consistent with that determined by noncompartmental PK analysis. The terminal T-HALF and Vss of ipilimumab calculated from the model were 15.4 days and 7.47 L, respectively, which are consistent with that determined by noncompartmental analysis. Volume of central compartment (Vc) and peripheral compartment were found to be 4.35 and 3.28 L, respectively, suggesting that ipilimumab first distributes into plasma volume and, subsequently, into extracellular fluid space. CL of ipilimumab and Vc were found to increase with increase in BW. However, there was no significant increase in exposure with increase in BW when dosed on a milligram/kilogram basis, supporting dosing of ipilimumab based on a weight normalized regimen. The PK of ipilimumab is not affected by age, gender, race, and immunogenicity (anti-drug antibody [ADA] status); concomitant use of chemotherapy; prior therapy; BW; performance status; or tumor type. Other covariates had effects that were either not statistically significant or were of minimal clinical relevance.

In subjects with mild and moderate renal impairment, the CL of ipilimumab was similar to that of subjects with normal renal function. No specific dose adjustment is necessary in subjects with mild to moderate renal impairment. Likewise, the CL of ipilimumab in subjects with mild and moderate hepatic impairment was similar to that of subjects with normal hepatic function.

Additional details are provided in the investigator brochure (IB).

1.4.3 Safety Summary

Nivolumab has been studied in over 12,300 subjects and is widely approved in multiple indications. Extensive details on the safety profile of nivolumab are available in the IB, and will not be repeated herein.

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 Maximum Tolerated Dose (MTD) reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.

A pattern of immune-related AEs has been defined, for which management algorithms have been developed; these are provided in Appendix 1. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

Additional details on the safety profiles of nivolumab and ipilimumab, including results from other clinical studies, are also available in the respective nivolumab and ipilimumab IBs.

1.5 Overall Risk/Benefit Assessment

Subjects with unresectable advanced, recurrent or metastatic ESCC represent an important unmet medical need. There is robust clinical data available to suggest the potential to improve clinical outcomes in ESCC:

- Clinical activity of nivolumab monotherapy in heavily treated ESCC patients in ONO-07 Japan Phase 2 study was observed with durable tumor responses and survival benefit (ORR by central

review 17.2%, mOS 10.78 months, and mPFS 1.51 months). The mOS of 10.78 is comparable to the OS with standard of care FP chemotherapy (6-10 months). Enhanced efficacy outcomes were seen in patients with PD-1 expression ≥ 1%. In this population, the safety profile of nivolumab was shown to be favorable.

- Clinical activity of nivolumab plus ipilimumab in first line NSCLC patients was observed in study CA209012 regardless of PD-L1 expression, although enrichment for response was seen in patients with PD-1 expression ≥ 1%, with an overall acceptable safety profile.
- Clinical activity of nivolumab plus platinum-based chemotherapy in first line NSCLC patients was observed in study CA209012 study regardless of PD-L1 expression, although enrichment for response was seen in patients with PD-1 expression ≥ 1%, with manageable toxicities.

Based on this clinical experience, subjects will be enrolled into the CA209648 regardless of PD-L1 tumor expression with stratification by PD-L1 at the expression level of 1% and the primary analysis of PFS/OS will be conducted in subjects with PD-L1 expressing tumor.

Overall the safety profile of nivolumab and ipilimumab is well characterized from a large safety database at different dose and schedules as monotherapy or in combination. Additional details on the safety profiles of nivolumab and ipilimumab, including results from other clinical studies, are also available in the respective nivolumab and ipilimumab IBs. Consistent with the mechanism of action of nivolumab and ipilimumab, the most frequently reported drug-related AEs observed in clinical trials are those associated with activation of the immune system. The most common types of immune-mediated adverse events include endocrinopathies, diarrhea/colitis, hepatitis, pneumonitis, nephritis and rash. In the combination regimen, the frequency and intensity of these events may vary and depend on the specific dose and schedule used. In the combination dosing schedule selected for this study (nivolumab 3 mg/kg mg Q2W plus ipilimumab 1 mg/kg Q6W), immune-mediated adverse events were mostly low grade and manageable with prompt use of corticosteroids.

In order to assure an ongoing favorable risk/benefit assessment for subjects treated in CA209648, the following safety measures will be employed throughout the conduct of the study:

- An independent Data Monitoring Committee (DMC) will be utilized to monitor the safety and clinical activity of nivolumab plus ipilimumab and nivolumab combined with fluorouracil plus cisplatin versus standard chemotherapy (FP regimen).
- Rigorous safety monitoring by BMS to ensure subjects' safety including regular and systematic review of safety data, close follow-up of reported safety events, intensive site and study investigator training/education on the implementation of the nivolumab and ipilimumab management algorithms as well as regular safety conference calls with study investigators.
- Open label drug administration of study drugs to allow for prompt and accurate assessment of the unique toxicities associated with study treatments.

In conclusion, the overall risk-benefit of nivolumab plus ipilimumab and nivolumab combined with fluorouracil plus cisplatin and fluoruracil in unresctable advanced, recurrent or metastatic

first-line ESCC is deemed acceptable and subjects will be randomized to 1 of 3 arms: nivolumab plus ipilimumab (Arm A), nivolumab combined with fluorouracil plus cisplatin (Arm B), or fluorouracil plus cisplatin (Arm C).

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 Council on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50) and applicable local requirements.

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

All potential serious breaches must be reported to Sponsor or designee immediately. A breach of the conditions and principles of GCP (occurring in any country) in connection with that study or the protocol related to the study which is likely to affect to a significant degree the safety or physical or mental integrity of 1 or more 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 the Health Insurance Portability and Accountability Act (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

This is a randomized Phase 3 study of nivolumab plus ipilimumab or nivolumab combined with fluorouracil plus cisplatin compared with fluorouracil and cisplatin combination in adult (≥ 18 years) male and female subjects with unresectable advanced, recurrent or metastatic ESCC. The total number of subjects to be randomized is expected to be approximately 939 subjects.

After signing the informed consent form, and upon confirmation of the subject's eligibility, subjects with unresectable advanced, recurrent or metastatic ESCC will be randomized in a 1:1:1 ratio to one of the following open-label treatments (Arms A, B and C):

- Arm A: Subjects will receive treatment with nivolumab 3 mg/kg as a 30-minute infusion every 2 weeks and ipilimumab as a 30-minute infusion 1 mg/kg every 6 weeks.
- Arm B: Subjects will receive treatment with nivolumab 240 mg as a 30-minute infusion on Day 1 and Day 15, fluorouracil 800 mg/m²/day as an IV continuous infusion on Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m² as a 30- to 120-minute infusion* on Day 1 of 4-week cycle.
- Arm C: Subjects will receive treatment with fluorouracil 800 mg/m²/day as an IV continuous infusion from Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m² as a 30- to 120-minute infusion* on Day 1 of 4-week cycle.

*Subjects are allowed to receive treatment with cisplatin 80 mg/m² as an IV infusion over a period of longer than 120 min if it is in accordance with local standard of care/local label.

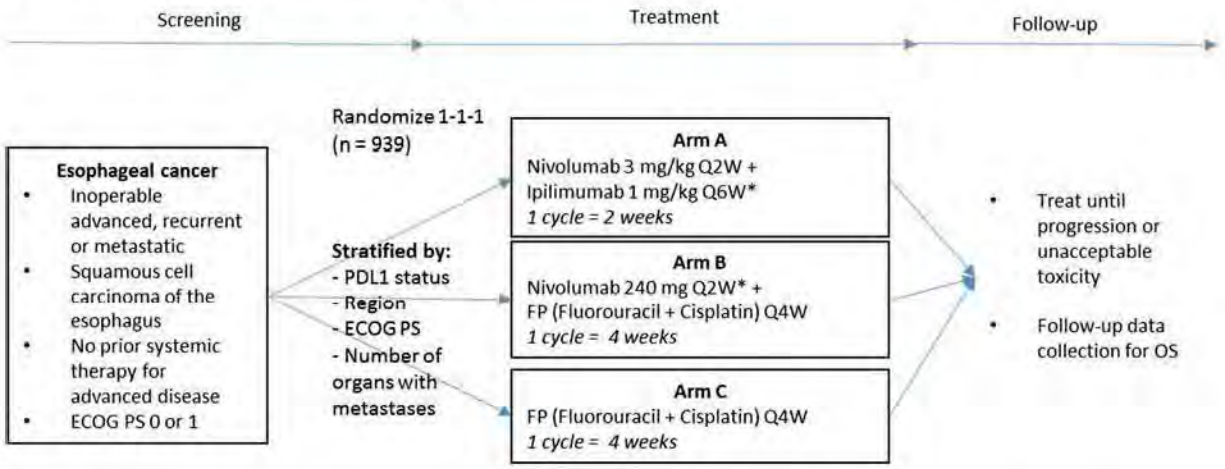
Stratification factors:

1. 1. PD-L1 status (≥ 1% vs < 1% [including indeterminate])*
2. 2. Region (East Asia [Japan, Korea, Taiwan] vs Rest of Asia vs Rest of world [RoW])
3. 3. Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1).
4. 4. Number of organs with metastases (≤ 1 vs ≥ 2).

*The proportions of subjects with or without PD-L1 tumor expression will be monitored and reassessed as needed to ensure that the sample size of randomized subjects with PD-L1 tumor expression ≥ 1% is adequate for analysis (ie, approximately 50% of all comers).

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

Figure 3.1-1: Study Design Schematic



*Treatment with nivolumab or nivolumab + ipilimumab will be limited to 2 year maximum duration

Treatment with nivolumab or nivolumab with ipilimumab will be given for up to 24 months in the absence of disease progression or inacceptable toxicity. Chemotherapy will be given as per the study dosing schedule until disease progression or unacceptable toxicity (see Section 4.5.5.2).

Baseline and all subsequent scans will be submitted to a BICR for analysis and archiving, once the subject is randomized and throughout the study period.

This study will consist of 3 phases: screening, treatment, and follow-up.

3.1.1 Screening Phase

- Begins by establishing the subject's initial eligibility and signing of the informed consent.
- Subject is enrolled using the Interactive Response Technology (IRT) system.
- Subjects must have PD-L1 immunohistochemistry (IHC) testing, with evaluable 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 if available, must be submitted for biomarker evaluation prior to randomization. The tumor tissue sample may be fresh or archival if obtained within 6 months prior to randomization, and there can have been no systemic therapy (eg, adjuvant) given after the sample was obtained. Tissue must be a core needle biopsy, excisional or incisional biopsy. Fine needle biopsies or drainage of pleural effusions with cytospins are not considered adequate for biomarker review and randomization. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable. If insufficient tumor tissue is provided for analysis, acquisition of additional tumor tissue (block and/or slides) for the biomarker analysis is required.
- Note that subjects with PD-L1 result will be randomized, but only subjects with PD-L1 expression ≥ 1% will be assessed as part of the primary objective.

This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, if subject has not been randomized). If re-enrolled, the subject must be re-consented and a new subject number must be assigned.

Subject is assessed for study eligibility according to the inclusion (Section 3.3.1) and exclusion (Section 3.3.2) criteria. The detailed procedures are described in Table 5.1-1.

3.1.2 Treatment Phase

The treatment phase begins when the treatment is assigned in the IRT.

Study treatment must begin within 3 calendar days of randomization.

- Adverse event assessments should be documented at each clinic visit and Women of Child-bearing Potential (WOCBP) must have a negative pregnancy test within 24 hours of first dose and then every 4 weeks (± 7 days).
- Treated subjects will be evaluated for tumor assessments every 6 weeks (± 7 days) starting on Week 7 up to and including Week 48, then every 12 weeks (± 7 days) thereafter.
- Biomarker sampling will follow the protocol-defined schedule (Table 5.6-1).
- Patient-reported outcomes (PRO) questionnaires EQ-5D-3L and FACT-E will be collected prior to other procedures on Cycle 1 Day 1 and then every 2 weeks until Week 7 and every 6 weeks thereafter.

Study assessments are to be collected as outlined in Section 5.

Treatment with nivolumab or nivolumab with ipilimumab (Arms A and B) will be given for up to 24 months in the absence of disease progression or inacceptable toxicity. Chemotherapy (Arms B, and C) will be given as per the study dosing schedule until disease progression or unacceptable toxicity (see Section 4.5.5.2). Then, the subject will enter the Follow-up Phase (Table 5.1-5).

3.1.2.1 Nivolumab plus Ipilimumab (Arm A)

- Nivolumab 3 mg/kg will be administered IV on Day 1 and then every 2 weeks.
- Ipilimumab 1 mg/kg will be administered IV on Day 1 and then every 6 weeks following the administration of nivolumab.
- When both nivolumab and ipilimumab are to be administered on the same day, nivolumab is to be administered first. The second infusion will always be ipilimumab, and will start at least 30 minutes after completion of the nivolumab infusion.
- Treatment beyond initial, investigator-assessed, RECIST 1.1-defined progression is permitted if the subject has investigator-assessed clinical benefit and is tolerating treatment, as specified in Section 4.5.6.
- PK and IMG sampling data will be collected as indicated in Table 5.5-1.

3.1.2.2 Nivolumab Combined with Fluorouracil plus Cisplatin (Arm B)

- Nivolumab combined with fluorouracil and cisplatin will be administered IV in a 4-week cycle. Nivolumab 240 mg will be administered IV every 2 weeks on Day 1 and Day 15 of

each cycle. Fluorouracil 800 mg/m²/day will be administered as an IV continuous infusion on Day 1 through Day 5 (for 5 days) and cisplatin 80 mg/m² will be administered IV on Day 1 of 4-week cycle .

- When both nivolumab and fluorouracil and cisplatin combination are to be administered on the same day, nivolumab is to be administered first. Infusion of fluorouracil and cisplatin will start at least 30 minutes after completion of the nivolumab infusion.
- Treatment with nivolumab beyond initial, investigator-assessed, RECIST 1.1-defined progression is permitted if the subject has investigator-assessed clinical benefit and is tolerating treatment, as specified in Section 4.5.6.
- PK and IMG sampling data will be collected as indicated in Table 5.5-1.

3.1.2.3 Fluorouracil and Cisplatin Combination (Arm C)

- Fluorouracil 800 mg/m²/day will be administered as an IV continuous infusion on Day 1 through Day 5 (for 5 days) and cisplatin 80 mg/m² will be administered IV on Day 1 of 4-week cycle.

3.1.3 Follow-up Phase

- Begins when the decision to discontinue a subject from study therapy is made (no further treatment with study therapy).
  - FU1 = 30 days from last dose (± 7 days) or coinciding with the date of discontinuation (± 7 days) if date of discontinuation is greater than 35 days after last dose
  - FU2 = 84 days from FU1 (± 7 days).
- Subjects who discontinue treatment for reasons other than tumor progression will continue to have tumor assessments as per the schedule for the assigned treatment arm until confirmed disease progression, withdrawal of consent or lost to follow-up.
- Subjects will be followed for all AEs until these resolve, return to baseline or are deemed irreversible. All AEs will be documented for a minimum of 100 days after the last dose of study treatment.
- After completion of the first two follow-up visits, subjects will be followed every 3 months (± 14 days) for survival via in-person visit or phone. Ad hoc survival data requests may be made during the study as well, particularly during database locks. Additional subsequent cancer therapy details such as regimen, setting of the regimen, line of therapy, start date and end date of each regimen, best response to the regimen and date of progression after second line therapy will be collected.
- The PRO questionnaires collection and biomarker sampling will continue as per time and event schedule. Study follow-up assessment data are to be collected as outlined in Table 5.1-5.

The start of the trial is defined as first visit for first subject screened . End of trial is defined as the last visit or scheduled procedure shown in the Time & Events schedule for the last subject. Study

completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study drug for the maximum treatment duration allowed by the study protocol. Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to BMS supplied study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.3 Study Population

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

3.3.1 Inclusion Criteria

- **Signed Written Informed Consent**
  - a) Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal subject care.
  - b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the study.
- **Target Population**
  - c) Subjects must have histologically confirmed squamous cell carcinoma or adenosquamous cell carcinoma (predominant squamous differentiation) of esophagus (per AJCC 7th edition,[55] see Appendix 4).
  - d) Subjects must have unresectable advanced, recurrent or metastatic ESCC (per AJCC 7th edition,[48] see Appendix 4).
  - e) Subjects must not be amenable to curative approaches such as definitive chemoradiation and/or surgery.
  - f) No prior systemic anticancer therapy given as primary therapy for advanced or metastatic disease
    - i) Prior adjuvant, neoadjuvant, or definitive, chemotherapy/ radiotherapy/ chemoradiotherapy for ESCC is permitted if given as part of curative intent regimen and completed before enrollment. A recurrence-free period is required for 24 weeks after completion of neoadjuvant or adjuvant chemotherapies, or after completion of multimodal therapies (chemotherapies and chemoradiotherapies) for locally advanced diseases
  - g) ECOG Performance Status of ≤ 1 (Appendix 3)
  - h) Subjects must have at least one measurable lesion by CT or MRI per RECIST 1.1 criteria; radiographic tumor assessment must be performed within 28 days prior to randomization.

i) Tumor tissue must be provided for biomarker analyses. Either 1 formalin-fixed paraffin embedded (FFPE) tumor tissue block or 15 unstained tumor tissue slides, with an associated pathology report if available, must be submitted for biomarker evaluation prior to study drug administration The tumor tissue sample may be fresh or archival if obtained within 6 months prior to randomization, and there can have been no systemic therapy (eg, adjuvant) given after the sample was obtained. Tissue must be a core needle biopsy, excisional or incisional biopsy. Fine needle biopsies or drainage of pleural effusions with cytospins are not considered adequate for biomarker review and randomization. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable.

2) In order to be randomized, a subject must have an evaluable PD-L1 expression classification ≥ 1% or < 1%, or indeterminate) as determined by the central lab.

   i) Subjects with non-evaluable results will not be allowed to be randomized.

   b) Subject Re-enrollment: this study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, if subject has not been randomized). If re-enrolled, the subject must be re-consented and a new subject number must be assigned.

   c) All baseline laboratory requirements will be assessed and should be obtained within 14 days prior to study drug administration. Screening laboratory values must meet the following criteria

      i) White Blood Cells (WBC) ≥ 2000/uL

      ii) Neutrophils ≥ 1500/uL

      iii) Platelets ≥ 100 x 10^3/uL

      iv) Hemoglobin ≥ 9.0 g/dL

      v) Calculated creatinine clearance (CrCl) > 60 mL/min (using the 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 = $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/ dL,}}$
- or, measured creatinine clearance (CrCl) > 60 mL/min (using a preferred method per local Standard of Care)

      vi) AST ≤ 3.0 x ULN (or ≤ 5.0 x ULN if liver metastases are present)

      vii) ALT ≤ 3.0 x ULN (or ≤ 5.0 x ULN if liver metastases are present)

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

- **Age and Reproductive Status**

   d) Males and Females ≥ 18 years of age

e) 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.

f) Women must not be breastfeeding

g) WOCBP randomized to the nivolumab -plus -ipilimumab arm or the nivolumab-plus-chemotherapy arm must agree to follow instructions for method(s) of contraception for the duration of study treatment and 5 months after the last dose of study treatment (i.e., 30 days [duration of ovulatory cycle] plus the time required for the investigational drug to undergo approximately five half-lives).

h) Males randomized to the nivolumab plus ipilimumab arm or the nivolumab-plus-chemotherapy arm and who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment and 7 months after the last dose of study treatment (i.e., 90 days [duration of sperm turnover] plus the time required for the investigational drug to undergo approximately five half-lives). In addition, male subjects must be willing to refrain from sperm donation during this time.

i) WOCBP randomized to the chemotherapy arms must also agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with chemotherapy plus 5 half-lives of chemotherapy plus 30 days (duration of ovulatory cycle) or a duration specified by the local labels of the chemotherapy drugs received, whichever is longer.

j) Males randomized to the chemotherapy arms who are sexually active with WOCBP must also agree to follow instructions for method(s) of contraception for the duration of treatment with chemotherapy plus 5 half lives of chemotherapy plus 90 days (duration of sperm turnover) or a duration specified by the local labels of the chemotherapy drugs received, whichever is longer. In addition, male subjects must be willing to refrain from sperm donation during this time. Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP, and male subjects who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception (Appendix 2), which have a failure rate of < 1% when used consistently and correctly.

3.3.2 Exclusion Criteria

- **Target Disease Exceptions**

  k) Subjects with adenocarcinoma.

  a) Patients with any metastasis in the brain or meninx that is symptomatic or requires treatment. Patients may be randomized if the metastasis is asymptomatic and requires no treatment.

  l) Patients at high risks of bleeding or fistula due to apparent invasion of tumor to organs (the aorta or the trachea) adjacent to esophageal lesions.

- **Medical History and Concurrent Diseases**

m) Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before randomization.

n) Prior malignancy requiring active treatment 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.

o) Subjects with active, known, or suspected autoimmune disease. Subjects with Type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll. For any cases of uncertainty, it is recommended that a BMS medical monitor be consulted prior to signing informed consent.

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

q) 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.

r) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug.

s) 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 study drug.

t) Patients with uncontrollable, tumor related pain.

u) Patients with significant malnutrition. Patients will be excluded if they are receiving intravenous hyperalimentation, or require continuous infusion therapy with hospitalization. Patients whose nutrition has been well controlled for ≥ 28 days prior to randomization may be enrolled.

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

w) Subjects with > Grade 1 peripheral neuropathy.

x) 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 locally.

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

z) Participants who have received a live / attenuated vaccine within 30 days of first treatment.

- **Physical and Laboratory Test Findings**

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

- **Allergies and Adverse Drug Reaction**

  bb) History of allergy or hypersensitivity to study drug components

  cc) Any contraindications to any of the study drugs of the chemotherapy regimen (fluorouracil or cisplatin). Investigators should refer to package insert of the chemotherapy drugs.

- **Other Exclusion Criteria**

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

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

  ff) Participation in any prior clinical study of nivolumab, including participants in comparator arms, in which overall survival is listed as the primary or co-primary endpoint and which has not completed analysis based on the primary endpoint.

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

WOCBP is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

*Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels.

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

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

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study (unless utilized to treat a drug related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 3.4.3)
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of EC).
- Botanical formulations with an approved indication for cancer treatment are [e.g. traditional Chinese medicines]; these should be discontinued (if used) at least 2 weeks prior to randomization.
- Any live / attenuated vaccine (eg varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella (MMR)) during treatment and until 100 days post last dose.

Investigators should refer to the local product labeling for the chemotherapy drugs selected for use in Arms B and C for additional prohibited and restricted concomitant medications.

3.4.2 Other Restrictions and Precautions

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

Subjects who are receiving coumarin-derivative anticoagulants such as warfarin concomitantly with fluorouracil should be closely monitor patients for INR or prothrombin time in order to adjust the anticoagulant dose accordingly.

3.4.3 Permitted Therapy

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

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

Subjects requiring palliative radiotherapy should be evaluated for objective evidence of disease progression prior to the initiation of such therapy, particularly if the most recent tumor assessment was more than 4 weeks prior to the start of local therapy. If progression per RECIST 1.1 is identified on any tumor assessments prior to the initiation of palliative local therapy, then subjects

must either discontinue study drug treatment or they must meet criteria to continue treatment beyond progression (Section 4.5.6) in order to resume immunotherapy after palliative local therapy. Palliative radiotherapy may also be permitted prior to discontinuation of study treatment in subjects who do not have evidence of overall clinical or radiographic progression per RECIST 1.1, provided that the lesions undergoing palliative local therapy are non-target lesions and the case is discussed with, and approved by, the BMS Medical Monitor.

In cases where palliative radiotherapy is required for a tumor lesion, then study treatment should be withheld for at least 1 week before, during, and 1 week after radiation. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs should resolve to Grade ≤ 1 prior to resuming study therapy.

3.5 Discontinuation of Subjects following any Treatment with Study Drug

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

- Subject's request to stop study treatment
- Any clinical 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 BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- Criteria listed in Section 4.5.5
- Disease progression as assessed by RECIST 1.1 criteria, unless the subject meets criteria for treatment beyond progression (Section 4.5.6).

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

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

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

All 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. Survival visits are every 3 months from FU2 until the end of the study and may be conducted during a clinic visit or via the phone.

3.6 Post Study Drug Study Follow up

In this study, OS and PFS are 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 outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

BMS may request that survival data be collected on all treated/randomized subjects outside of the protocol defined window (see Section 5). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contacts or is lost to follow-up.

3.6.1 Withdrawal of Consent

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

3.6.2 Lost to Follow-Up

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

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained

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

4 STUDY DRUG

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

- Nivolumab Solution for Injection
- Ipilimumab Solution for Injection
- Cisplatin Concentrate for Solution for Infusion
- Fluorouracil Solution for Injection.

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, the investigational products are nivolumab solution for injection, ipilimumab solution for injection, cisplatin solution for infusion, and fluorouracil solution for injection (Table 4.1-1).

Table 4.1-1: Study Drugs for CA209648:

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[a]	100 mg (10 mg/mL)	IP	Open label	10 mL vial. Clear to opalescent, colorless to pale yellow liquid. May contain particles.	2° to 8°C. Protect from light and freezing.
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	IP	Open label	40 mL vial Clear to opalescent, colorless to pale yellow liquid. May contain particles.	2° to 8°C. Protect from light and freezing.
Cisplatin Concentrate for Solution for Infusion[b,c]	100 mg (1 mg/mL)	IP	Open label	Clear, colorless solution (100 mL/ vial)	Do not store above 25°C. Do not refrigerate or freeze. Store in outer carton.
Fluorouracil Solution for Injection[b,c]	1g/vial (50 mg/ mL)	IP	Open label	Clear, colorless or slightly yellow solution. 1 g/20 mL	Do not store above 25°C. Do not refrigerate or freeze. Store in outer carton.

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

[b] These products may be obtained as local commercial product in certain countries if allowed by local regulations. In these cases, products may be a different pack size/potency than listed in the table. These products should be prepared/stored/administered in accordance with the package insert or summary of product characteristics (SmPC).

[c] Potency, packaging and storage conditions may vary for China. Storage conditions will be indicated on the clinical labels.

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: any medications used to treat nivolumab or ipilimumab infusion-related reactions (eg, steroids). These non-investigational products should be sourced by the investigator sites if available and permitted by local regulations.

4.3 Storage of Study Drug

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

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

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

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

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

Please refer to the current versions of the IBs, SpC or package inserts and/or pharmacy manual for complete storage, handling, dispensing, and infusion/dosing information for nivolumab, ipilimumab, fluorouracil and cisplatin.

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 the IRT system to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in the IRT system. Specific instructions for using the IRT system 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 the IRT, subjects that have met all eligibility criteria (including the required tumor tissue received and evaluable result obtained by the central laboratory and the pathology report

approved by the investigator) will be ready to be randomized through the IRT. The following information is required for subject randomization:

- Subject number
- Date of birth
- Gender: male vs female
- Region: East Asia (Japan, Korea, Taiwan) vs Rest of Asia vs rest of world
- ECOG performance status: 0 vs 1
- PD-L1 evaluable status (the result of PD-L1 expression [≥ 1% or < 1% or indeterminate] inserted by the central laboratory vendor into the IRT and both the site and the BMS study team remain blinded to the result).
- Number of organs with metastases (≤ 1 vs ≥ 2).
- Weight

Subjects meeting all eligibility criteria will be randomized in a 1:1:1 ratio to either the nivolumab and ipilimumab arm (Arm A), or the nivolumab plus fluorouracil and cisplatin arm (Arm B), or the fluorouracil and cisplatin combination arm (Arm C). Randomization will be stratified by the following factors:

3) 1. PD-L1 status (≥ 1% vs < 1% [including indeterminate])*
4) 2. Region (East Asia (Japan, Korea, Taiwan) vs Rest of Asia vs rest of world)
5) 3. ECOG performance status (0 vs 1).
6) 4. Number of organs with metastases (≤ 1 vs ≥ 2)

* During enrollment, the proportion of subjects with or without PD-L1 tumor expression will be monitored, and may be re-assessed in case it does not reflect study assumptions (ie, subjects with PD-L1 tumor expression ≥ 1% is approximately 50% of all comers).

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

4.5 Selection and Timing of Dose for Each Subject

4.5.1 Dosing

4.5.1.1 Nivolumab plus Ipilimumab Dosing (Arm A)

Subjects randomized to Arm A will receive nivolumab at a dose of 3 mg/kg as a 30-minute IV infusion, on Day 1 of each treatment cycle every 2 weeks and ipilimumab at a dose of 1 mg/kg every 3 cycles (ie, every 6 weeks) until progression, unacceptable toxicity, withdrawal of consent, completion of 24 months of treatment, or the study ends, whichever occurs first.

Subjects should begin study treatment within 3 calendar days of randomization. See Table 4.5.1.1-1 for details on the dosing schedule of nivolumab plus ipilimumab in Arm A.

Dosing calculations should be based on the body weight assessed at baseline. It is not necessary to re-calculate subsequent doses if the subject weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up or to the nearest milligram per institutional standard.

When study treatments (nivolumab and ipilimumab) are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study treatment and will start after the infusion line has been flushed, filters changed and patient has been observed to ensure no infusion reaction has occurred.

There will be no dose escalations or reductions of nivolumab and ipilimumab allowed. Subjects may be dosed with nivolumab no less than 12 days from the previous dose of nivolumab and may be dosed with ipilimumab no less than 37 days from the previous dose of ipilimumab. There are no premedications recommended.

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 4.5.8.

Doses of nivolumab and/or ipilimumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment. Please refer to Section 4.5.2.1 (dose delays), Section 4.5.4.1 (resuming treatment) and Section 4.5.5.1 (dose discontinuation).

Table 4.5.1.1-1: Dose Schedule of Nivolumab and Ipilimumab in Arm A

Treatment Group	Drug Name	Cycle 1 (Week 1)	Cycle 2[a] (Week 3)	Cycle 3[a] (Week 5)	Cycle 4[a] (Week 7)	Cycle 5[a] (Week 9)	Cycle 6[a] (Week 11) till EOT
Nivolumab + Ipilimumab	Nivolumab 3 mg/kg	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1
	Ipilimumab[b] 1 mg/kg	Day 1			Day 1		

[a] Cycle 2 till EOT: Subsequent nivolumab doses may be administered within 3 days before or after the scheduled date if necessary. There should be no less than 12 days between doses.

[b] Ipilimumab dose is administered Q6W, within 5 days before or after the scheduled date if necessary. There should be no less than 37 days between ipilimumab doses.

4.5.1.2 Nivolumab Combined with Fluorouracil plus Cisplatin Dosing (Arm B)

Subjects randomized to Arm B will receive treatment with nivolumab 240 mg as a 30-minute infusion on Day 1 and Day 15 (ie, every 2 weeks), fluorouracil 800 mg/m²/day as an IV continuous

infusion on Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m² as a 30- to 120-minute infusion* on Day 1 of 4-week cycle.

*Subjects are allowed to receive treatment with cisplatin 80 mg/m² as an IV infusion over a period of longer than 120 min if it is in accordance with local standard of care/local label.

Treatment will continue until progression, unacceptable toxicity, withdrawal of consent, the study ends, whichever occurs first. The treatment with nivolumab will be given for up to 24 months in the absence of disease progression or unacceptable toxicity. Chemotherapy will be given as per the study dosing schedule.

Subjects should begin study treatment within 3 calendar days of randomization. See Table 4.5.1.2-1 for details on the dosing schedule of nivolumab combined with fluorouracil plus cisplatin in Arm B.

Dosing calculations of fluorouracil and cisplatin should be based on the body weight assessed at baseline. It is not necessary to re-calculate subsequent doses if the subject weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up or to the nearest milligram per institutional standard.

When both nivolumab and fluorouracil and cisplatin combination are to be administered on the same day, nivolumab is to be administered first. Infusion of fluorouracil and cisplatin will start at least 30 minutes after completion of the nivolumab infusion.

Pretreatment hydration for cisplatin can follow local standard of care, or use 1 to 2 liters of fluid (per local standards) infused IV for 8 to 12 hours prior to cisplatin infusion is recommended. Adequate hydration and urinary output must be maintained for at least 24 hours following cisplatin administration. Administration and monitoring should be performed according to local standards. Use of mannitol following the cisplatin infusion should also follow local standards-of-care.

Premedications for use with fluorouracil/cisplatin: Antiemetic premedication will be administered according to local standards. Recommended antiemetic treatments are dexamethasone (dosing according to local standards; an equivalent dose of another corticosteroid may be substituted) and a 5-HT3 receptor antagonist (type per investigator discretion and local standards-of-care). Dexamethasone is allowed as premedication in arm B during the platinum-based chemotherapy. Additional use of antiemetic premedications may be employed at the discretion of the Investigator. Refer to the local product label for more detail. There are no premedications recommended for nivolumab treatment.

Doses of fluorouracil and/or cisplatin may be interrupted, delayed, reduced, or discontinued depending on how well the subject tolerates the treatment See the following sections for more details: 4.5.2 (dose delays) and 4.5.3 (dose reductions), 4.5.4 (retreatment), and 4.5.5 (dose discontinuations).

If either fluorouracil or cisplatin is discontinued the other study treatments may be continued for the remainder of the cycles.

In subjects who required fluorouracil dose reduction due to toxicity during the fluorouracil/cisplatin combination cycles, the dose of fluorouracil may be re-escalated to 800 mg/m^2 after the discontinuation of cisplatin, at the investigator's discretion and according to local standards, if the prior toxicity was felt to be related mainly to cisplatin.

All subjects who will be receiving cisplatin should have audiometric testing performed prior to initiation of therapy and prior to subsequent doses of cisplatin, or as per local standards of care.

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment. There will be no dose escalations or reductions of nivolumab allowed. Subjects may be dosed with nivolumab no less than 12 days from the previous dose of nivolumab.

Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to Section 4.5.8.

Table 4.5.1.2-1: Dose Schedule of Nivolumab plus FP in Arm B

Treatment Group	Drug Name	Cycle 1 (Week 1)	Cycle 2 (Week 5)	Cycle 3 (Week 9)	Cycle 4 (Week 13)	Cycle 5 (Week 17)	Cycle 6 (Week 21) till EOT
Nivolumab + fluorouracil + cisplatin	Nivolumab[a] 240 mg	Day 1 and Day 15	Day 1 and Day 15	Day 1 and Day 15	Day 1 and Day 15	Day 1 and Day 15	Day 1 and Day 15
	Fluorouracil 800 mg/m^2	Days 1, 2, 3, 4 and 5	Days 1, 2, 3, 4 and 5	Days 1, 2, 3, 4 and 5	Days 1, 2, 3, 4 and 5	Days 1, 2, 3, 4 and 5	Days 1, 2, 3, 4 and 5
	Cisplatin 80 mg/m^2	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1

[a] Cycle 1 on Day 15 till EOT: Subsequent nivolumab doses may be administered within 3 days before or after the scheduled date if necessary. There should be no less than 12 days between doses.

4.5.1.3 Fluorouracil plus Cisplatin Dosing (Arm C)

Subjects randomized to Arm C will receive treatment with fluorouracil 800 mg/m^2/day as an IV continuous infusion on Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m^2 as a 30- to 120-minute infusion* on Day 1 of 4-week cycle. Treatment will continue until progression, unacceptable toxicity, withdrawal of consent, the study ends, whichever occurs first.

*Subjects are allowed to receive treatment with cisplatin 80 mg/m^2 as an IV infusion over a period of longer than 120 min if it is in accordance with local standard of care/local label.

Doses of fluorouracil and/or cisplatin may be interrupted, delayed, reduced, or discontinued depending on how well the subject tolerates the treatment See the following sections for more details: 4.5.2 (dose delays) and 4.5.3 (dose reductions), 4.5.4 (retreatment), and 4.5.5 (dose discontinuations).

If either fluorouracil or cisplatin is discontinued the other study treatments may be continued for the remainder of the cycles.

In subjects who required fluorouracil dose reduction due to toxicity during the fluorouracil/cisplatin combination cycles, the dose of fluorouracil may be re-escalated to 800 mg/m^2 after the discontinuation of cisplatin, at the investigator's discretion and according to local standards, if the prior toxicity was felt to be related mainly to cisplatin.

Subjects should begin study treatment within 3 calendar days of randomization. See Table 4.5.1.3-1 for details on the dosing schedule of fluorouracil plus cisplatin in Arm C.

Dosing calculations of fluorouracil and cisplatin should be based on the body weight assessed at baseline. It is not necessary to re-calculate subsequent doses if the subject weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up or to the nearest milligram per institutional standard.

Pretreatment hydration for cisplatin can follow local standard of care, or use 1 to 2 liters of fluid (per local standards) infused IV for 8 to 12 hours prior to cisplatin infusion is recommended. Adequate hydration and urinary output must be maintained for at least 24 hours following cisplatin administration. Administration and monitoring should be performed according to local standards. Use of mannitol following the cisplatin infusion should also follow local standards-of-care.

Premedications: Antiemetic premedication will be administered according to local standards. Recommended antiemetic treatments are dexamethasone (dosing according to local standards; an equivalent dose of another corticosteroid may be substituted) and a 5-HT3 receptor antagonist (type per investigator discretion and local standards-of-care). Dexamethasone is allowed as premedication in arm C during the platinum-based chemotherapy. Refer to the local product label for more detail. Additional use of antiemetic premedications may be employed at the discretion of the Investigator.

All subjects who will be receiving cisplatin should have audiometric testing performed prior to initiation of therapy and prior to subsequent doses of cisplatin, or as per local standards of care.

Table 4.5.1.3-1: Dose Schedule of FP (Fluorouracil + Cisplatin) in Arm C

Treatment Group	Drug Name	Cycle 1 (Week 1)	Cycle 2 (Week 5)	Cycle 3 (Week 9)	Cycle 4 (Week 13)	Cycle 5 (Week 17)	Cycle 6 (Week 21) till EOT
Fluorouracil + cisplatin	Fluorouracil[a] 800 mg/m^2	Days 1, 2, 3, 4 and 5	Days 1, 2, 3, 4 and 5	Days 1, 2, 3, 4 and 5	Days 1, 2, 3, 4 and 5	Days 1, 2, 3, 4 and 5	Days 1, 2, 3, 4 and 5
	Cisplatin[a] 80 mg/m^2	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1

[a] Fluorouracil and cisplatin will be given every 4 weeks. FP dose on Day 1 is administered within 3 days before or after the scheduled date if necessary.

4.5.2 Dose Delay Criteria

4.5.2.1 Dose Delay Criteria for Nivolumab and/or Ipilimumab (Arms A and B)

Nivolumab and/or ipilimumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related AE, with the following exception:
  - Grade 2 drug-related fatigue does not require a treatment delay.
- Grade 2 drug-related creatinine,
- Any Grade ≥ 3 skin, drug-related AE
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, AST, ALT, or total bilirubin and asymptomatic amylase or lipase abnormalities:
  - Grade 3 lymphopenia does not require dose delay
  - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
  - If a subject has baseline AST, ALT, or total bilirubin within the grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity
  - Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects who have drug-related toxicities that meet the criteria for dose delay should have both drugs (ipilimumab and nivolumab) delayed until retreatment criteria are met(exceptions apply to the retreatment criteria after dose delay of ipilimumab and nivolumab for Grade ≥ 3 amylase and lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and that are attributed to ipilimumab alone).

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

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.

Rescheduling:

- Nivolumab may be delayed until the next planned ipilimumab dose if the next ipilimumab dose is scheduled within the next 12 days. This will permit periodic ipilimumab dosing to be synchronized with nivolumab dosing.
- Ipilimumab should be dosed at the specified interval regardless of any delays in intervening nivolumab doses. However, in order to maintain periodic synchronized dosing of ipilimumab and nivolumab, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted ± 5-day window, as long as consecutive nivolumab doses are given at least 12 days apart. Ipilimumab may be delayed beyond the 5-day window if needed to synchronize with the next nivolumab dose.
- If an ipilimumab dose is delayed beyond 6 weeks from the prior ipilimumab dose, then subsequent ipilimumab doses should rescheduled to maintain the 6-week interval between consecutive ipilimumab doses.

- Dosing delays of ipilimumab which results in an interruption of ipilimumab dosing > 12 weeks requires discontinuation ipilimumab, with exceptions as noted in Section 4.5.5.1.

4.5.2.2 Dose Delay Criteria for Fluorouracil and Cisplatin Combination (Arm C)

In Arms B and C, dosing of both drugs in the fluorouracil and cisplatin combination selected should be delayed for any of the following on the Day 1 of each cycle:

- Absolute neutrophil count (ANC) < 1500/μL
- Platelets < 100,000/mm^3
- Any Grade ≥ 2 non-skin, non-hematologic, drug-related adverse event (excluding Grade 2 alopecia, Grade 2 fatigue, and Grade 2 laboratory abnormalities)
- Any Grade ≥ 3 skin, drug-related adverse event
- Any Grade ≥ 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia does not require dose delay.
  - If a subject has a baseline AST. ALT or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication. Investigators should consult local labeling for the chemotherapy drugs being administered to any given subject for additional guidance on dose delays.

Rescheduling:

If any non-hematologic adverse event meeting the dose delay criteria above is felt to be related to only one particular agent in the fluorouracil and cisplatin combination regimen, then that agent alone may be omitted for that cycle while the other agent is given. In order to maintain synchronized dosing of the regimen, the omitted agent should be resumed with the next scheduled cycle once the AE has improved and retreatment criteria are met. Please refer to Section 4.5.3 to determine if dose reduction of the resumed agent is required.

If both drugs in fluorouracil and cisplatin combination regimen are delayed, then the subject should be re-evaluated weekly or more frequently if clinically indicated until re-treatment criteria are met (as per Section 4.5.4).

4.5.2.3 Dose Delay Criteria for Nivolumab Combined with Fluorouracil plus Cisplatin Platinum in Arm B

In Arm B, dosing of all drugs should be delayed if any criteria in Sections 4.5.2.1 (Arm A, nivolumab and/or ipilimumab) or 4.5.2.2 (Arm C, fluorouracil and cisplatin combination) are met.

That is, nivolumab should be delayed if criteria for delay of chemotherapy are met, and chemotherapy should be delayed if criteria for delay of nivolumab are met.

4.5.3 Dose Reductions

4.5.3.1 Dose Reductions for Nivolumab or Ipilimumab

There will be no dose reductions for nivolumab or ipilimumab.

4.5.3.2 Dose Reductions for Fluorouracil and Cisplatin combination

Dose reductions of fluorouracil and cisplatin combination may be required, and will be performed according to Table 4.5.3.2-1. The dosing reduction criteria will apply to Arms B and C. Chemotherapy dose reductions are permanent; once the dose of any chemotherapy agent is reduced, it may not be re-escalated in subsequent cycles. The dose reductions for each agent in the fluorouracil and cisplatin combination regimen are not linked and may be adjusted independently as summarized below.

In subjects who required fluorouracil dose reduction due to toxicity during the fluorouracil/cisplatin combination cycles, the dose of fluorouracil may be re-escalated to 800 mg/m^2 after the discontinuation of cisplatin, at the investigator's discretion and according to local standards, if the prior toxicity was felt to be related mainly to cisplatin.

If either fluorouracil or cisplatin is discontinued the other study drugs may be continued for the remainder of the cycles.

Table 4.5.3.2-1: Dose Modifications of FP

Dose Level	Fluorouracil	Cisplatin
Starting dose	800 mg/m^2	80 mg/m^2
First dose reduction	600 mg/m^2 (25% reduction)	60 mg/m^2 (25% reduction)
Second dose reduction	400 mg/m^2 (50% reduction)	40 mg/m^2 (50% reduction)
Third dose reduction	Discontinue	Discontinue

Any subjects with 2 prior dose reductions for one agent who experiences a toxicity that would cause a third dose reduction must be discontinued from that agent.

Criteria for dose reduction due to postponement of starting a treatment cycle

If the patient does not meet the criteria for starting a treatment at the start of a treatment cycle and has to postpone the start of the cycle:

- The dose of cisplatin and 5-FU will be the same as those used in the previous cycle when a treatment cycle is resumed by Day 15 of postponement (Day 1 is defined as the planned day of starting the next cycle of FP therapy). However, when a treatment cycle is resumed between Day 9 and Day 15 (Day 1 is defined as the planned day of starting the next cycle of FP therapy)

for two consecutive cycles, the dose of attributable agent(s) should be reduced by 1 level in the second of such cycles.

- When a treatment cycle is resumed between Day 16 and Day 29 (Day 1 is defined as the planned day of starting the next cycle of FP therapy), the dose of the attributable agent(s) should be reduced by 1 level.

4.5.3.2.1 Fluorouracil and Cisplatin - Dose Reductions for Hematologic Toxicity

Dose modifications for hematologic toxicities (according to CTCAE version 4) are summarized in Table 4.5.3.2.1-1. Dose adjustments are based on nadir blood counts (assessed as per local standards) since the preceding drug administration. Dose level adjustments for fluorouracil and cisplatin combination are relative to that of the preceding administration. Generally, both chemotherapy agents in the fluorouracil and cisplatin combination regimen should be dose reduced together for hematologic toxicity. After the first cycle, G-CSF may be used to assist hematologic recovery. Use local standards of care in the use of these supportive measures. Additionally, prophylactic antibiotics may be used according to local standards of care. Please report any antibiotic or growth factor use on the eCRF.

Table 4.5.3.2.1-1: Dose Modifications for Hematologic Toxicity (Arms B and C)

Toxicity[a]	Fluorouracil	Cisplatin
Neutrophils (ANC) < 500/mm3 lasting ≥ 5 days	Reduce one dose level	Reduce one dose level
Febrile neutropenia (body temperature ≥ 38.5°C and ANC < 1,000/mm3)	Reduce one dose level	Reduce one dose level
Platelet < 25,000/mm3	Reduce one dose level	Reduce one dose level
Platelets < 50,000/mm3 with significant bleeding or requiring blood transfusion	Reduce one dose level	Reduce one dose level
Grade 4 hemoglobin (< 6.5 g/100 mL)	Reduce one dose level	Reduce one dose level

[a] If considered in the best interest of the subject, and consistent with local practice, investigators may decide to use supportive measures/treatment, and/or secondary prophylaxis instead of dose reductions for the next cycle. Also, if toxicity can clearly be attributed to one of the drugs, the investigator may choose to only dose reduce one of the cytotoxic agents.

4.5.3.2.2 Fluorouracil and Cisplatin - Dose Reductions for Non-hematologic Toxicity

Dose adjustments for fluorouracil and cisplatin combination for non-hematologic toxicities during treatment are described in Table 4.5.3.2.2-1. All dose reductions should be made based on the worst CTCAE grading. Subjects experiencing any of the toxicities detailed in Section 4.5.2.2 during the previous cycle should have their chemotherapy delayed until retreatment criteria are met (per Section 4.5.4 and then reduced for all subsequent cycles by 1 or 2 dose level or discontinued as appropriate. Dose levels for the two drugs in the fluorouracil and cisplatin

combination regimen are not linked and may be reduced independently, as summarized in the table below.

Table 4.5.3.2.2-1: Dose Modifications for Non-hematologic Toxicity (Arms B and C)

Toxicity[a]	Fluorouracil	Cisplatin
Febrile Neutropenia Grade ≥ 3	Reduce one dose level	Reduce one dose level
Diarrhea Grade ≥ 3	Reduce one dose level	Reduce one dose level
Stomatitis Grade ≥ 3	Reduce one dose level	Reduce one dose level
Neuropathy Grade 2 lasting > 7days OR Grade 3 lasting ≤ 7days	No change	Reduce two dose level
Neuropathy Grade 3 lasting > 7days OR Grade 4	No change	Discontinue
Nephrotoxicity 50-59 mL/min or Grade 3 Creatinine	No change (Consider reduction in severe renal toxicity)	Reduce two dose level (< 50 mL/min or Grade 4 creatinine requires Discontinue)[b]
Total bilirubin > 1.5 x ULN	50% of previous dose	No change
Total bilirubin > 2.5 x ULN	25% of previous dose	No change
Total bilirubin > 4.0 x ULN	Discontinue	No change
Other Grade ≥ 3 toxicity (except for fatigue and transient arthralgia and myalgia)	Adjust as medically indicated	Adjust as medically indicated
Allergic reaction[c] Grade ≥ 3	Discontinue	Discontinue

[a] If considered in the best interest of the subject, and consistent with local practice, investigators may decide to use supportive measures/treatment, and/or secondary prophylaxis instead of dose reductions for the next cycle. Also, if toxicity can clearly be attributed to one of the drugs, the investigator may choose to only dose reduce one of the cytotoxic agents.

[b] Unless corrected within ± 7 days of the scheduled dosing. CrCl should be determined consistently with the exact same method used to determine eligibility ie either the Cockcroft-Gault formula or the preferred method for measured CrCl determination per local standard of care.

[c] Only the drug(s) causing the hypersensitivity reaction or acute infusion reaction (≥ Grade 3) require(s) discontinuation. All other drugs may be continued.

4.5.4 Criteria to Resume Dosing

4.5.4.1 Criteria to Resume Nivolumab or Ipilimumab (Arms A and B)

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

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- For subjects with Grade 2 AST, ALT, or total bilirubin 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 BMS Medical Monitor.
- Subjects with Grade < 4 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor.

If dose delay is necessary, both nivolumab and ipilimumab must be delayed until treatment can resume. However, if a nivolumab-related infusion reaction prevents subsequent infusion of ipilimumab on the same day, the dose of ipilimumab should be replaced as soon as possible. In such instances, at least 37 days must elapse between the replacement dose of ipilimumab and the administration of the next dose of nivolumab combined with ipilimumab.

4.5.4.2 Criteria to Resume Fluorouracil and Cisplatin Combination (Arm C)

- Subjects may resume treatment when the ANC returns to ≥1500/µl, the platelet count returns to ≥ 100,000/mm^3.
- All other drug-related toxicities have returned to baseline or Grade ≤ 1 (or Grade ≤ 2 for alopecia and fatigue).
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin.
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.5.5.2) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed.
- If a subject fails to meet criteria for re-treatment, then re-treatment should be delayed, and the subject should be re-evaluated weekly or more frequently as clinically indicated. Any subject who fails to recover from toxicity attributable to fluorouracil and cisplatin combination to baseline or Grade ≤ 1 (except Grade 2 alopecia and fatigue) within 8 weeks from the last dose given should discontinue the drug(s) that caused the delay.

When resuming fluorouracil and cisplatin combination treatment, please follow the dose reduction recommendations in Section 4.5.3.2.

4.5.4.3 Criteria to Resume Nivolumab Combined with Fluorouracil and Cisplatin (Arm B)

Subjects in Arm B may resume dosing only when criteria for BOTH resumption of nivolumab (Section 4.5.4.1) AND chemotherapy (Section 4.5.4.2) are met. That is, nivolumab and chemotherapy must be administered together until treatment discontinuation criteria (Section 4.5.5).

4.5.5 Treatment Discontinuation Criteria

4.5.5.1 Nivolumab and/or Ipilimumab Treatment Discontinuation (Arms A and B)

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 ≥ 2 pneumonitis with or without a causal relationship to nivolumab and/or ipilimumab
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, diarrhea, colitis, neurologic toxicity, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related diarrhea, colitis, neurologic toxicity, myocarditis, uveitis, bronchospasm, 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
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation
      - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN
- Any Grade 4 drug-related AE 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 sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Any drug-related Grade 4 endocrinopathy and Grade 3 adrenal insufficiency requires discontinuation
- Any treatment delay resulting in an interruption in nivolumab dosing > 8 weeks, or interruption in ipilimumab > 12 weeks, , with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
  - Dosing delays lasting >8 weeks for nivolumab and >12 weeks for ipilimumab 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 > 8 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

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

In nivolumab plus ipilimumab combination treatment (Arm A), if a subject meets the criteria for discontinuation of ipilimumab but not nivolumab, treatment with nivolumab may not resume until the AE has fully resolved and the subject has discontinued steroids, if they were required for treatment of the AE. The relationship to ipilimumab should be well documented in the source documents. Nivolumab should be resumed at a dose of 3 mg/kg every 2 weeks.

If a subject meets the criteria for discontinuation of nivolumab but not for ipilimumab, both nivolumab and ipilimumab must be discontinued due to the lack of clinical efficacy of ipilimumab monotherapy (Section 1.1.6).

If a subject in the nivolumab and ipilimumab combination arm (Arm A) meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the subject should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study.

4.5.5.2 Fluorouracil and Cisplatin Dose Discontinuation (Arms B and C)

Except where specified below, both chemotherapy drugs in the fluorouracil and cisplatin combination regimen should be discontinued for any of the following (applies to Arms B and C):

- Any drug-related Grade 4 toxicity including laboratory abnormalities the subject will be discontinued from the relevant study drug, with the following exceptions:

  - Isolated Grade 4 electrolyte abnormalities not associated with clinical sequelae and are adequately managed and corrected within 72 hours of onset
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions:
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation, except for the following scenarios:
    - Grade ≥ 3 drug-related thrombocytopenia associated with clinically significant bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria requires discontinuation:
- AST or ALT > 8 x ULN
- Total bilirubin > 5 x ULN
- Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
    - Any cisplatin-related decrease in creatinine clearance to < 50 mL/min (using the Cockcroft Gault formula or any chosen measured creatinine clearance method) requires discontinuation of cisplatin, unless corrected within ± 7 days of the scheduled dosing
- Grade 3 lasting > 7 days OR Grade 4 peripheral neuropathy
- Any drug-related adverse event which recurs after two prior dose reductions for the same drug-related adverse event (as specified in Section 4.5.3.2) requires discontinuation of the drug(s) which was/were previously dose reduced.
- Any Grade ≥ 3 drug-related hypersensitivity reaction or infusion reaction requires discontinuation of the drug(s) felt to be causing the reaction. The drug not felt to be related to the hypersensitivity reaction or infusion reaction may be continued.
- Any event that leads to delay in dosing of any study drug(s) for > 8 weeks from the previous dose requires discontinuation of that drug(s) with the following exception:
  - Dosing delays > 8 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor. Prior to re-initiating treatment in a subject with a dosing delay lasting > 8 weeks, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued treatment.

Subjects could be discontinued from any or both of the study drugs on the FP regimen if, in the opinion of the investigator it is inappropriate to continue on the basis of safety or efficacy.

Subjects who discontinue one of the study drugs on the FP regimen may at the investigators discretion continue administration of the other study drugs. For example, if Cisplatin is discontinued, 5FU may be continued at the intended dose and schedule.

For subjects in Arm B, if the investigator is unable to determine whether an adverse event is due to nivolumab or to fluorouracil and cisplatin combination, then all drugs must be discontinued.

The assessments for discontinuation of chemotherapy and/or nivolumab in Arm B should be made separately. It is allowed to continue nivolumab alone when chemotherapy has been discontinued. Chemotherapy doublet or single drug is allowed to continue if nivolumab met its discontinuation criteria.

4.5.6 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[56]

Subjects will be permitted to continue on nivolumab alone or in combination with ipilimumab (Arm A) or chemotherapy (Arm B) for treatment beyond initial RECIST 1.1 defined PD, assessed by the investigator up to a maximum of 24 months from date of first dose as long as they meet the following criteria:

- Investigator-assessed clinical benefit.
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Subject provides written informed consent prior to receiving additional nivolumab alone or in combination with ipilimumab (Arm A) or chemotherapy (Arm B). All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

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

If the investigator feels that the subjects treated with nivolumab or nivolumab plus ipilimumab or nivolumab plus fluorouracil and cisplatin continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the Time and Events Schedule in Section 5.1.

For the subjects in Arms A or B who continue nivolumab alone or in combination with ipilimumab (Arm A) or chemotherapy (Arm B) beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial PD and an appearance of another new lesion. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD. Nivolumab alone or in combination with ipilimumab (Arm A) or chemotherapy

(Arm B) treatment should be discontinued permanently upon documentation of further progression.

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

4.5.7 Management Algorithms for Immuno-oncology Agents

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

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological

The above algorithms are found in the nivolumab Investigator Brochure and Appendix 1 of this protocol.

4.5.8 Treatment of Nivolumab or Ipilimumab Related Infusion Reactions

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

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

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

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

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

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

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

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

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

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

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

4.8 Destruction or Return of Investigational Product

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

If...	Then...
IP supplied by BMS (including its vendors)	Any unused IP supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless IP containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If IP will be returned, the return will be arranged by the responsible Study Monitor.
IP sourced by site, not supplied by BMS (or its vendors) (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

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

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

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

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

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

4.9 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline - All Subjects (CA209648)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	Contact IRT to obtain study subject number. Study allows for re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, if subject has not been randomized). If re-enrolled, the subject must be re-consented and assigned a new subject number from IRT.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed during screening and confirmed prior to randomization.
Disease Status		
Medical History	X	
Tumor Tissue Samples	X	Recent sample or archival. Sufficient tumor tissue (either a FFPE tissue block or minimum 15 slides*) must be available within 6 months prior to randomization and sent to a central laboratory for biomarker analysis. PD-L1 status must be assessed prior to randomization. Tissue must be a core needle biopsy, excisional or incisional biopsy. Fine needle biopsies are not considered adequate for biomarker review and randomization. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable. * If, despite best efforts, a minimum 15 slides are not obtainable, discuss with Sponsor.
Safety Assessments		
Physical Examination	X	Within 14 days prior to randomization. Including audiometric assessment if required as per local standards of care.
Physical Measurements	X	Include Height, Weight and BSA Within 14 days prior to randomization.

Table 5.1-1: Screening Procedural Outline - All Subjects (CA209648)		
Procedure	**Screening Visit**	**Notes**
Vital Signs	X	Including BP, HR and 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.
Assessment of Signs and Symptoms	X	Within 14 days prior to randomization.
Serious Adverse Event (SAE)	X	After informed consent is signed
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, albumin, Na, Ca, K, Cl, glucose and phosphate 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 (HBsAg, HCV antibody or HCV RNA), 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 prior to first dose of study therapy. For females under the age of 55 years a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL is required to confirm menopause.
Efficacy Assessment		
Baseline Tumor Imaging Assessment	X	CT Chest, CT/MRI scan of abdomen, pelvis, and any clinically indicated sites within 28 days prior to randomization. CT/MRI scan prior to ICF signature might be acceptable if performed within 28 days prior to randomization.
IRT		
IRT	X	IRT must be contacted for subject number assignment at the time informed consent is obtained.

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

Table 5.1-2: On-treatment Assessments - Subjects in Nivolumab 3 mg/kg and Ipilimumab 1 mg/kg - Arm A in CA209648

Procedure	Cycle 1 (2 Weeks Cycle) Day 1	Each Subsequent Cycle Day 1	Note A cycle refers to nivolumab every 2 weeks
Safety Assessments			
Physical Examination	X	X	To be performed within 72 hours of nivolumab dosing
Vital Signs	X	X	Obtain vital signs within 72 hours prior to nivolumab dose. Including BP, HR, and temperature.
Weight and ECOG Performance Status	X	X	Within 72 hours of dosing See protocol appendices for ECOG Performance Status scale
Adverse Events Assessment	Continuously		
Serious Adverse Event (SAE)	Continuously		
Review of concomitant medications	X	X	
Laboratory Tests	X	See Note	Within 72 hours prior to each nivolumab dose through Week 23 visit and every 2 cycles thereafter. Include CBC w/differential, ALT, AST, ALP, T-Bil, BUN or serum urea level, creatinine, Ca, Na, K, Cl, LDH, glucose and phosphate. TSH (with reflexive Free T4 and Free T3: Total T3/T4 are acceptable if Free T3/T4 are not available) every 6 weeks starting on first cycle. Note: Laboratory tests do not need to be repeated on C1D1 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 and then every 4 weeks (± 1 week) regardless of dose delays; if collected with a dosing visit, then obtain within 24 hrs prior to administration of study drug: urine or serum.
PK and Immunogenicity Sampling			
PK and immunogenicity blood samples	See Table 5.5-1 for details regarding specific sample timing		
Efficacy Assessments			

Table 5.1-2:	**On-treatment Assessments - Subjects in Nivolumab 3 mg/kg and Ipilimumab 1 mg/kg - Arm A in CA209648**		
Procedure	**Cycle 1 (2 Weeks Cycle) Day 1**	**Each Subsequent Cycle Day 1**	**Note** **A cycle refers to nivolumab every 2 weeks**
Tumor Imaging Assessment		See Note	CT Chest, CT/MRI scan of abdomen, pelvis and all clinical indicated sites. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks from the date of first dose, or sooner if clinically indicated. Every 6 weeks (± 7 days) from first dose up to and including Week 48, then every 12 weeks (± 7 days) regardless of treatment schedule until disease progression (unless treatment beyond progression is permitted, see Section 4.5.6). Use same imaging method as was used at screening/baseline
Collection of biomarker sampling	See Table 5.6-1 for Biomarker Sampling Schedule		
Outcomes Research Assessments			
FACT-E	X	See Note	Assessed on Cycle 1 Day 1 and then every 2 weeks, up to Week 7 and every 6 weeks (± 3 days) thereafter; regardless of treatment schedule; if administered on a dosing day, assessment should take place prior to any other study procedures. PRO administrations not coinciding with another study assessment visit can be done via a phone contact
EQ-5D	X	See Note	
Health Care Resource Utilization	X	X	Assessed and completed by the site at every dosing visit

Table 5.1-2:	**On-treatment Assessments - Subjects in Nivolumab 3 mg/kg and Ipilimumab 1 mg/kg - Arm A in CA209648**		
Procedure	**Cycle 1 (2 Weeks Cycle) Day 1**	**Each Subsequent Cycle Day 1**	**Note** **A cycle refers to nivolumab every 2 weeks**
Study Drug			
Dispense Study Treatment	X	X	First dose to be administered within 3 calendar days after randomization. Nivolumab 3 mg/kg and ipilimumab 1 mg/kg doses may be administered within 5 days before or after the scheduled date if necessary. Interval between ipilimumab doses should not be less than 37 days and 12 days in between nivolumab doses. Every 3 cycles, Ipilimumab 1 mg/kg is administered. Vials may be assigned up to 3 calendar days prior to every dose date.

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

Table 5.1-3:	**On-Treatment Assessments - Subjects in Nivolumab 240 mg Combined with Fluorouracil plus Cisplatin - Arm B in CA209648**				
Procedure	**Cycle 1 Day 1**	**Cycle 1 Day 15**	**Cycles 2 and beyond Day 1**	**Cycles2 and beyond Day 15**	**Note A cycle (4 weeks) refers to the nivolumab Q2W + FP Q4W**
Safety Assessments					
Physical Examination	X	X	X	X	To be performed within 72 hours of nivolumab dosing Including audiometric assessment if required as per local standards of care.
Vital Signs	X	X	X	X	Obtain vital signs within 72 hours prior to nivolumab dose. Including BP, HR, and temperature.
Weight, BSA and ECOG Performance Status	X	X	X	X	Within 72 hours prior to nivolumab dosing See protocol appendices for ECOG Performance Status scale
Adverse Events Assessment	Continuously				Assessed using NCI CTCAE v. 4
Serious Adverse Event (SAE)	Continuously				Assessed using NCI CTCAE v. 4
Review of concomitant medications	X	X	X	X	
Laboratory Tests	X	See Note			Within 72 hours prior to each nivolumab dose through Week 23 visit and every 2 nivolumab doses thereafter. Include CBC w/differential, ALT, AST, ALP, T-Bil, BUN or serum urea level, creatinine, Ca, Na, K, Cl, LDH, glucose and phosphate. TSH (with reflexive Free T4 and Free T3: Total T3/T4 are acceptable if Free T3/T4 are not available) every 6 weeks. Note: Laboratory tests do not need to be repeated on C1D1 if performed within 14 days prior to first dose.

Table 5.1-3:	**On-Treatment Assessments - Subjects in Nivolumab 240 mg Combined with Fluorouracil plus Cisplatin - Arm B in CA209648**				
Procedure	**Cycle 1 Day 1**	**Cycle 1 Day 15**	**Cycles 2 and beyond Day 1**	**Cycles2 and beyond Day 15**	**Note** **A cycle (4 weeks) refers to the nivolumab Q2W + FP Q4W**
Pregnancy Test (WOCBP only)	X		See Note		Serum or urine within 24 hours prior to the initial administration of study drug and then every 4 weeks (± 1 week) regardless of dose delays; if collected with a dosing visit, then obtain within 24 hrs prior to administration of study drug: urine or serum.
PK and Immunogenicity Sampling					
PK and immunogenicity blood samples	See Table 5.5-2 for details regarding specific sample timing				
Efficacy Assessments					
Tumor Imaging Assessment		See Note			CT Chest, CT/MRI scan of abdomen, pelvis and all clinical indicated sites. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks from the date of first dose, or sooner if clinically indicated. Every 6 weeks (± 7 days) from first dose up to and including Week 48, then every 12 weeks (± 7 days) regardless of treatment schedule until disease progression (unless treatment beyond progression is permitted, see Section 4.5.6). Use same imaging method as was used at screening/baseline
Collection of biomarker sampling	See Table 5.6-1 for Biomarker Sampling Schedule				

Table 5.1-3: On-Treatment Assessments - Subjects in Nivolumab 240 mg Combined with Fluorouracil plus Cisplatin - Arm B in CA209648

Procedure	Cycle 1 Day 1	Cycle 1 Day 15	Cycles 2 and beyond Day 1	Cycles2 and beyond Day 15	Note A cycle (4 weeks) refers to the nivolumab Q2W + FP Q4W
Outcomes Research Assessments					
FACT-E	X	See Note			Assessed on Cycle 1 Day 1 and then every 2 weeks, up to Week 7, and every 6 weeks (± 3 days) thereafter; regardless of treatment schedule; if administered on a dosing day, assessment should take place prior to any other study procedures.PRO administrations not coinciding with another study assessment visit can be done via a phone contact
EQ-5D	X	See Note			
Health Care Resource Utilization	X	X			Assessed and completed by the site at every dosing visit
Study Drug					
Dispense Study Treatment	X	X	X	X	First dose to be administered within 3 calendar days after randomization. Subsequent nivolumab 240 mg + FP doses may be administered within 3 days before or after the scheduled date if necessary. Subjects may be dosed no less than 12 days between nivolumab doses. Vials may be assigned up to 3 calendar days prior to every dose date.

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

Table 5.1-4: On-Treatment Assessments - Subjects in Fluorouracil and Cisplatin (FP) - Arm C in CA209648			
Procedure	**Cycle 1 Day 1**	**Cycles 2 and beyond Day 1**	**Note A cycle (4 weeks) refers to the FP Q4W**
Safety Assessments			
Physical Examination	X	X	To be performed within 72 hours of cisplatin dosing Including audiometric assessment if required as per local standards of care.
Vital Signs	X	X	Obtain vital signs within 72 hours prior to fluorouracil dose. Including BP, HR, and temperature.
Weight, BSA and ECOG Performance Status	X	X	Within 72 hours prior to dosing See protocol appendices for ECOG Performance Status scale
Adverse Events Assessment	Continuously		Assessed using NCI CTCAE v. 4
Serious Adverse Event (SAE)	Continuously		Assessed using NCI CTCAE v. 4
Review of concomitant medications	X	X	
Laboratory Tests	X	See Note	Within 72 hours prior to each fluorouracil dose. Include CBC w/differential, ALT, AST, ALP, T-Bil, BUN or serum urea level, creatinine, Ca, Na, K, Cl, LDH, glucose\ and phosphate. Note: Laboratory tests do not need to be repeated on C1D1 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 and then every 4 weeks (± 1 week) regardless of dose delays; if collected with a dosing visit, then obtain within 24 hrs prior to administration of study drug: urine or serum.
Efficacy Assessments			
Tumor Imaging Assessment		See Note	CT Chest, CT/MRI scan of abdomen, pelvis and all clinical indicated sites. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks from the date of first dose, or sooner if clinically indicated.

Table 5.1-4: On-Treatment Assessments - Subjects in Fluorouracil and Cisplatin (FP) - Arm C in CA209648			
Procedure	**Cycle 1 Day 1**	**Cycles 2 and beyond Day 1**	**Note A cycle (4 weeks) refers to the FP Q4W**
			Every 6 weeks (± 7 days) from first dose up to and including Week 48, then every 12 weeks (± 7 days) regardless of treatment schedule until disease progression, unless treatment beyond progression is permitted. Use same imaging method as was used at screening/baseline
Collection of biomarker sampling	See Table 5.6-1 for Biomarker Sampling Schedule		
Outcomes Research Assessments			
FACT-E	X	See Note	Assessed on Cycle 1 Day 1 and then every 2 weeks, up to week 7, and every 6 weeks (± 3 days) thereafter; regardless of treatment schedule: if administered on a dosing day, assessment should take place prior to any other study procedures.. PRO administrations not coinciding with another study assessment visit can be done via a phone contact
EQ-5D	X	See Note	
Health Care Resource Utilization	X	X	Assessed and completed by the site at every dosing visit
Study Drug			
Dispense Study Treatment	X	X	First dose to be administered within 3 calendar days after randomization. Subsequent FP doses may be administered within 3 days before or after the scheduled date (Day 1) if necessary. Subjects may be dosed no less than 26 days between cisplatin doses. Vials may be assigned up to 3 calendar days prior to every dose date.

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

Table 5.1-5: Follow-Up Procedural Outline - All subjects (CA209648)			
Procedure	**Follow-up Phase Visits** **FU1[a] - 30 Days (± 7 Days) after Last Dose** **FU2 - 84 Days (± 7 Days) after FU1**	**Survival Phase Visits** **Every 3 Months (± 14 days) from FU2**	**Notes**
Safety Assessments			
Targeted Physical Examination	X		
Adverse Events Assessment	X		Assessed using NCI CTCAE v. 4
Review of Subsequent Cancer Therapy	X	X	
Laboratory Tests	X		Include CBC w/differential, ALT, AST, ALP, T-Bil, BUN or serum urea level, creatinine, albumin, Na, Ca, K, Cl, LDH, glucose. If there are ongoing AE, monthly lab tests will be conducted till FU2.
Pregnancy Test (WOCBP only)	X	See Note	Serum or urine Only for FU1, unless testing is required for a longer period per local regulations
Efficacy Assessments			
Tumor Imaging Assessment	See Note	See Note	For subjects who discontinue study treatment for reasons other than radiographic PD, follow-up scans should be performed every 6 weeks (± 7 days) up to and including Week 48, then every 12 weeks until PD, lost to follow-up, or withdrawal of consent. CT Chest, CT/MRI scan of abdomen, pelvis and any clinical indicated sites. Use same imaging method as was used at screening/baseline.

Table 5.1-5: Follow-Up Procedural Outline - All subjects (CA209648)			
Procedure	**Follow-up Phase Visits** **FU1[a] - 30 Days (± 7 Days) after Last Dose** **FU2 - 84 Days (± 7 Days) after FU1**	**Survival Phase Visits** **Every 3 Months (± 14 days) from FU2**	**Notes**
Outcomes Research Assessments			
FACT-E	X		After FU1 and FU2, every 3 months (± 14 days), during a clinic visit or via a phone contact.
ECS		X	
FACT-G7		X	
EQ-5D	X		
Health Care Resource Utilization	X		
Collection of biomarker sampling	See Table 5.6-1 for Biomarker Sampling Schedule		
Subject Status			
Collection of Survival Status and Subsequent Therapy Information	X	X	Every 3 months (± 14 days) or more frequently as needed after FU2, may be performed by phone contact or office visit, to include subsequent anticancer therapy. Additional subsequent cancer therapy details such as regimen, setting of the regimen, line of therapy, start date and end date of each regimen, best response to the regimen and date of progression after second line therapy will be collected.

[a] Or coinciding with the date of discontinuation (± 7 days) if date of discontinuation is greater than 35 days after last dose.
Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

5.1.1 Retesting During Screening

Retesting of laboratory parameters and/or other assessments within any single Screening 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 treatment assignment) 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
- Nivolumab Investigator Brochure
- Ipilimumab Investigator Brochure
- Pharmacy Binder
- Imaging Manual
- Laboratory Manuals for collection and handling of blood samples (including biomarker and immunogenicity samples) and tissue specimens.
- Site manual for operation of IRT system, including enrollment/randomization worksheets
- Manual for entry of local laboratory data
- Pregnancy Surveillance Forms
- Subject Questionnaires: FACT-E, EQ-5D, FACT-G7, and ECS
- AJCC Cancer Staging Manual for Esophageal Cancers, See Appendix 4
- NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers
- ESMO Clinical Practice Guidelines for Oesophageal Cancer.

5.3 Safety Assessments

5.3.1 Screening Safety Assessments

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

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

Screening pregnancy tests for WOCBP must be performed within 24 hours prior to the initial administration of study drug. For females under the age of 55 years a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL is required to confirm menopause.

The following screening local laboratory assessments should be done within 28 days prior to treatment assignment: Thyroid panel including TSH, free T3, and free T4, Hepatitis B and C testing (HBsAg and HCV Ab or HCV RNA).

5.3.2 On-Treatment Safety Assessments

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

Thyroid function testing (TSH with reflexive fT3 and fT4) is to be done every 6 weeks (every 3 cycles) for subjects receiving nivolumab at 3mg/kg q2w (i.e. Arm A), and every 6 weeks for subjects receiving nivolumab at 240 mg q2w (Arm B). Total T3/T4 are acceptable if free T3/T4 are not available.

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

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

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

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

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

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

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

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

Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or

assessments may be performed as clinically necessary or where required by institutional or local regulations.

5.3.3 Follow-up Safety Assessments

Adverse events will be assessed and subsequent cancer therapy will be reviewed as indicated in Table 5.1-5. A physical examination will be performed at FU1 and FU2 visit. Laboratory and pregnancy tests will be performed as described in Table 5.1-5.

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. At the sponsor's discretion, scans may be collected for review. Any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled timepoints and/or at an outside institution) should be collected for tumor assessment and submitted to the BICR.

5.4 Efficacy Assessments

Study evaluations will take place in accordance with the flow charts in Section 5.1. Baseline tumor assessments should be performed within 28 days prior to randomization. In addition to chest, abdomen, pelvis, clinically indicated sites as determined by the treating investigator should be assessed at baseline. Subjects with brain metastasis adequately treated at least 2 weeks prior to treatment assignment must be reassessed by brain Magnetic resonance imaging (MRI) at baseline. Subsequent assessments should include all sites that were assessed at baseline and should use the same imaging method as was used at baseline.

Subjects will be evaluated for disease progression every 6 weeks from the date of first dose (± 7 days) up to and including Week 48, and then every 12 weeks (± 7 days) thereafter, regardless of treatment schedule, until disease progression or the subject discontinues the study, whichever comes first. Subjects with a history of brain metastasis (eg, a CR case treated prior to treatment assignment) should have surveillance MRI approximately every 12 weeks from the date of first dose, or sooner if clinically indicated.

Contrast-enhanced CT with PO/IV contrast or contrast-enhanced MRI are the preferred imaging modalities for assessing radiographic tumor response. If a subject has a known allergy to contrast material, local prophylaxis standards may be used to obtain the assessment with contrast if at all possible, or use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice. Should a subject have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast enhanced MRI of the abdomen, pelvis, clinically indicated sites may be obtained. Every attempt should be made to image each subject using an identical acquisition protocol and the same method for all imaging time points.

Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Change in tumor measurements and tumor response will be assessed by the Investigator using the RECIST 1.1 criteria. See Appendix 5.

All radiologic images from the study will be submitted to a central imaging core lab for analysis by a BICR. The BICR will review tumor images in all randomized subjects to determine RECIST 1.1 response for the analyses of PFS and ORR.

Details of the BICR responsibilities and procedures will be specified in the BICR charter.

5.5 Pharmacokinetic Assessments

Pharmacokinetic (PK) and immunogenicity (IMG) assessment data will be collected from study subjects assigned to the nivolumab-plus-ipilimumab (Arm A) and nivolumab-plus-chemotherapy arm (Arm B) at the time points indicated in Table 5.5-1, and Table 5.5-2. All time points are relative to the start of study drug administration. All on-treatment time points are intended to align with days on which study drug is administered; if dosing occurs on a different day, the PK and IMG sampling should be adjusted accordingly. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual. PK samples will be analyzed for nivolumab/ipilimumab by a validated ligand binding assay. Immunogenicity samples will be analyzed for anti-nivolumab/anti-ipilimumab antibodies by a validated immunogenicity assay; samples may also be analyzed for neutralizing antibodies by a validated method. Serum samples may be analyzed by an exploratory method that measures anti-drug antibodies for technology exploration purposes; exploratory results will not be reported. Serum samples designated for PK or biomarker assessments may also be used for immunogenicity analysis if required (eg, insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity related AE).

PK and immunogenicity assessments will be collected from study subjects assigned to the **nivolumab 3 mg/kg and ipilimumab 1 mg/kg arm (Arm A)** at the time points indicated in Table 5.5-1.

Table 5.5-1: Pharmacokinetic and Immunogenicity Sampling Schedule for Nivolumab and Ipilimumab in Arm A						
Study Cycle/Day One Cycle = Every 2 weeks (Nivo administered every 2 weeks, Ipi every 6 weeks)	**Event (Relative to Start of Infusion)**	**Time (Relative to Start of Nivolumab Infusion) Hour:Min**	**Nivolumab PK Blood Samples**	**Nivolumab Immunogenicity Blood Samples**	**Ipilimumab PK Blood Samples**	**Ipilimumab Immunogenicity Blood Sample**
Cycle 1 Day 1	Predose[a,b]	00:00	X	X	X	X
Cycle 2 Day 1	Predose[a,b]	00:00	X	X	X	X
Cycle 4 Day 1	Predose[a,b]	00:00	X	X	X	X
Cycle 5 Day 1	Predose[a,b]	00:00	X	X	X	X
Cycle 7 Day 1	Predose[a,b]	00:00	X	X	X	X
Cycle 15 Day 1	Predose[a,b]	00:00	X	X	X	X
Cycle 23 Day 1	Predose[a,b]	00:00	X	X	X	X
Cycle 35 Day 1	Predose[a,b]	00:00	X	X	X	X
Cycle 47 Day 1	Predose[a,b]	00:00	X	X	X	X

[a] If ipilimumab is discontinued and nivolumab continues, ipilimumab PK and ADA should be collected only for the next 2 time points (corresponding to nivolumab sample collection) according to the PK table

[b] Predose samples should be collected just before the administration of the first drug (preferably within 30 minutes). If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

PK and immunogenicity assessments will be collected from study subjects assigned to **nivolumab 240 mg combined with fluorouracil and cisplatin, Arm B** at the time points indicated in Table 5.5-2.

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

Table 5.5-2: Pharmacokinetic and Immunogenicity Sampling Schedule for the Nivolumab + Chemotherapy Arm B

Study Cycle/Day One Cycle = Every 4 weeks Nivolumab= every 2 weeks	Event (Relative to Start of Nivolumab Infusion)	Time (Relative to Start of Nivolumab Infusion) Hour:Min	Nivolumab PK Blood Sample	Nivolumab IMG Blood Sample
Cycle 1 Day 1	Predose[a,b]	00:00	X	X
Cycle 2 Day 1	Predose[a,b]	00:00	X	X
Cycle 3 Day 1	Predose[a,b]	00:00	X	X
Cycle 7 Day 1	Predose[a,b]	00:00	X	X
Cycle 9 Day 1	Predose[a,b]	00:00	X	X
Cycle 17 Day 1	Predose[a,b]	00:00	X	X
Cycle 25 Day 1	Predose[a,b]	00:00	X	X

[a] If nivolumab is discontinued and chemotherapy continues, nivolumab PK and ADA should be collected only for the next 2 time points according to the PK table

[b] Predose samples should be collected just before the administration of the first drug (preferably within 30 minutes). If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

5.6 Biomarker Assessments

Tumor tissue, blood, and stool samples will be collected prior to treatment. Peripheral blood samples will also be collected at selected timepoints on treatment. If a biopsy or surgical resection is performed at the time of progression or suspected progression, tumor samples (block or slides) should be submitted for analysis. If biomarker samples are drawn but study drug(s) is not administered, samples will be retained. A detailed description of each assay system is described below and a schedule of pharmacodynamic evaluations is provided in Table 5.6-1.

Table 5.6-1: Biomarker Sampling Schedule						
Collection Timing[a]	**Tumor**	**Whole Blood DNA**	**Plasma**	**Serum**	**PBMC**	**Stool**
Screening	X[b]					
Day 1 (D1Wk1)		X	X	X	X[c]	X
Day 15 (D1Wk3)		X	X	X		
Day 43 (D1Wk7)		X	X	X		
Day 85 (D1Wk13)		X	X	X		
Upon Progression	X[b]	X	X	X		

[a] Biomarker sampling occurs prior to dosing of study drug and can occur ±7 days from the scheduled time but must be prior dosing.

[b] Tumor tissue prior to therapy is mandatory. If a recent as defined by protocol archived biopsy is not available at screening, a tumor tissue will be taken at any point prior to treatment and will be formalin fixed and paraffin embedded. Tumor tissue during study therapy (eg, at suspected tumor progression) is optional.

[c] Peripheral blood samples will be taken at designated time points for PBMC preparation, except at sites where the stability of the samples after shipment to the central laboratory cannot be guaranteed. Samples must be shipped within 48 hours to a BMS-designated central laboratory for processing.

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 to the central lab prior to treatment assignment. In situations where on-treatment biopsies or surgeries are performed, tumor samples should be sent for central pathology reading. The tissue submitted will be assessed for quality with an H&E stain and only those participants who have met tissue quality thresholds can be assigned study drug.

A tumor tissue obtained within 6 months prior to randomization with no prior systemic therapy administered in the interval time between sample collection and randomization is required to ensure that biomarker analysis of the tumor sample is not impacted by effects of prior therapy, age of specimen or insufficiency of tissue.

5.6.1.1 Tumor Sample Collection Details

Collection of tumor tissue at diagnostic surgery is required for study eligibility. If clinically appropriate, additional biopsies obtained at any time, eg, if progression is suspected, may also be collected.

An assessment of tissue quality by a local pathologist is strongly encouraged at the time of the procedure. The tumor tissue that is obtained will be formalin fixed and paraffin-embedded.

Detailed instructions of the obtaining, processing, labeling, handling, storage and shipment of specimens will be provided in a separate Procedure Manual at the time of study initiation.

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

IHC or equivalent methods will be used to assess the number and composition of immune infiltrates in order to define the immune cell subsets present within FFPE tumor tissue before and after exposure to therapy. These IHC analyses may include, but not necessarily be limited to, the following markers: CD4, CD8, FOXp3, PD-1, PD-L1, and PD-L2.

5.6.1.3 Characterization of T cell Repertoire

As described above, DNA sequencing may be performed on pre-and post-treatment tumor tissue to assess the composition of the T cell repertoire.

5.6.1.4 Gene Expression Profiling

Tumor tissue will be examined for mRNA gene expression to detect expression of selected cancer and immune related genes.

5.6.1.5 Tumor Genotyping, Mutational Analysis, and Tumor Antigen Profiling

RNA and DNA from tumor samples will be analyzed using whole-exome and transcriptome sequencing to determine the number of mutations found within a given sample relative to a normal host tissue, such as adjacent non-transformed cells or PBMC. In addition to tumor mutational burden (TMB), mutational analyses of cancer related genes and genes relevant for immunotherapy may be performed. Mutations that are detected may be analyzed for their ability to bind the major histocompatibility complex (MHC) I and MHC II proteins using prediction algorithms, such as NetMHC. Evaluating the ability of tumor mutations to bind MHC molecules will provide evidence that these mutations are serving as antigens that are recognized the immune system and are potential rejection antigens.

5.6.1.6 Microsatellite instability status

Microsatellite instability (MSI) is emerging as a predictive biomarker for checkpoint blockade therapy. Different from gastric cancer, esophageal cancer, especially ESCC, has much lower MSI prevalence. MSI status may be determined where possible.

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 taken from all subjects prior to or during treatment. Data from these investigations will be evaluated for associations with response, survival, and/or safety (adverse event) data. Several analyses will be completed and are described briefly below.

5.6.2.1 Soluble Biomarkers

Soluble factors, such as cytokines, chemokines, soluble receptors, and antibodies to tumor antigens will be characterized and quantified by immunoassays in serum. Analyses may include, but not necessarily be limited to, soluble CD25, soluble PD-1, soluble LAG-3, and CXCL-9.

Collected serum samples may also be used for the assessment of tumor antigen-specific responses elicited following treatment with monotherapy and combination therapy to explore which antitumor antibodies are most associated with clinical response. Antibody levels to cancer test antigens may be assessed.

5.6.2.2 Immunophenotyping

The proportion of specific lymphocyte subsets and expression levels of T-cell co-stimulatory markers in PBMC preparations will be quantified. Analyses may include, but not necessarily be limited to, the proportion of T, B, and NK cells, granulocytes, the proportion of memory and effector T-cell subsets, and expression levels of PD-1, PD-L1, other B7 family members, ICOS, and Ki67.

5.6.2.3 T cell Repertoire Analysis

Low diversity of the peripheral T cell compartment has been shown to correlate with poor overall survival in metastatic breast cancer. A standing theory in immuno-oncology suggests a diverse and activated immune environment is better adept at eradicating tumor compared to a skewed repertoire of naïve and tolerized T cells. In order to explore whether a diverse T cell repertoire is predictive of response to therapy, the composition of the T cell repertoire prior to and during therapy may be assessed.

5.6.2.4 Whole Blood for Germline DNA

Whole blood will be collected from all subjects prior to treatment to generate genomic DNA for genetic variant analyses and to serve as a reference for tumor genomic testing. These analyses will focus on genetic variant within genes associated with PD1 and other immunoregulatory signaling pathways to determine if natural variation within those genes is associated with response to nivolumab and/or with adverse events during treatment.

5.6.2.5 Plasma for circulating tumor DNA

The presence of cell-free DNA in circulating blood is a well-documented phenomenon. Fragments of DNA are shed into the blood stream from dividing cells during cell proliferation or cell death. In participants with cancer, a fraction of this DNA is tumor-derived and is termed circulating tumor DNA (ctDNA). Several studies have detected mutations in ctDNA that exactly correspond to mutations from the parent tumor. Early decrease in ctDNA following treatment with immunotherapy was associated with improved outcomes[57]. Plasma samples will be analyzed to determine the presence and frequency of ctDNA.

5.6.2.6 Stool for microbiome

The gut microbiome influences cancer development and response to therapy. The efficacy of cancer immunotherapy with checkpoint blockade could be diminished with the administration of antibiotics. Clinical efficacy has been associated with microbiome composition and the presence of specific microbe species.[58, 59, 60] The association of microbiome with efficacy and safety will be evaluated using stool samples collected before treatment.

5.7 Outcomes Research Assessments

Subjects will be asked to complete the EQ-5D-3L and FACT-E on each Cycle 1 Day 1 every 2 weeks until Week 7 and every 6 weeks thereafter, 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, FACT-E, and the FACT-G7. The questionnaires will be provided in the subject's preferred language, if 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, and FACT-G7, though subjects will be provided with hard copies of these questionnaires to take home and use as visual aids during telephone interviews. Section 5.1 provides information regarding the timing of patient-reported outcomes assessments.

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) for patients.

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 to the FACT-G, 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 for each Cohort, which provides an overall indicant of generic HRQL. The FACT-G

and ECS scores can be combined to produce a total score for the FACT-E, which provide 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. However, to minimize subject response and administrative burden, only the FACT-G7 and ECS will be administered during the survival follow-up phase.

In addition to the aforementioned patient-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 Additional research collection

This protocol will include residual sample storage for additional research (AR).

For All US sites:

Additional research participation is required for all investigational sites in the US.

For non-US Sites:

Additional research is optional for all study participants, except where retention and/or collection is prohibited by local laws or regulations, ethics committees, or institutional requirements.

This collection for additional research is intended to expand the translational R&D capability at Bristol-Myers Squibb, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc.

All requests for access to samples or data for additional research will be vetted through a diverse committee of the study sponsor's senior leaders in Research and Development (or designee) to ensure the research supports appropriate and well-defined scientific research activities.

Residual blood, serum and tumor tissue will also be retained for additional research purposes

Samples kept for future research will be stored at the BMS Biorepository in Hopewell, NJ, USA or an independent, BMS-approved storage vendor.

- The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than 15 years after the end of the study or the maximum allowed by applicable law.
- Transfers of samples by research sponsor to third parties will be subject to the recipient's agreement to establish similar storage procedures.

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key is securely held by the Investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

Further details of sample collection and processing will be provided to the site in the procedure 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.)

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

6.1 Serious Adverse Events

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

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical,

surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

-

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

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

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

NOTE:

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

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

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing. For subjects randomized/assigned to treatment and never treated with study drug, SAE information should be collected for 30 days from the date of randomization.

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

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

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

SAEs, whether related or not related to study drug, and pregnancies must be reported to Sponsor or designee within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

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

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

All SAEs must be followed to resolution or stabilization.

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

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

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

Every adverse event must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the 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 electronic) as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

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

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

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the Sponsor or designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please call the Sponsor or designee within 24 hours of awareness of the pregnancy.

The investigator must immediately notify the Sponsor or designee of this event and complete and forward a Pregnancy Surveillance Form to Sponsor or designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to Sponsor or designee. In order for BMS to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

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:

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

7) AND

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

8) AND

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

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

6.7.1 Adverse Events of Interest

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

which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the subject's case report form.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

7.1 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be utilized. A DMC will be established to provide oversight of safety and efficacy considerations in CA209648. 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 plus ipilimumab and nivolumab plus fluorouracil and cisplatin. 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.

DMC will review the safety data from the study when approximately (dependent on the accrual speed) 45 subjects (about 5% of subjects) have been treated and followed for at least 4 weeks.

Details of the DMC responsibilities and procedures will be specified in the DMC charter.

7.2 Independent Review of Progression at the Time of Investigator-Assessed Progression

At the time of investigator-assessed initial radiographic progression per RECIST 1.1 in any given subject, the site must request the blinded independent review of progression from the third party radiology vendor.

Tumor assessments for each subject should be submitted to the radiology vendor as they are performed on an ongoing basis. The blinded, independent radiologists will review all available tumor assessments for that given subject and determine if RECIST 1.1 criteria for progression have been met. The independent assessment of whether or not the given subject met RECIST 1.1 criteria for progression will be provided to the site. Subjects whose disease progression is not confirmed centrally will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule. Subsequent tumor assessments must be submitted to the third party radiology vendor for subsequent review and may be discontinued when the investigator and independent radiologists both assess the subject to have met RECIST 1.1 criteria for progression.

In addition, subjects receiving treatment beyond progression must continue tumor assessments until such treatment has been discontinued.

If clinically acceptable, subsequent therapy should begin only after RECIST 1.1 progression has been assessed by Blinded Independent Central Review. For subjects who start palliative local therapy or subsequent therapy without prior assessment of RECIST 1.1 progression by central review, the Investigator must continue tumor assessments (if clinically feasible) according to the protocol-specified schedule and submit them to the third-party radiology vendor. When RECIST 1.1 progression is assessed by the investigator (whether assessed before or after the start of palliative local therapy or subsequent therapy), the Blinded Independent Central Review must be

requested. Tumor assessments may be discontinued when the independent radiologist assesses the subject to have met RECIST 1.1 criteria for progression.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

It is now established that time-to-events endpoints in I-O clinical trials tend to display specific characteristics. First, there may be long-term survival benefits in patients treated with immunotherapy - observed as a long lasting plateau towards the tail of the survival curve ("cure"). Second, some results also suggested a delayed effect - observed as late separation of survival curves between experimental and control arms. Both long-term survival and delayed onset of benefit may be linked to the mechanisms of action of I-O drugs. As these phenomena are expected to be observed in the current disease setting as well, a piecewise mixture cure rate model was used for the design setup.

Sample size calculations assume that the prevalence of subjects with PD-L1 tumor expression level ≥ 1% is approximately 50%. (During enrollment, the proportion of subjects with or without PD-L1 tumor expression will be monitored, and may be re-assessed in case it does not reflect study assumptions.)

In addition, proportion of patients in the chemotherapy arm who receive I-O as subsequent therapy will be monitored; protocol may be amended accordingly.

The sample size is based on the primary objectives, ie, on the comparisons of the PFS/OS distributions of subjects with PD-L1 expressing tumors between those who were randomized to receive nivolumab plus ipilimumab vs those randomized to receive chemotherapy, and between those who were randomized to receive nivolumab plus chemotherapy vs those randomized to receive chemotherapy.

For both experimental arms, the same OS distributions and the same PFS distributions are assumed (see Table 8.1-1). As a result, for each of the nivolumab plus ipilimumab vs chemotherapy and nivolumab plus chemotherapy vs chemotherapy comparisons:

- 250 PFS events in approximately 313 subjects with PD-L1 expressing tumors will provide approximately 90% power to detect an average HR of 0.62 with a Type I error of 1.5% (two-sided);
- 250 OS events in approximately 313 subjects with PD-L1 expressing tumors will provide approximately 90% power to detect an average HR of 0.6 with a Type I error of 1% (two-sided).

To have approximately 313 randomized subjects with PD-L1 expressing tumors for each comparison, approximately 470 subjects with PD-L1 expressing tumors need to be randomized in in a 1:1:1 ratio in the 3 arms. Which therefore translates to a total of approximately 939 subjects (with any PD-L1 result) to be randomized in a 1:1:1 ratio to the nivolumab plus ipilimumab or nivolumab plus chemotherapy or chemotherapy arms. Assuming a piecewise constant accrual rate, it is estimated that these 939 subjects will be accrued within 29 months.

Although for the comparison of both experimental arms with the control arm, the same treatment effect is assumed, observed treatment effects may vary. Therefore, the events of interest (OS, PFS) observed in the chemotherapy arm *only* will be used for determining the timing of the interim and final efficacy analyses. Final PFS analysis is planned when 136 PFS events per BICR are observed among the PD-L1 expressing subjects in the chemotherapy arm. This is expected to be reached after approximately 33 months. If the planned number of PFS events is unlikely to be reached for any unforeseen reasons, the final PFS analysis may occur when at least 12 months minimum follow-up (defined as the time from the date when the last patient was randomized to the clinical cutoff date) is reached. Should this scenario occur, corresponding to PFS events of 110 and 121, the power would be 80% and 85%, respectively (details of this scenario are discussed in Appendix 7 of the SAP). Final OS analysis is planned when 140 events are observed among the PD-L1 expressing subjects in the chemotherapy arm. This is expected to be reached after approximately 49 months. (At the time of the final PFS analysis, a formal interim analysis for OS will be conducted, see Section 8.5.)

Details of the sample size calculations for the subjects whose tumors express PD-L1 are provided in Table 8.1-1.

Table 8.1-1: Subjects whose Tumors Express PD-L1 - Summary of Sample Size Parameters and Schedule of Analyses (Nivolumab plus Ipilimumab vs Chemotherapy and Nivolumab plus Chemotherapy vs Chemotherapy)

	OS	PFS
# of randomized subjects	≈313 (total in the 3 arms: ≈470)	
Hypothesized delayed effect	3 months	1 month
Hypothesized cure rate in experimental arms	15%	0
Hypothesized HR after delayed effect, in non-cure subjects	0.65	0.55
Hypothesized median: control vs experimental	9 months* vs 14.4 months	4 months vs 6.4 months
Significance level	0.01	0.015
FINAL ANALYSIS		
Criteria for time of LPLV	140 events are observed among the PD-L1 expressing subjects in the chemotherapy arm	136 events are observed among the PD-L1 expressing subjects in the chemotherapy arm
Projected time of LPLV (from randomization)	49 months	33 months
Projected # of events	250	250
Significance level	[0.009][a]	0.015
Power	90%	90%

Table 8.1-1:	**Subjects whose Tumors Express PD-L1 - Summary of Sample Size Parameters and Schedule of Analyses (Nivolumab plus Ipilimumab vs Chemotherapy and Nivolumab plus Chemotherapy vs Chemotherapy)**	
	OS	**PFS**
Hypothesized overall HR	0.6	0.62
Critical HR (b) / Minimal difference in median (c)	0.72 / 3.5 months	0.73 / 1.4 months
INTERIM ANALYSIS for OS		
Criteria for time of LPLV	At the time of PFS final analysis	N/A
Projected # of events	≈175 (70% of all events)	N/A
Significance level	[0.002] (a)	N/A
Probability of crossing boundary	29%	N/A
Hypothesized overall HR	0.67	N/A
Critical HR[b] / Minimal difference in median[c]	0.62 / 5.6 months	N/A

[a] For OS, significance levels will be recalculated based on the actual number of deaths at interim analysis

[b] Largest observed HR at which a statistically significant difference would be observed

[c] Difference in median, corresponding to a minimal clinically significant effect size

* Asia: 10 months, RoW: 6 months

Analyses on OS and PFS in all randomized subjects will be carried out at the time of the primary analysis (in subjects whose tumors express PD-L1); OS and PFS in all randomized subjects are expected to be mature by that time. They will be tested only if significance level is passed on them. Details of the related power calculations are provided in Table 8.1-2.

Table 8.1-2:	**All Randomized Subjects - Summary of Power Calculation Parameters and Schedule of Analyses (Nivolumab plus Ipilimumab vs Chemotherapy and Nivolumab plus Chemotherapy vs Chemotherapy)**	
	OS	**PFS**
# of randomized subjects	626 (total in the 3 arms: 939)	
Hypothesized delayed effect	3 months in PD-L1+, 4 months in PD-L1-	1 month in PD-L1+, 2 months in PD-L1-
Hypothesized cure rate in experimental arms	15% in PD-L1+, 10% in PD-L1-	0

Table 8.1-2: All Randomized Subjects - Summary of Power Calculation Parameters and Schedule of Analyses (Nivolumab plus Ipilimumab vs Chemotherapy and Nivolumab plus Chemotherapy vs Chemotherapy)

	OS	PFS
Hypothesized HR after delayed effect, in non-cure subjects	0.65 in PD-L1+, 0.85 in PD-L1-	0.55 in PD-L1+, 0.75 in PD-L1-
Hypothesized median: control vs experimental	9 months* vs 12.3 months	4 months vs 5.5 months
Significance level[a]	0.01	0.015
FINAL ANALYSIS		
Criteria for time of LPLV	At the time of the PD-L1+ LPLV	At the time of the PD-L1+ LPLV
Projected # of events	≈514	≈512
Significance level[a]	[0.009][b]	0.015
Power[c]	94%	90%
Hypothesized overall HR	0.68	0.72
Critical HR[d] / Minimal difference in median[e]	0.80 / 2.3 months	0.81 / 0.9 months
INTERIM ANALYSIS for OS		
Criteria for time of LPLV	At the time of PFS final analysis	N/A
Projected # of events	≈362 (70.4% of all events)	N/A
Significance level[a]	[0.002] (a)	N/A
Probability of crossing boundary[c]	33%	N/A
Hypothesized overall HR	0.75	N/A
Critical HR[b] / Minimal difference in median[e]	0.74 / 3.1 months	N/A
Accrual rate per month	Gradually increasing accrual rates (max = 45 subjects per months)	
Accrual Duration	29 months	

[a] In case the significance level from the corresponding primary endpoint is passed. (Note that endpoint-specific [i.e. initially allocated] significance level is 0.)

[b] For OS, significance levels will be recalculated based on the actual number of deaths at interim analysis

[c] Not accounting for hierarchy

[d] Largest observed HR at which a statistically significant difference would be observed

[e] Difference in median, corresponding to a minimal clinically significant effect size

* Asia: 10 months, RoW: 6 months

Simulations were conducted in R-v3.1.3.

8.2 Populations for Analyses

- The following definitions of populations will be applicable for subjects whose tumors express PD-L1 and also for subjects regardless of PD-L1 expression.
- All Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IRT
- All Randomized Subjects: All enrolled subjects who were randomized to any treatment arm in the study
- All Treated Subjects: All randomized subjects who received at least one dose of study drug during the study
- PK Subjects: All randomized subjects with available serum time-concentration data.
- Outcome Research subjects: All randomized subjects who have an assessment at screening/baseline and at least 1 follow-up assessment
- Immunogenicity subjects: All randomized subjects who have an assessment at screening/baseline and at least 1 follow-up assessment
- Biomarker subjects: All randomized subjects with available biomarker data.

8.3 Endpoints

8.3.1 Primary Endpoint

- Overall survival (OS) in subjects with PD-L1 expressing tumors. OS is defined as the 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.

- Progression-free Survival (PFS) (as assessed by BICR) in subjects with PD-L1 expressing tumors. PFS is defined as the time from randomization to the date of the first documented PD per BICR or death due to any cause. Subjects who die without a reported prior PD per BICR (and die without start of subsequent therapy) will be considered to have progressed on the date of death. Subjects who did not have documented PD per BICR per RECIST1.1 criteria and who did not die, will be censored at the date of the last evaluable tumor assessment on or prior to initiation of the subsequent anti-cancer therapy. Subjects who did not have any on-study tumor assessments and did not die (or died after initiation of the subsequent anti-cancer therapy) will be censored at the randomization date. Subjects who started any subsequent anti-cancer therapy without a prior reported PD per BICR will be censored at the last tumor assessment on or prior to initiation of the subsequent anti-cancer therapy.

8.3.2 Secondary Endpoint(s)

- Overall survival (OS) in All Randomized subjects. OS is defined the same way as for the primary endpoint (for subjects with PD-L1 expressing tumors).
- Progression-free Survival (PFS) (as assessed by BICR) in All Randomized subjects. PFS is defined the same way as for the primary endpoint (for subjects with PD-L1 expressing tumors).
- Objective Response Rate (ORR) (as assessed by BICR) in subjects with PD-L1 expressing tumors and All Randomized subjects. It is defined as the number of subjects with a best overall response (BOR) of CR or PR divided by the number of randomized subjects in the population

for each treatment group. BOR is defined as the best response designation as determined by BICR, recorded between the date of randomization and the date of objectively documented progression (per RECIST 1.1 as determined by BICR) or the date of subsequent anti-cancer therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first. For subjects without documented progression or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination.

8.3.3 Exploratory Endpoint(s)

- Progression-free Survival (PFS) (as assessed by investigator) in subjects with PD-L1 expressing tumors and All Randomized subjects. PFS is defined the same way as for the primary and secondary endpoints (as assessed by BICR) - except that only PD assessments by investigator will be taken into account.
- Objective Response Rate (ORR) (as assessed by investigator) in subjects with PD-L1 expressing tumors and All Randomized subjects. ORR is defined the same way as for the primary and secondary endpoints (as assessed by BICR) - except that only tumor assessments by investigator will be taken into account.
- Duration of Response (DOR) (as assessed by BICR and as assessed by investigator) is defined as the time between the date of first documented response (CR or PR) to the date of the first disease progression, per RECIST 1.1 or death due to any cause, whichever occurs first. For subjects who neither progress nor die, the duration of objective response will be censored at the same time they were censored for the primary definition of PFS.
- PFS2/TSST in subjects with PD-L1 expressing tumors and all randomized subjects. PFS2/TSST is defined as the time from randomization to the date of investigator-defined documented second objective disease progression or start of second subsequent therapy or death due to any cause, whichever comes first. Clinical deterioration will not be considered as progression. Details for censoring will be provided in the SAP.
- Safety and tolerability objective will be measured by the incidence of adverse events (AEs), serious adverse events (SAEs), deaths, and laboratory abnormalities.
- PK will be measured using serum concentration-time data.

Assessments for other exploratory endpoints are discussed in other sections of the protocol, including biomarker analysis (Section 5.6), immunogenicity (Section 5.5), and outcomes research (Section 5.7). Corresponding endpoints will be detailed in the statistical analysis plan(s) (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 subjects with PD-L1 expressing tumors and for all randomized subjects.

8.4.2 Efficacy Analyses

Primary Endpoints

Progression free survival (PFS) in subjects with PD-L1 expressing tumors will be compared

- Between nivolumab plus ipilimumab vs chemotherapy using a two-sided log rank test and an endpoint-specific (i.e. initially allocated) significance level of 1.5%; and
- Between nivolumab plus chemotherapy vs chemotherapy using a two-sided log rank test and an endpoint-specific significance level of 1.5%.

OS in subjects with PD-L1 expressing tumors will be compared

- Between nivolumab plus ipilimumab vs chemotherapy using a two-sided log rank test and an endpoint-specific overall significance level of 1% defined for the groups sequential testing procedure (see Section 8.5);
- Between nivolumab plus chemotherapy vs chemotherapy using a two-sided log rank test and an endpoint-specific overall significance level of 1% defined for the groups sequential testing procedure (see Section 8.5).

All tests will be stratified by region (East Asia [Japan, Korea, Taiwan] vs Rest of Asia vs RoW), ECOG status (0 vs 1), and number of organs with metastases (≤ 1 vs ≥ 2) as recorded in the IRT. Endpoint-specific significance levels are split based on the conservative Bonferroni method and may be updated through graphical approach where the family-wise error rate will be protected in the strong sense. Rules for updating endpoint-specific significance levels following the Bonferroni-based graphical approach by Maurer and Bretz (2013)[61] will be detailed in the SAP.

For each comparison, the HR with its associated two-sided 100*(1 - adjusted α)% confidence intervals (CI) will be estimated via a stratified Cox model with treatment arm as the only covariate in the model. Both PFS and OS for each treatment arm will be estimated and plotted using the Kaplan-Meier (KM) product-limit method. Median survival time along with 95% CI will be constructed based on a log-log transformed CI for the survival function.

Secondary Endpoints

Time-to-event endpoints (OS and PFS as assessed by BICR in all randomized subjects) will be estimated and plotted using the KM product-limit method for each treatment arm. Median survival time along with 95% CI will be constructed based on a log-log transformed CI for the survival function. The HR with its associated two-sided 95% CI will be estimated via a stratified Cox model with treatment arm as the only covariate in the model.

Overall Survival and PFS in all randomized subjects will be tested only if significance level is passed on them. Rules for passing on significance levels will be defined together with the graphical approach in the SAP. Comparisons will use a two-sided log rank test, stratified by the same stratification factors as the primary endpoint and by PD-L1 status (≥ 1% vs < 1% [including indeterminate]) as recorded in IRT.

ORR as assessed by BICR and by investigator in subjects with PD-L1 expressing tumors and in all randomized subjects will be computed in each treatment group along with the exact 95% CI using Clopper-Pearson method. An estimate of the difference in ORRs, and corresponding 95% CI will be calculated using Cochran-Mantel-Haenszel (CMH) methodology and adjusted by the randomization stratification factors. The stratified odds ratios (Mantel-Haenszel estimator) between the treatments will be provided along with the 95% CI.

ORR as assessed by BICR in subjects with PD-L1 expressing tumors and in all randomized subjects will be tested only if significance level is passed on them. Rules for passing on significance levels will be defined together with the graphical approach in the SAP. Comparisons will use a two-sided CMH test.

Exploratory Endpoints

Progression free survival, PFS2/TSST, and ORR as assessed by investigator (in subjects with PD-L1 expressing tumors and in all randomized subjects) will be described using the same methods as the corresponding secondary endpoints.

Duration of Response (as assessed by BICR and as assessed by investigator) in each treatment group will be estimated using KM product-limit method for subjects who achieve PR or CR. Median values along with two-sided 95% CI will be calculated.

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 by treatment group. All on-study AEs, treatment-related AEs, SAEs, and treatment-related SAEs will be tabulated using worst grade per NCI CTCAE version 4 criteria by system organ class and preferred term (PT). On-study lab parameters including hematology, chemistry, liver function, and renal function will be summarized using worst grade NCI CTCAE version 4 criteria.

8.4.4 Pharmacokinetic Analyses

The nivolumab and/or ipilimumab 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/or ipilimumab 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

Details for biomarker analyses will be described in the SAP(s). These analyses will be descriptive and not adjusted for multiplicity.

8.4.6 Outcomes Research Analyses

The analysis of EQ-5D-3L and FACT-E (including 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. The 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-3L data will be described by treatment group as randomized in the following ways:

- EQ-5D-3L 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-3L 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-3L health state (ie, 5-digit vector), EQ-5D-3L 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 treatment group as randomized in the following ways:

- ECS, FACT-G7, 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-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.

During the survival follow-up phase, data for the ECS and FACT-G7 will be described by treatment group as randomized 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 Analysis

At the time of the final PFS analysis, a formal interim analysis for OS in subjects with PD-L1 expressing tumors is planned. If no superiority is claimed at interim of OS, the trial will continue (regardless of the final PFS analysis results), and a final OS analysis will take place. Lan-DeMets α spending function with O'Brien and Fleming type of boundary will be used. The stopping boundary will depend on the actual number of deaths at the time of the interim analysis. For example, if the interim analysis is performed at 175 deaths (70% of all expected deaths), endpoint-specific significance level at the interim analysis will be 0.002. An independent statistician external to BMS will perform the analysis; results will be evaluated by the DMC.

The endpoint-specific significance level for the final look after 250 deaths would be 0.009. All events in the database at the time of the lock will be used.

In addition to the formal planned interim analysis for OS, the DMC will have access to periodic unblinded interim reports of efficacy and safety to allow a risk/benefit assessment. No formal test will be performed and the study will not stop for superiority. Details will be included in the DMC charter.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

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

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

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

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

9.1.2 Monitoring

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

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

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

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

9.1.2.1 Source Documentation

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

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

9.2 Records

9.2.1 Records Retention

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

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

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

9.2.2 Study Drug Records

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

If	Then
Supplied by BMS (or its vendors):	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 (e.g., lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number

If	Then
	• amount dispensed to and returned by each subject, including unique subject identifiers • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

9.2.3 Case Report Forms

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

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

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

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

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

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

9.3 Clinical Study Report and Publications

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

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

- External Principal Investigator designated at protocol development
- Other criteria (as determined by the study team)

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

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	Complete Abstinence is defined as complete avoidance of heterosexual intercourse and 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. Women must continue to have pregnancy tests. Acceptable alternate methods of highly or less effective contraception's must be discussed in the event that the subject chooses to forego complete abstinence.
PD-L1 Evaluable Status	Sufficient quantity of tissue sample available for analysis
PD-L1 Indeterminate Status	Inconclusive result

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ADA	Anti Drug Antibody
AIDS	Acquired Immunodeficiency Syndrome
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
BICR	Blinded Independent Central Review
BLQ	below limit of quantification
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BSA	Body surface area
BSC	Best Supportive Care
BUN	blood urea nitrogen
C	Celsius
Ca++	calcium
Cavg	average concentration
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
Cl-	chloride
CrCl	creatinine clearance
CLR	renal clearance
CLT	total body clearance
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CNS	Central nervous system
CRF	Case Report Form, paper or electronic

Term	Definition
CV	coefficient of variation
CR	Complete response
CT	computerized tomography
DCR	Disease Control rate
dL	deciliter
DILI	Drug Induced Liver Injury
EAC	Esophageal Adenocarcinoma
EBV	Epstein-Barr Virus
EC	Esophageal Cancer
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ECS	Esophageal Cancer Subscale
EDC	Electronic Data Capture
eg	exempli gratia (for example)
EoT	End of treatment
ESCC	Esophageal Squamous Cell Cancer
ESMO	European Society of Medical Oncology
FA	final analysis
FACT-G7	Functional Assessment of Cancer Therapy - General
FACT-Ga	Functional Assessment of Cancer Therapy - Gastric
FACT-E	Functional Assessment of Cancer Therapy - Esophageal
FDA	Food and Drug Administration
FFPE	Formalin-Fixed Paraffin-Embedded
FSH	follicle stimulating hormone
g	gram
GaCS	Gastric Cancer Subscale
GC	Gastric Cancer
GCP	Good Clinical Practice
GEC	Gastric-Esophageal Junction Cancer
GERD	Gastro-Esophageal Reflux Disease
GFR	glomerular filtration rate

Term	Definition
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	heart rate hazard ratio
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator Brochure
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IFN	Interferon
IMG	Immunogenicty
IMP	investigational medicinal products
IND	Investigational New Drug
IO	Immuno-Oncology
IRB	Institutional Review Board
IRCC	Immune related Response Criteria
IRT	Interactive Response Technology
IU	International Unit
IV	intravenous
K+	potassium
kg	kilogram
L	liter
LDH	lactate dehydrogenase
mg	milligram

Term	Definition
Mg++	magnesium
min	minute
mL	milliliter
MLR	Mixed Lymphocytes reaction
mmHg	millimeters of mercury
mOS	Median overall survival
mDOR	Median duration of response
MRI	Magnetic resonance imaging
MSI	Microsatellite Instability
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
Na+	sodium
N/A	not applicable
NCCN	National Comprehensive Cancer Network
ng	nanogram
NIMP	non-investigational medicinal products
NSCLC	Non Small Cell Lung Cancer
OS	Overall Survival
ORR	Objective Response Rate
PBMC	Peripheral Blood Mononuclear cell
PD	Disease Progression
PD-L1	Programmed Death Ligand 1
PFS	Progression Free Survival
PK	pharmacokinetics
PPK	Population pharmacokinetic
PRO	Patient Reported Outcomes
QxW	Every x weeks
QoL	Quality of Life
RCC	Renal Cell Carcinoma

Term	Definition
RECIST	Response Evaluation Criteria In Solid Tumors
RT PCR	Real-time Polymerase Chain Reaction
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SNP	Single Nucleotide Polymorphism
SOC	Standard of Care
SOP	Standard Operating Procedures
SPC	Summary of Product Characteristic
Subj	subject
t	temperature
T	time
T-HALF	Half life
TCR	T-cell receptor
TMB	Tumor mutational burden
TSST	Time to second subsequent therapy
TTP	Time to progression
TTR	Time to response
Vc	Volume of Central compartment
Vss/F (or Vss)	apparent volume of distribution at steady state
Vz	Volume of distribution of terminal phase (if IV and if multi-exponential decline)
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

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APPENDIX 1 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.

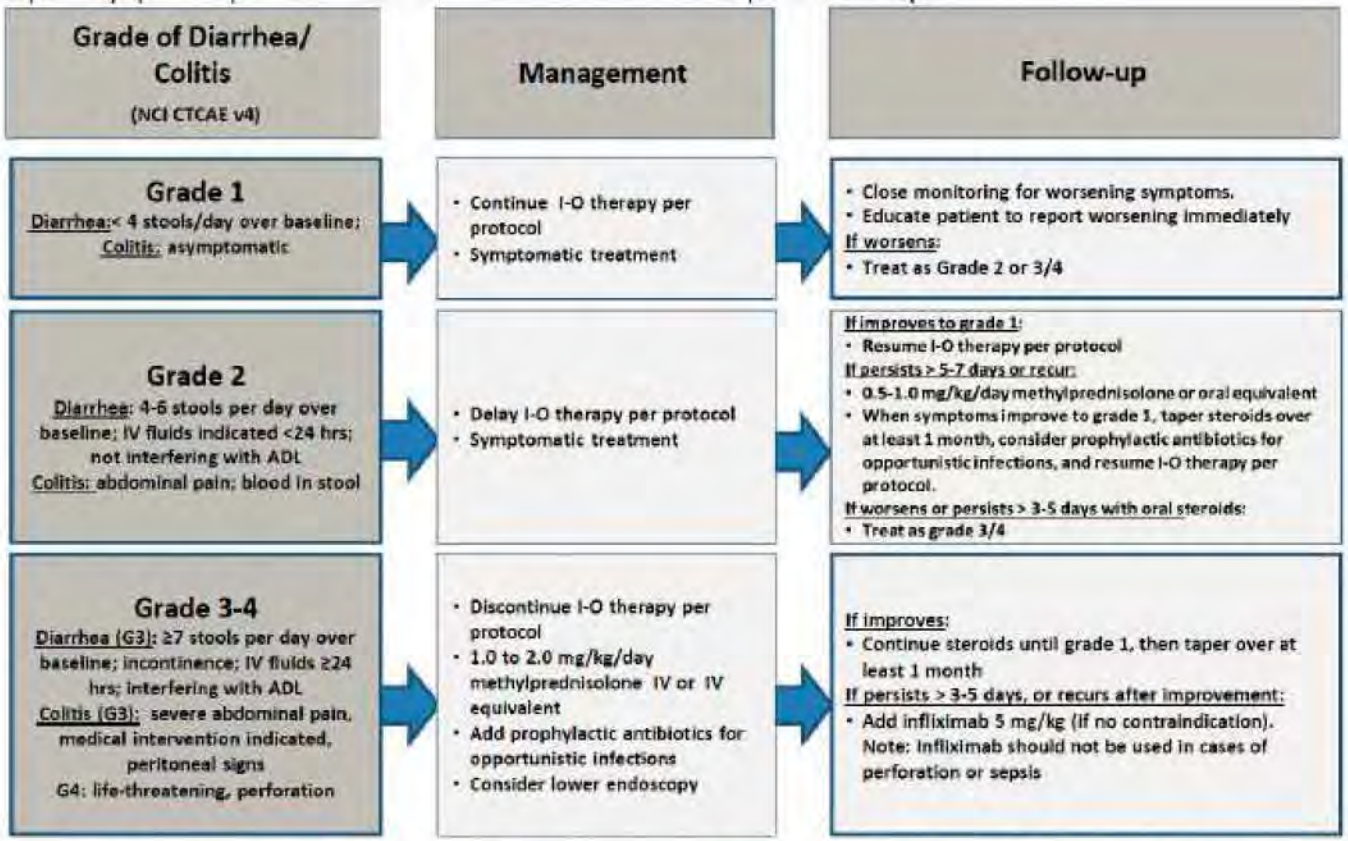
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

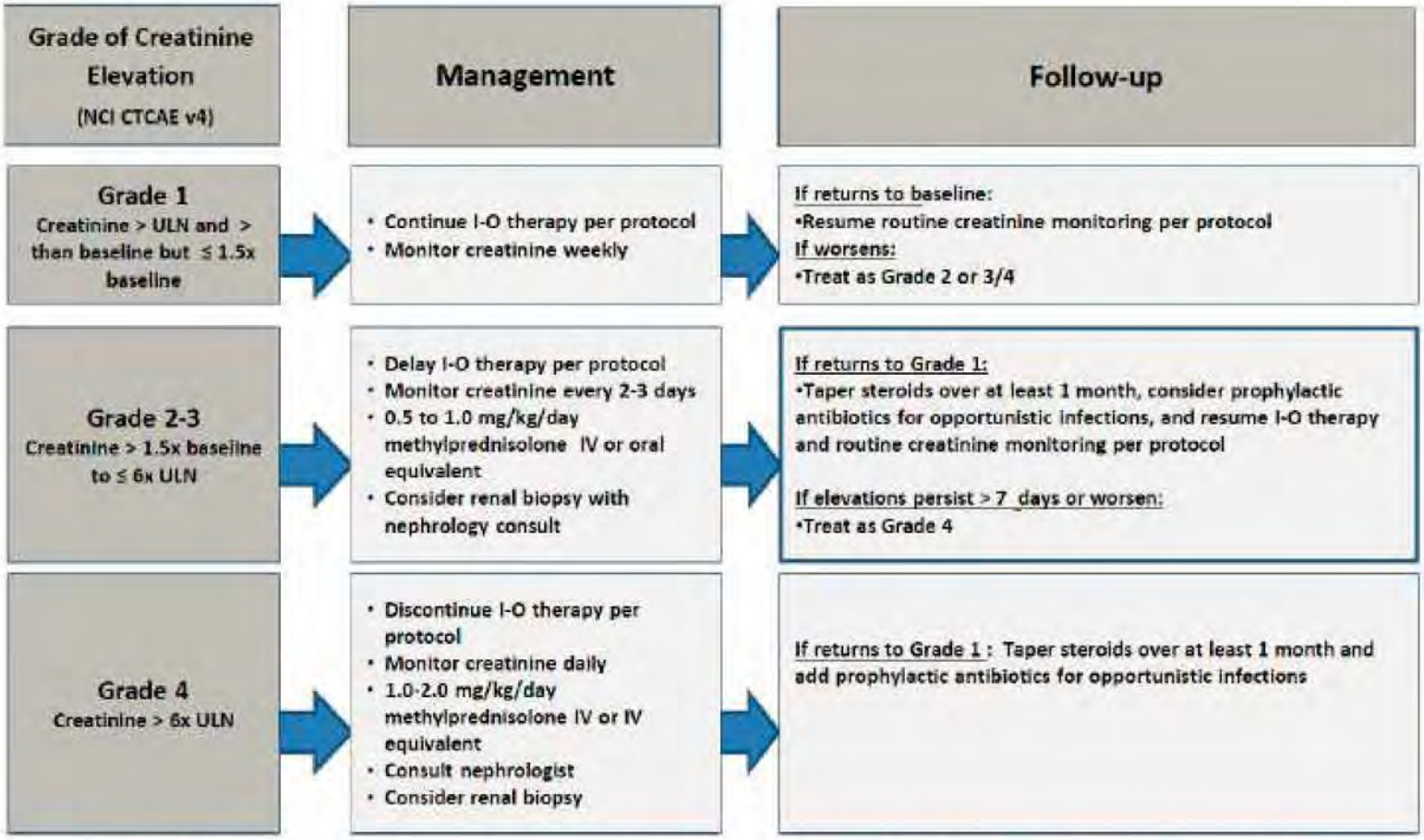


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

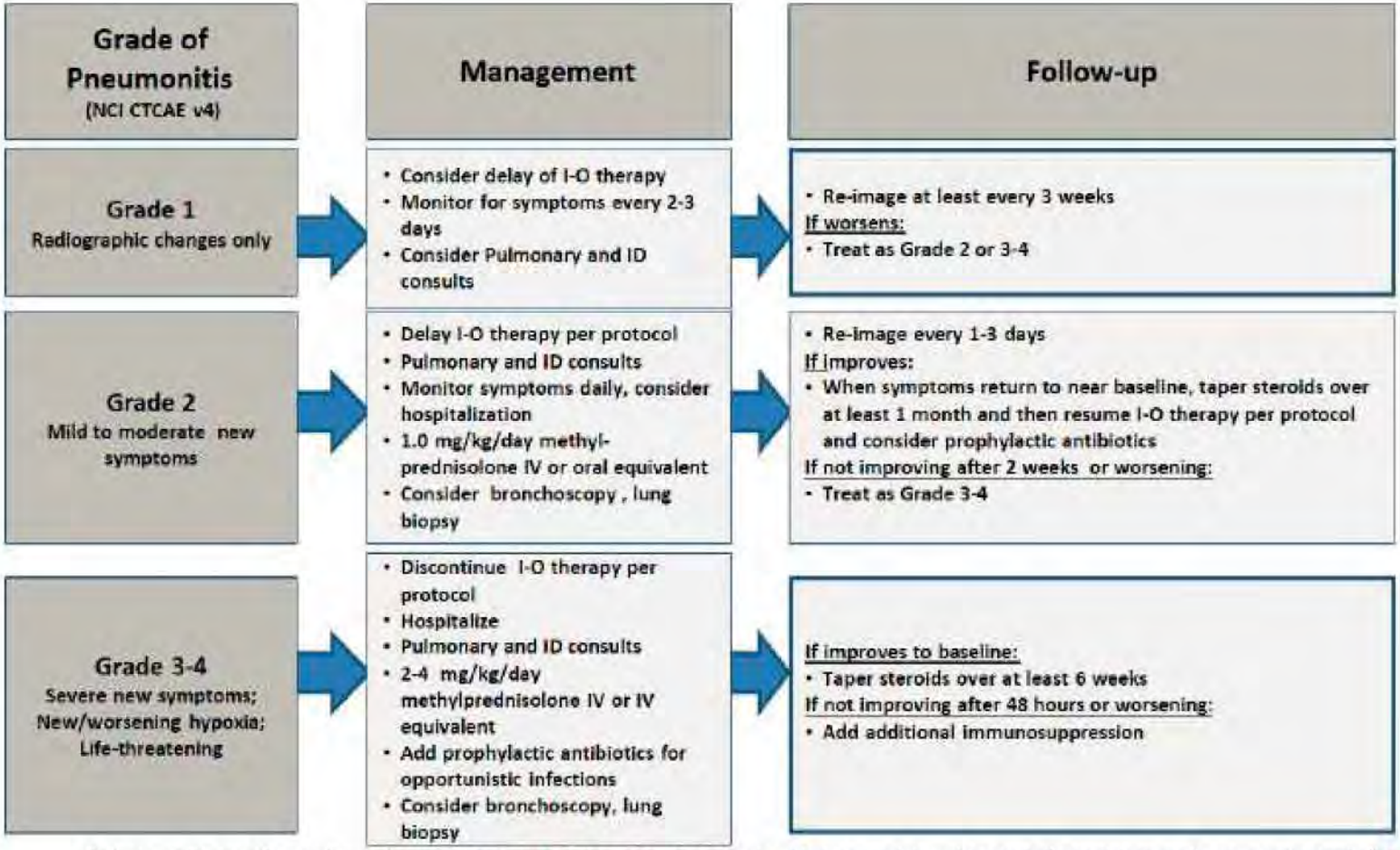


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

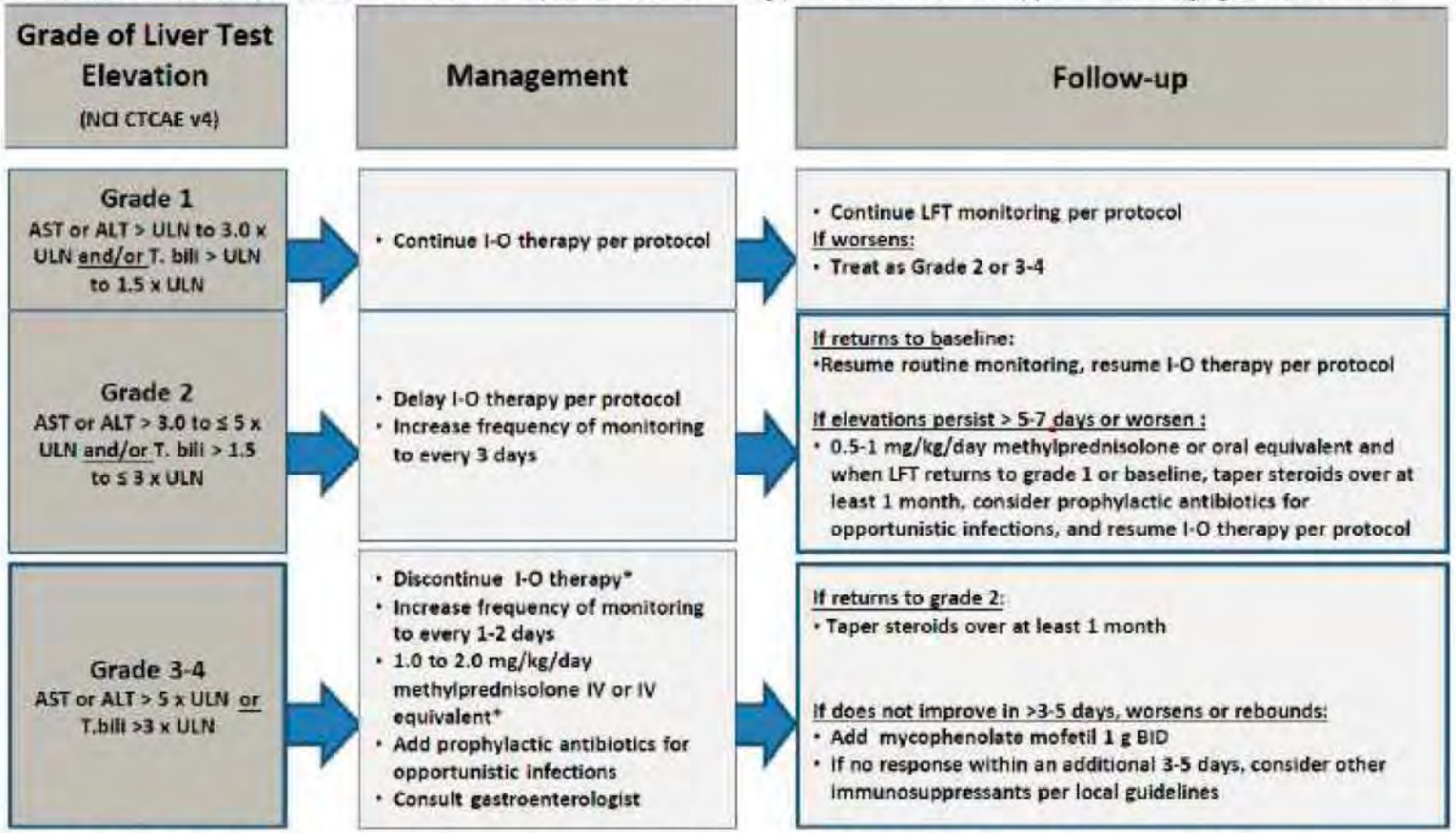


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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



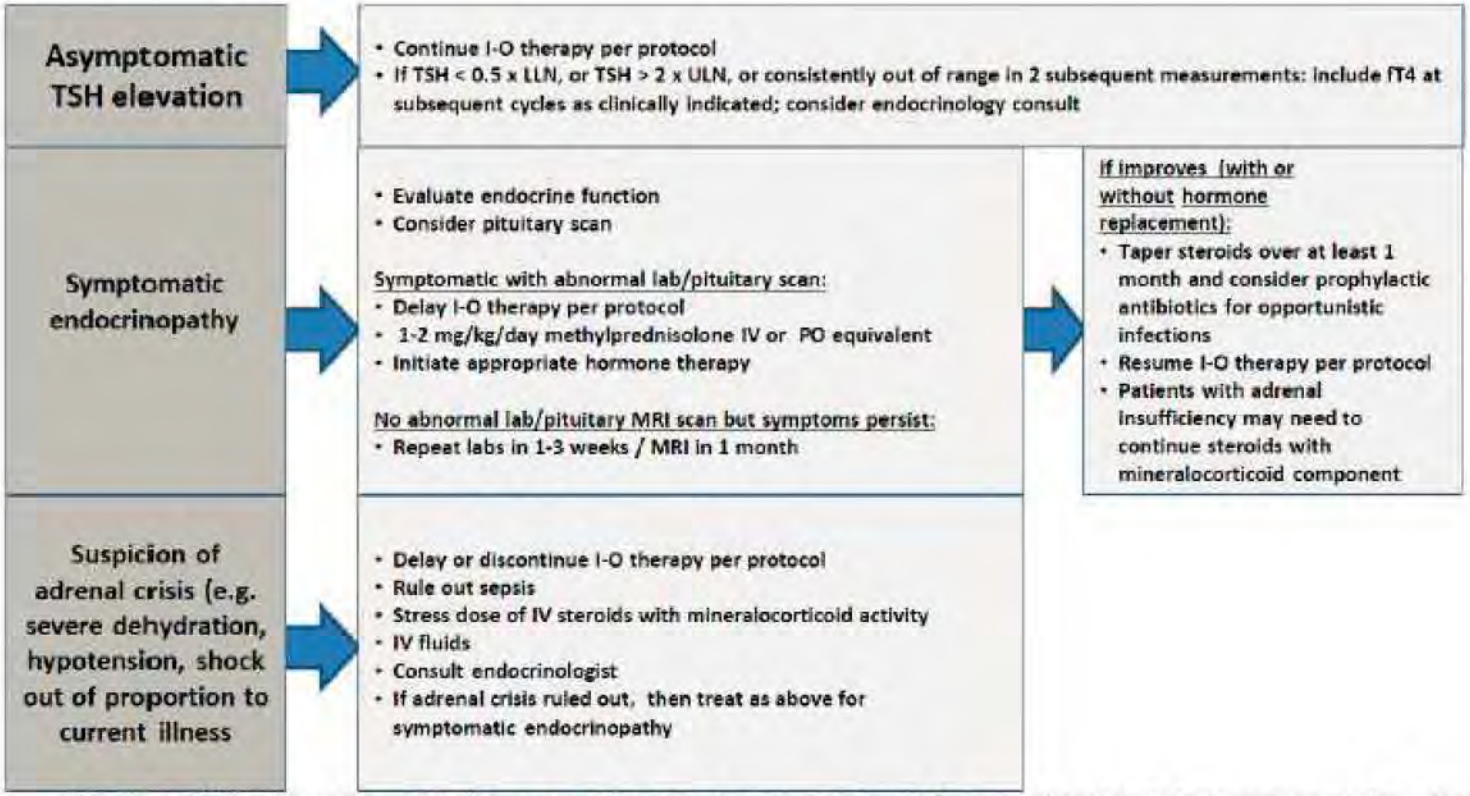
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

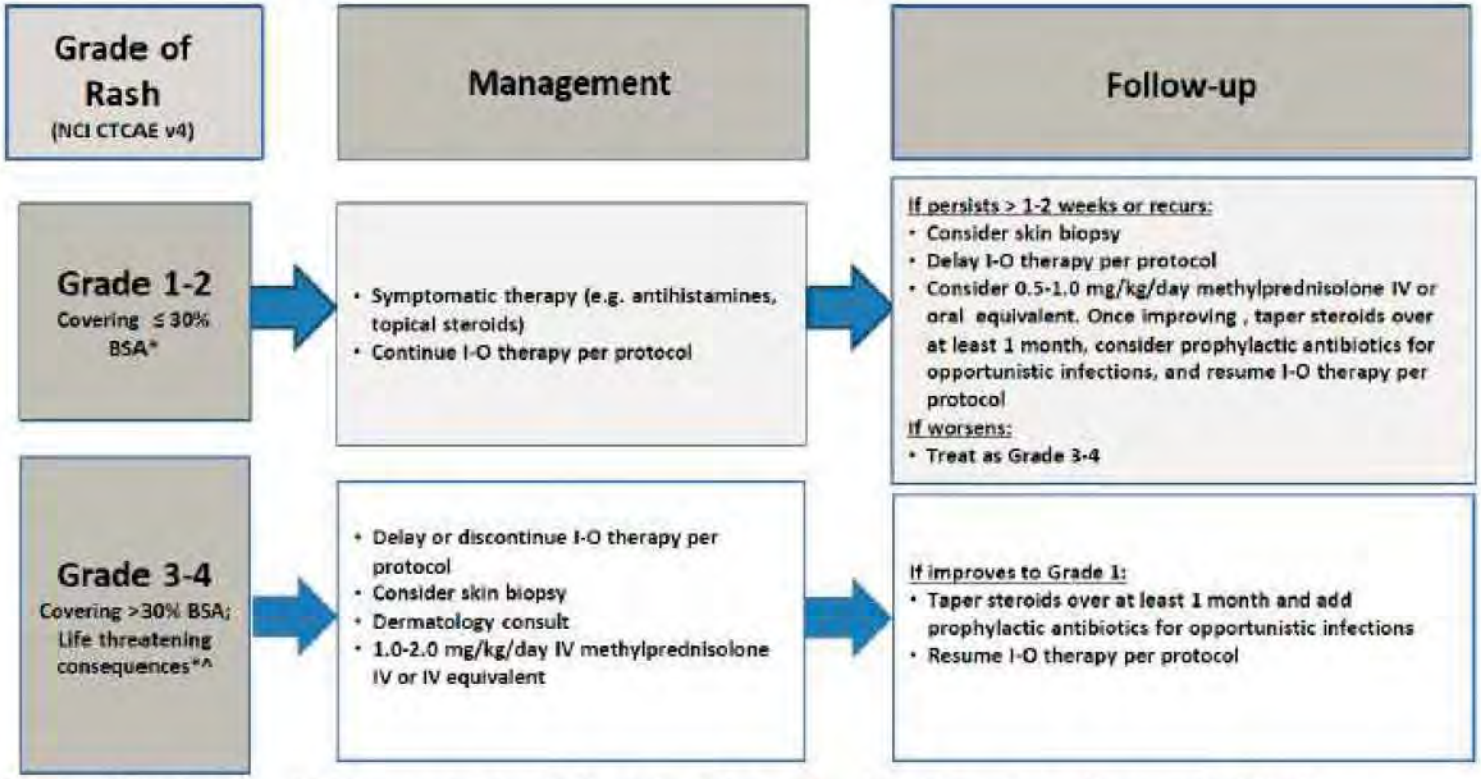


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

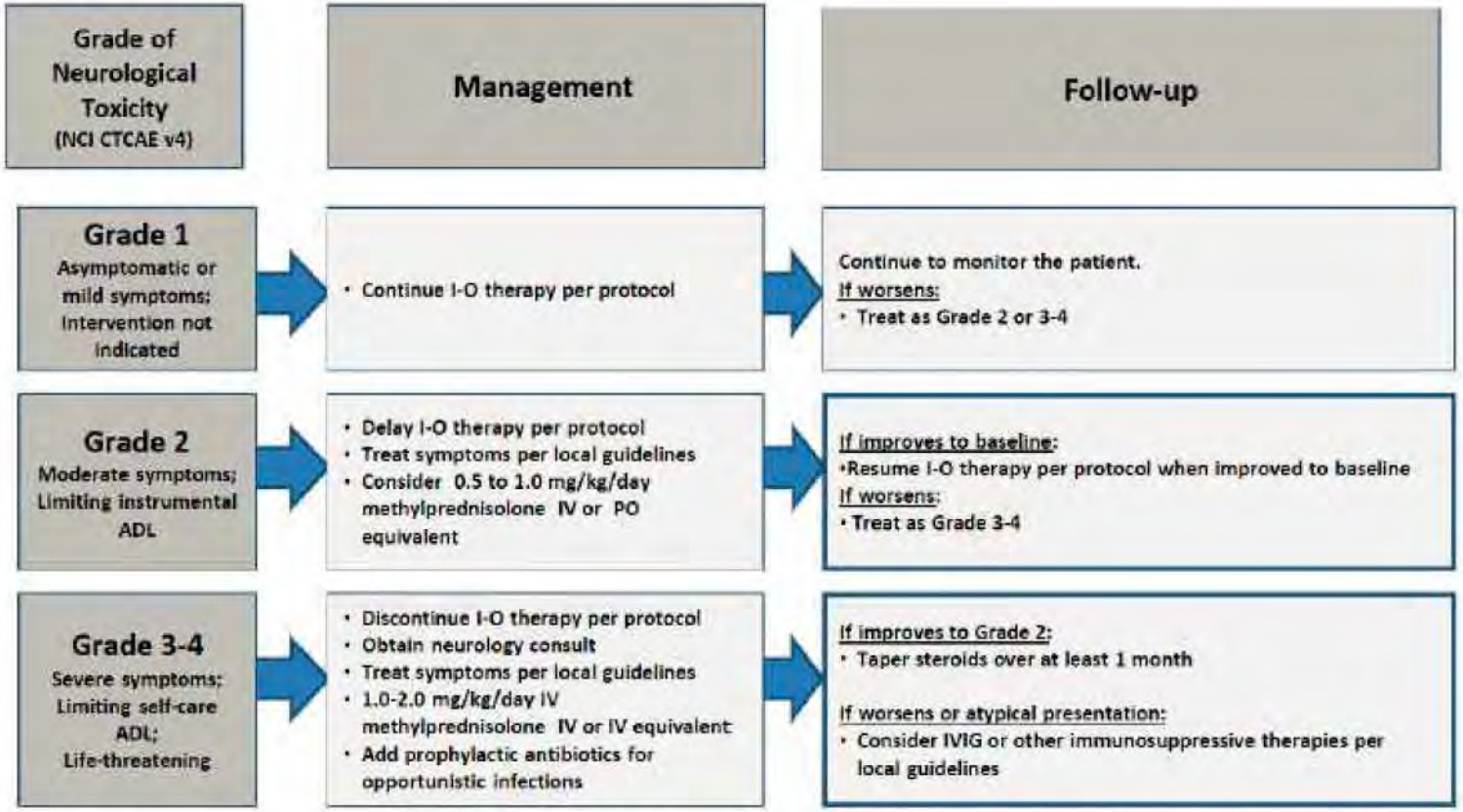
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^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 2 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 for female participants of childbearing potential treated with nivolumab plus ipilimumab, and 5 half-lives plus 30 days, or the duration specified by the local labels of chemotherapy drugs received, whichever is longer.

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

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)

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 if treated with nivolumab plus ipilimumab, and 5 half-lives plus 90 days or a duration specified by local labels of chemotherapy, whichever is longer.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure as defined above.
- 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 the end of relevant systemic exposure as defined above.
- Refrain from donating sperm for the duration of the study treatment until the end of relevant exposure period defined as: 7 months after the end of study treatment if treated with nivolumab plus ipilimumab, and 5 half-lives plus 90 days or a duration specified by local labels of chemotherapy, whichever is longer.

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 3 ECOG PERFORMANCE STATUS

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

Source: Oken MM, Creech RH, Tomey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655.

APPENDIX 4 7TH EDITION OF THE AJCC CANCER STAGING MANUAL : ESOPHAGUS AND ESOPHAGOGASTRIC JUNCTION

7th Edition of the AJCC *Cancer Staging Manual:* Esophagus and Esophagogastric Junction

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In previous editions of the American Joint Committee on Cancer (AJCC) *Cancer Staging Manual*, esophageal cancer staging was neither data driven nor harmonized with stomach cancer. The new staging system presented in the 7th edition of the AJCC *Cancer Staging Manual*, in contrast, is data driven and harmonized.[1] This commentary describes development of the new system and highlights the changes and additions.

DATA AND ANALYSIS

At the request of the AJCC, worldwide data were assembled to develop the 7th edition staging system for esophageal cancer.[1] The Worldwide Esophageal Cancer Collaboration (WECC) was inaugurated in 2006. Thirteen institutions from five countries and three continents (Asia, Europe, and North America) submitted deidentified data by July 2007. These were used to construct a database of 4,627 esophagectomy patients who had no induction or adjuvant therapy to develop a staging system based on the pathologic tumor, node, metastasis (TNM) system.[2]

Several previously proposed revisions of esophageal cancer staging have examined goodness of fit or *P* values to test for a statistically significant effect of stage on survival. However, staging for the 7th edition used Random Forest (RF) analysis, a machine-learning technique that focuses on predictiveness for future patients.[3] RF analysis makes no a priori assumptions about patient survival, is able to identify complex interactions among variables, and accounts for nonlinear effects.

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RF analysis first isolated cancer characteristics of interest from other factors influencing survival by generating risk-adjusted survival curves for each patient. Unlike previous approaches that began by placing cancer characteristics into proposed groups, RF analysis produced distinct groups with monotonically decreasing risk-adjusted survival without regard to cancer characteristics. Then anatomic and nonanatomic cancer characteristics important for stage group composition were identified within these groups. Homogeneity within groups guided both amalgamation and segmentation of cancer characteristics between adjacent groups to arrive at the proposed stage groups.[4]

The final step involved consensus panels within WECC and with the AJCC Gastric Task Force, AJCC, and International Union Against Cancer (UICC) aimed at filling certain gaps in the data, meeting AJCC and UICC definitions and requests, and harmonizing with gastric cancer staging.[1]

CLASSIFICATIONS: CHANGES AND ADDITIONS IN THE 7TH EDITION

T classification has been changed for Tis and T4 cancers (Table 1). Tis is now defined as high-grade dysplasia and includes all noninvasive neoplastic epithelium that was previously called carcinoma-in-situ. T4, tumors invading local structures, have been subclassified as T4a and T4b. T4a tumors are resectable cancers invading adjacent structures such as pleura, pericardium, or diaphragm. T4b tumors are unresectable cancers invading other adjacent structures, such as aorta, vertebral body, and trachea.

A regional lymph node has been redefined to include any paraesophageal node extending from cervical nodes to celiac nodes (Table 1). In classifying N, the data support convenient coarse groupings of number of cancer-positive

nodes (0, 1–2, 3–6, ≥7). These have been designated N0 (none), N1 (1–2), N2 (3–6), and N3 (≥7) and are identical to gastric N classifications.

The subclassifications M1a and M1b have been eliminated, as has MX (Table 1). Distant metastases are simply designated M0, no distant metastasis, and M1, distant metastasis.

Nonanatomic classifications identified as important for stage grouping were histopathologic cell type, histologic grade, and tumor location (Table 1). The difference in survival between adenocarcinoma and squamous-cell carcinoma was best managed by separate stage groupings for stages I and II. Increasing histologic grade was associated with incrementally decreasing survival for early-stage cancers. For adenocarcinoma, the distinction of G1 and G2 (well and moderately differentiated) from G3 (poorly differentiated) was important for stage I and stage IIA cancers. For squamous-cell carcinoma, the distinction of G1 from G2 and G3 was important for stage I and II cancers. Tumor location (upper and middle thoracic vs. lower thoracic) was important for grouping T2-3N0M0 squamous-cell cancers.

STAGE GROUPINGS

Stage groupings and corresponding risk-adjusted survival curves are presented in Tables 2 and 3 and Figs. 1 and 2, respectively.

TABLE 1 Summary of changes in anatomic classifications and additions of nonanatomic cancer characteristics

Changes in anatomic classifications	
T classification	
Tis is redefined and T4 is subclassified	
Tis	High-grade dysplasia
T4a	Resectable cancer invades adjacent structures such as pleura, pericardium, diaphragm
T4b	Unresectable cancer invades adjacent structures such as aorta, vertebral body, trachea
N classification	
Regional lymph node is redefined	
Any periesophageal lymph node from cervical nodes to celiac nodes	
N is subclassified	
N0	No regional lymph node metastases
N1	1 to 2 positive regional lymph nodes
N2	3 to 6 positive regional lymph nodes
N3	≥7 positive regional lymph nodes
M classification	
M is redefined	
M0	No distant metastases
M1	Distant metastases
Additions of nonanatomic cancer characteristics	
Histopathologic cell type	
Adenocarcinoma	
Squamous-cell carcinoma	
Histologic grade	
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated
Cancer location	
Upper thoracic	20–25 cm from incisors
Middle thoracic	>25 to 30 cm from incisors
Lower thoracic	>30 to 40 cm from incisors
Esophagogastric junction	Includes cancers whose epicenter is in the distal thoracic esophagus, esophagogastric junction, or within the proximal 5 cm of the stomach (cardia) that extend into the esophagogastric junction or distal thoracic esophagus (Siewert III). These stomach cancers are stage grouped similarly to adenocarcinoma of the esophagus

TABLE 2 Adenocarcinoma stage groupings

Stage	T	N	M	G
0	is (HGD)	0	0	1
IA	1	0	0	1–2
IB	1	0	0	3
	2	0	0	1–2
IIA	2	0	0	3
IIB	3	0	0	Any
	1–2	1	0	Any
IIIA	1–2	2	0	Any
	3	1	0	Any
	4a	0	0	Any
IIIB	3	2	0	Any
IIIC	4a	1–2	0	Any
	4b	Any	0	Any
	Any	N3	0	Any
IV	Any	Any	1	Any

TABLE 3 Squamous-cell carcinoma stage groupings

Stage	T	N	M	G	Location
0	is (HGD)	0	0	1	Any
IA	1	0	0	1	Any
IB	1	0	0	2–3	Any
	2–3	0	0	1	Lower
IIA	2–3	0	0	1	Upper, middle
	2–3	0	0	2–3	Lower
IIB	2–3	0	0	2–3	Upper, middle
	1–2	1	0	Any	Any
IIIA	1–2	2	0	Any	Any
	3	1	0	Any	Any
	4a	0	0	Any	Any
IIIB	3	2	0	Any	Any
IIIC	4a	1–2	0	Any	Any
	4b	Any	0	Any	Any
	Any	N3	0	Any	Any
IV	Any	Any	1	Any	Any

ESOPHAGOGASTRIC JUNCTION CANCERS

Besides being data driven, the 7th edition staging system harmonizes cancer staging across the esophagogastric junction. Previous staging produced different stage groupings for these cancers depending on use of either esophageal or gastric stage groupings. The 7th edition staging system is for cancers of the esophagus and esophagogastric junction and includes cancer within the first 5 cm of the stomach that extend into the esophagogastric junction or distal thoracic esophagus (Siewert III).

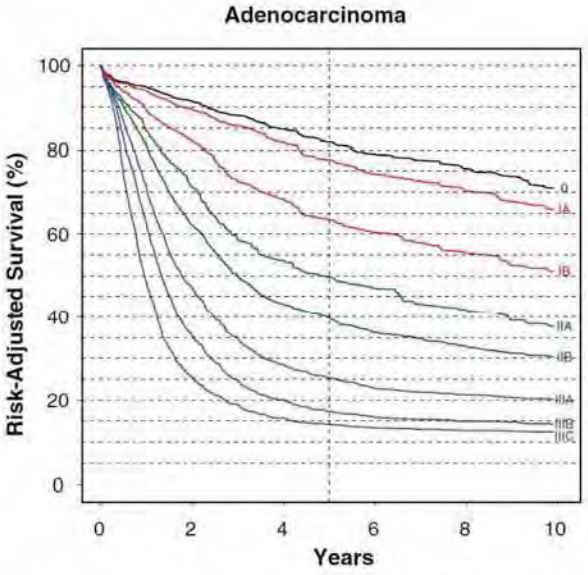

FIG. 1 Risk-adjusted survival for adenocarcinoma according to the American Joint Committee on Cancer *Cancer Staging Manual*, 7th edition, stage groups

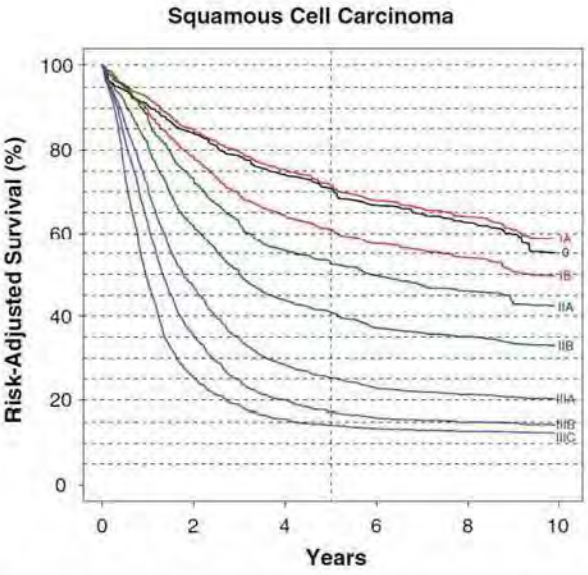

FIG. 2 Risk-adjusted survival for squamous-cell carcinoma according to the American Joint Committee on Cancer *Cancer Staging Manual*, 7th edition, stage groups

CONCLUSIONS

Previous stage groupings of esophageal cancer were based on a simple, orderly arrangement of increasing anatomic T, then N, then M classifications. These groupings were not consistent with data or cancer biology.

Explanations for discrepancies relate to the interplay among TNM classifications, histopathologic type, biologic activity of the tumor (histologic grade), and cancer location. In contrast, the 7th edition staging system is data driven; it is based on a risk-adjusted RF analysis of worldwide data, and it accounts for interactions of anatomic and nonanatomic cancer characteristics.

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Source: Ann Surg Oncol 2010;17:1721-1724 DOI 10.1245/s10434-010-1024-1

APPENDIX 5 RADIOLOGIC EVALUATION CRITERIA IN SOLID TUMOURS VERSION 1.1 (RECIST CRITERIA 1.1)

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least 1 measurable tumor lesion. When computed tomography (CT) scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

At baseline, tumor lesions/lymph nodes will be categorized measurable or nonmeasurable, which are discussed below.

1.1 Measurable Lesions

Measurable lesions must be accurately measured in at least 1 dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by CT/magnetic resonance imaging (MRI) scan - (CT/MRI scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as nonmeasurable)
- 20 mm by chest x-ray
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

1.2 Non-measurable Lesions

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions
- Lesions considered truly nonmeasurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.3 Special Considerations Regarding Lesion Measurability

1.3.1 Bone Lesions

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components that can be evaluated by cross sectional imaging techniques such as CT or MRI, can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are nonmeasurable.

1.3.2 Cystic Lesions

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

1.3.3 Lesions with Prior Local Treatment

Tumor lesions situated in a previously irradiated area or in an area subjected to other locoregional therapy are usually not considered measurable, unless there has been demonstrated progression in the lesion. Measurable lesions may be in an irradiated field as long as there is documented progression, and the lesion(s) can be reproducibly measured.

1.4 Specifications by Methods of Measurements

1.4.1 Measurement of Lesions

All measurements should be recorded in metric notation (mm). All baseline evaluations should be performed as close as possible to the treatment start and never more than 30 days before the beginning of the treatment.

1.4.2 Method of Assessment

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

1.4.2.1 CT/MRI Scan

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

1.4.2.2 Chest X-ray

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

1.4.2.3 Clinical Lesions

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

1.4.2.4 Ultrasound

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

1.4.2.5 Endoscopy, Laparoscopy

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

1.4.2.6 Tumor Markers

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

2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

2.1 Target Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to **a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as *target lesions*** and will be recorded and measured at baseline.

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

A **sum of the diameters** (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the **baseline sum diameters.** If lymph nodes are to be included in the sum, then as noted below, only the **short** axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

2.1.1 Lymph Nodes

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes, which are defined as measurable and may be identified as target lesions, must meet the criterion of a **short axis of ≥ 15 mm by CT scan**. Only the short axis of these nodes will contribute to the baseline sum. Nodes that have a short axis < 10 mm are considered nonpathological and should not be recorded or followed.

2.2 Non-target Lesions

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as **non-target lesions** and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as **'present', 'absent', or in rare cases, 'unequivocal progression'.** In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3 TUMOR RESPONSE EVALUATION

3.1 Evaluation of Target Lesions

- Complete Response (CR): **Disappearance of all target lesions.** Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.
- Partial Response (PR): At least a **30% decrease in the sum of diameters of target lesions,** taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a **20% increase in the sum of diameters of target lesions,** taking as reference the **smallest sum on study** (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an **absolute increase of at least 5 mm**. (Note: The appearance of 1 or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study.

3.1.1 Special Notes on the Assessment of Target Lesions

3.1.1.1 Lymph Nodes

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes, which are defined as measurable and may be identified as target lesions, must meet the criterion of a **short axis of ≥ 15 mm by CT scan**. Only the short axis of these nodes will contribute to the baseline sum. Nodes that have a short axis <10 mm are considered nonpathological and should not be recorded or followed.

3.1.1.2 Target Lesions That Become 'Too Small to Measure'

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

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

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: In case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this

circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).

3.1.1.3 Target Lesions that Split or Coalesce on Treatment

- When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum.
- As lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'

3.2 Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- CR: Disappearance of all non-target lesions. All lymph nodes must be nonpathological in size (< 10 mm short axis).
- PD: Unequivocal progression of existing non-target lesions. (Note: The appearance of 1 or more new lesions is also considered progression).
- NonCR/NonPD: Persistence of 1 or more non-target lesion(s).

3.2.1 Special Notes on Assessment of Non-target Lesions

The concept of progression of non-target disease requires additional explanation as discussed below.

3.2.1.1 When the Subject Also has Measurable Disease

- To achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease, such that even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest 'increase' in the size of 1 or more non-target lesions is usually not sufficient to quality for unequivocal progression status.

3.2.1.2 When the Subject has Only Non-measurable Disease

- To achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening, such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest increase in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

- Because worsening in non-target disease cannot be easily quantified (by definition, if all lesions are nonmeasurable), a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, ie, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'.
- If unequivocal progression is seen, the subject should be considered to have had overall PD at that point.

3.2.1.3 Tumor Markers

Tumor markers will not be used to assess objective tumor responses.

3.3 New Lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some new bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the subject's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a new cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was **not** scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study, has a CT or MRI brain scan ordered that reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

4 RESPONSE CRITERIA

4.1 Time Point Response

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

For subjects who have **measurable disease** at baseline, Table 4.1-1 provides a summary of the overall response status calculation at each time point.

Table 4.1-1: Subjects with Target (+/– Non-target) Disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	NonCR/nonPD	No	PR
CR	Not evaluated	No	PR
PR	NonPD or not all evaluated	No	PR
SD	NonPD or not all evaluated	No	SD
Not all evaluated	NonPD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

4.1.1 Missing Assessments and Not Evaluable Designation

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

4.1.2 Confirmation Scans

Verification of Response: Confirmation of PR and CR is required at least after 4 weeks from the initial scan reporting response to ensure that the responses identified are not the result of measurement error.

4.2 Best Overall Response: All Time Points

The best overall response is determined once all the data for the subject is known. It is the best response recorded from the start of the study treatment until the end of treatment, taking into account any requirement for confirmation. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Best response is defined as the best response across all time points with subsequent confirmation. CRs or PRs may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later).

In this circumstance, the best overall response can be interpreted as specified in Table 4.2-1. When SD is believed to be best response, it must meet the protocol specified minimum time from baseline. Measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6 to 8 weeks). For this protocol best response of SD

can be made after the subject is on study for a minimum of 6 weeks (42 days) ± 7 days with a minimum on study time of 35 days.

Table 4.2-1: Best Overall Response When Confirmation of CR and PR is Required

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

[a] Abbreviations: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable.
If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

4.3 Duration of Response

4.3.1 Duration of Overall Response

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

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

4.3.2 Duration of Stable Disease

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

Reference: Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-247.

APPENDIX 6 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 04, 12-Sep-2018

The revised protocol restricts study entry to participants of previous nivolumab clinical studies where overall survival was listed as a primary or co-primary endpoint since participation in CA209-648 could confound the interpretation of efficacy results in these studies. Live /attenuated vaccines were prohibited to address any potential safety risks and the inclusion criterion related to the assessment of renal function was expanded to allow the consideration of measured creatinine clearance instead of calculated creatinine clearance per Cockcroft-Gault formula on the basis that measured creatinine clearance represents an accurate estimation of GFR. Cisplatin infusion times longer than 120 minutes were allowed if deemed necessary by investigator per local standard of care/local label. PFS2/TSST was added as an exploratory endpoint to help understand the relevance of meaningful improvements in PFS. The section on biomarker assessments was revised to reflect current prioritizations in the biomarker analyses plan. Additionally, program updates were added and internal inconsistencies were corrected.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04

Section Number & Title	Description of Change	Brief Rationale
Section 1.3.3, Exploratory Objectives, bullet 4	An exploratory objective was added.	PFS2/TSST is included as an exploratory objective to help understand the relevance of meaningful improvements in PFS.
Bullets 9 - 12	Revised biomarker exploratory objectives.	Biomarker objectives were revised to reflect current prioritizations in the biomarker analyses plan.
Section 2.1, Good Clinical Practice	Minor revisions to paragraph 2.	Revised to align with the most recent language for BMS studies
Section 3.1, Study Design and Duration; Section 4.5.1.2, Nivolumab Combined with Fluorouracil plus Cisplatin Dosing (Arm B); Section 4.5.1.3, Fluorouracil plus Cisplatin Dosing (Arm C); Synopsis	Added a note to allow for longer cisplatin infusion times.	The duration of cisplatin infusion may exceed 120 minutes if required by local standard of care/local label in order to prevent/reduce potential toxicities.
Section 3.1.3, Follow-up Phase, bullet 4	Additional study assessments were added to bullet 4.	Added study assessments pertinent to PFS2/TSST.
Section 3.3.1, Inclusion Criteria, 2) Target Population, i) v) Calculated creatinine clearance	Added measured creatinine clearance (CrCl)	Measured CrCl represents an accurate estimate of GFR and can be used instead of the Cockcroft-Gault formula if preferable and feasible.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.3.2, Exclusion Criteria, 2) Medical History and Concurrent Diseases; Section 3.4.1, Prohibited and/or Restricted Treatments	Added exclusion criterion 2) n) Added bullet 5	Alignment with current BMS standards for studies using nivolumab. This restriction is based on theoretical risk of adverse effects for nivolumab and ipilimumab and not on clinical or safety data. The administration of live vaccines is contraindicated in patients receiving cisplatin and fluorouracil chemotherapy.
Section 3.3.2, Exclusion Criteria, 5) Other Exclusion Criteria, c)	Added to exclude participation in any prior clinical study of nivolumab.	Study participation may confound OS results in other nivolumab studies.
Section 3.5, Discontinuation of Subjects following any Treatment with Study Drug, bullet 4	Added a note to bullet 4.	Revised to align with the most recent language for BMS studies
Table 4.5.3.2.2-1, Dose Modifications for Non-hematologic Toxicity (Arms B and C)	Revised footnote b.	To clarify that CrCl should be assessed prior to dose with the same method used to determine eligibility
Section 4.5.5.1, Nivolumab and/or Ipilimumab Treatment Discontinuation (Arms A and B)	Revised dash-bullet 1, under bullet 3, to include myocarditis. Removed asterisk-and corresponding statement regarding Grade 3 AST or ALT elevation.	Nivolumab and or ipilimumab dose discontinuation criteria were updated for safety and to align with program standards.
Section 4.5.5.2, Fluorouracil and Cisplatin Dose Discontinuation (Arms B and C)	Revised diamond-bullet 3, under bullet 2.	To allow measured creatinine in addition to calculated creatinine by the Cockcroft Gault formula.
Table 5.1-5, Follow-Up Procedural Outline - All subjects (CA209648), Subject Status	Revised survival status to include subsequent therapy information.	Additional data collection for PFS 2 analyses.
Section 5.6, Biomarker Assessments, Table 5.6-1, Biomarker Sampling Schedule	Revised content regarding samples collected.	Biomarker collections were revised to reflect current prioritizations in the biomarker analyses plan.
Biomarker Sections 5.6.1.1 - Section 5.6.2.6	Section 5.6.1.1 - Section 5.6.1.5 were revised. Section 5.6.1.6 was added. Section 5.6.2.1 - Section 5.6.2.4 were revised. Section 5.6.2.5 and Section 5.6.2.6 were added.	Biomarker assessments sections were revised to reflect current prioritizations in the biomarker analyses plan and sections were added regarding microsatellite instability, plasma for circulating tumor DNA, and stool for microbiome.
Section 8.3.3, Exploratory Endpoint(s); Section 8.4.2, Efficacy Analyses, Exploratory Endpoints	Added bullet 4. Revised paragraph 1.	PFS2/TSST was added to the exploratory endpoints.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 1, Hepatic Adverse Event Management Algorithm	Footnote *, regarding delay of I-O therapy was deleted.	Hepatic algorithm updated to align with most recent guidance in the IB.
Appendix 2, Women of Childbearing Potential Definitions and Methods of Contraception, Highly Effective Methods That Are User Independent	Revised bullet 2.	To align with program standards.
All	Minor formatting and typographical corrections.	Minor, therefore have not been summarized

Overall Rationale for the Revised Protocol 03, 02-Feb-2018

The optimal duration of immunotherapy is an important question and continues to be investigated. Clinical trials across different tumors types in the nivolumab and ipilimumab development program indicate that most of the responses occur early, with a median time to response of 2-4 months, and emerging data suggests that benefit can be maintained in the absence of continued treatment. A recent analysis in a melanoma study suggests the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment (Schadendorf et al., 2016). Furthermore, a limited duration of ipilimumab, including only 4 induction doses, resulted in long term survival in patients with metastatic melanoma, with a sustained plateau in survival starting around 2 years after the start of treatment (Schadendorf et al., 2015).

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long term benefit. CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with previously treated advanced solid tumors (including 129 subjects with NSCLC), specified a maximum treatment duration of 2 years. Among 16 subjects with non-small cell lung cancer (NSCLC) who discontinued nivolumab after completing 2 years of treatment, 12 subjects were alive >5 years and remained progression-free without any subsequent therapy. In the CA209003 NSCLC cohort, the overall survival (OS) curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years (Brahmer et al., 2017). These survival outcomes are similar to phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2 year OS rates of 23% and 29%, and 3 year OS rates of 16%-18% for squamous and non-squamous NSCLC respectively) (Felip et al., 2017).

Similar results have been reported in clinical studies of pembrolizumab, another PD-1 inhibitor. Keynote-010 was a randomized phase 3 trial of pembrolizumab (at either 2 mg/kg or 10 mg/kg every 3 weeks) versus docetaxel in subjects with previously treated, PD-L1-positive, advanced NSCLC which specified a maximum treatment duration of 2 years for pembrolizumab. OS was significantly longer with both pembrolizumab 2 mg/kg (HR 0.72, $p = 0.00017$) and pembrolizumab 10 mg/kg (HR 0.60, $p < 0.00001$) compared to docetaxel, with an OS plateau

developing beyond 2 years in both pembrolizumab arms. Among 690 patients who received pembrolizumab, 47 patients completed 2 years of pembrolizumab and stopped treatment. Most were able to maintain their response, including those with stable disease, with only 2 patients (4%) having confirmed progression after stopping at 2 years (Herbst et al., 2016).

Keynote-006 was a randomized phase 3 study of pembrolizumab versus ipilimumab in patients with advanced melanoma, which also specified a maximum 2 year duration of pembrolizumab treatment. 104 (19%) of 556 patients randomized to pembrolizumab completed 2 years of treatment. With a median follow-up of 9 months after completion of pembrolizumab, the estimated risk of progression or death was 9% in these patients (Robert et al., 2017).

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

In contrast, a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated patients with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153, patients with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 patients still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in progression-free survival (PFS) compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached vs 10.3 months, respectively; HR=0.42 (95% CI, 0.25 to 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for patients on continued treatment to live longer (OS HR = 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (i.e., 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years (Spigel et al., 2017).

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

This revised protocol applies to all patients in Study CA209-648

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s) **Section 1.1.9** Rationale for Two-Year Duration of Treatment **Section 3.1** Study Design and Duration **Section 3.1.2** Treatment Phase	Removed treatment reinitiation procedures after disease progression for up to 1 additional year.	There is minimal, if any, benefit derived from continuing immuno-oncology treatment beyond two years in advanced tumors. Treatment beyond 2 years is no longer allowed in studies with nivolumab.
Section 4.5.6 Treatment Beyond Disease Progression	Added language for the 24 month maximum duration of treatment for nivolumab	There is minimal, if any, benefit derived from continuing immuno-oncology treatment beyond two years in advanced tumors. Treatment beyond 2 years is no longer allowed in studies with nivolumab.

Overall Rationale for the Revised Protocol 02, 25-Oct-2017

Protocol was amended to rectify inconsistencies, add clarifications and implement changes requested by health authorities

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1: Introduction and Study Rationale	Clarified terminology in description of study subjects, replacing "inoperable" with "unresectable" advanced, recurrent or metastatic esophageal squamous cell carcinoma	Revised to ensure consistency of terminology used across the study protocol
Section 1.1.6: Rationale for Dose Selection of Nivolumab in Combination with Ipilimumab (Arm A) and Chemotherapy (Arm B) in First-line ESCC Subjects	Expanded the rationale for dose selection in Arms A and B	The dose and schedule of the combination of nivolumab and ipilimumab tested in other tumor types and perceived to be safe and efficacious is been tested in this ESCC trial as well. Rationale for Arm B updated to reflect current approval by FDA of nivolumab 240mg for a variety of tumor types including melanoma UC and MSI-

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
		H/dMMR CRC, in addition to the tumor types already stated in the previous protocol version. Furthermore this dose is under review by other health authorities.
Section 3.1.1: Screening Phase	Clarified that an evaluable PD-L1 IHC test result by central lab would be required for randomization	Revised to specify the term "evaluable" (Sufficient quantity of tissue sample available for analysis) versus an indeterminate test conclusion (inconclusive results)
Section 3.1.1: Screening Phase; Section 5.1, Table 5.1-1 Screening Procedural Outline - All Subjects (CA209648); Section 5.3.1: Screening Safety Assessments	Removed the 28 day window for performance of screening assessments and procedures	Each screening assessment will have its own window and it is detailed in Table 5.1-1.
Section 3.1.3: Follow-up Phase; Section 3.5: Discontinuation of Subjects following any Treatment with Study Drug; Table 5.1-5: Follow-Up Procedural Outline - All subjects (CA209648)	Follow up 1 criteria date of discontinuation is greater than 30 days after last dose changed to 35 days	Correction of a protocol inconsistency; aligning with Section 3.5
Section 3.3.1: Inclusion Criteria	Clarified that an evaluable PD-L1 IHC test result by central lab would be required for subject randomization	Revised to clarify that a non-evaluable test result will not be accepted for subject randomization
Section 3.3.1: Inclusion Criteria	Revised length of contraception adherence for subjects of child bearing potential randomized to chemotherapy arms: duration of study treatment plus 5 half-lives of chemotherapy plus an additional 30 days for women and 90 days for men or per local chemotherapy drugs label, whichever is longer	Revised to meet requirements for duration of contraception as set by local labels for the chemotherapy drugs
Section 3.4.1: Prohibited and/or Restricted Treatments	Prohibited the use of botanical formulations approved for the treatment of cancer and added a wash out window period of 2 weeks prior to randomization	Botanical formulations approved for the treatment of cancer may potentially interfere with the interpretation of the study results therefore added to the prohibited medication list. A wash out period of two weeks prior to randomization is deemed adequate due to the low likelihood of DDI.
Section 3.4.1: Prohibited and/or Restricted Treatments	Added language to refer investigators to the local product labeling for the	Raise awareness and ensure investigator compliance to the local product labeling information for the chemotherapy drugs

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	chemotherapy drugs for additional prohibited and restricted concomitant medications	with regards additional prohibited and restricted concomitant medications not explicitly stated in the study protocol.
Section 3.4.3: Permitted Therapy	Clarified that regular concomitant use of bisphosphonates and RANK-L inhibitors for prevention or reduction of skeletal-related events in subjects with bone metastases is allowed if initiated prior to first dose of study therapy	Specified circumstances were the use of bisphosphonates and RANK-L inhibitors is allowed taking into consideration that these agents might be necessary for the prevention or reduction of skeletal-related events in patients with bone metastases
Section 3.4.3: Permitted Therapy	Added instructional text regarding subjects requiring concurrent palliative radiotherapy	Considering that the study has a PFS co-primary end-point and measurable disease is an inclusion criterion, palliative radiotherapy would permitted for non-target lesions only since this will lessen the chances of rendering a subject unevaluable per RECIST 1.1. Where palliative radiotherapy is required for a tumor lesion, then study treatment should be withheld for at least 1 week before, during, and 1 week after radiation and AEs should resolve to Grade $\leq$ 1 prior to resuming study therapy in order to minimize toxicities.
Section 4.5.1.1: Nivolumab plus Ipilimumab Dosing (Arm A	Removed the text referring to the 30 minute timeframe between infusions of nivolumab and ipilimumab	The detailed instructions are removed as they can be found in the pharmacy manual
Section 4.5.1.1, Table 4.5.1.1-1 Dose Schedule of Nivolumab and Ipilimumab in Arm A; Section 5.1. Table 5.1-2: On-treatment Assessments - Subjects in Nivolumab 3 mg/kg and Ipilimumab 1 mg/kg - Arm A in CA209648	Dosing of ipilimumab Q6W, window was extended from within 3 days before or after the scheduled date if necessary to 5 days	Increased window flexibility for ipilimumab to taking into account that drug is administered every 6 weeks to permit better synchronization with nivolumab dosing
Section 4.5.2.1: Dose Delay Criteria for Nivolumab and/or Ipilimumab (Arms A and B)	Removed dose delay for Grade 2 and 3 AST, ALT or Total Bilirubin abnormalities	Removed as this criterion is explicated under the 'Laboratory abnormalities' bullet point further below in the same section
Section 4.5.2.1: Dose Delay Criteria for Nivolumab and/or Ipilimumab (Arms A and B); Section 4.5.5.1: Nivolumab and/or Ipilimumab Treatment	Changed the dose delay requiring discontinuation of ipilimumab from > 8 weeks to > 12 weeks	> 8 weeks dose delay resulting to discontinuation would be too restrictive taking into consideration that ipilimumab is dosed every 6 weeks

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Discontinuation (Arms A and B)		
Section 4.5.4.2: Criteria to Resume Fluorouracil and Cisplatin Combination (Arm C)	Changed the timing criteria for discontinuation of treatment due to failure of recovery of chemotherapy toxicity from 6 weeks to 8 weeks	To correct a typo; duration was already stated 8 weeks elsewhere in the protocol
Section 4.5.5.1: Nivolumab and/or Ipilimumab Treatment Discontinuation (Arms A and B)	Added colitis, neurologic toxicity, as exceptions for discontinuation due to adverse events lasting > 7 days or recurring	Revised to align with the nivolumab IB
Section 4.5.5.1: Nivolumab and/or Ipilimumab Treatment Discontinuation (Arms A and B)	Added instructional text regarding discontinuation for Grade≥ 3 AST, ALT and bilirubin elevations and investigator consideration of abnormal ALT, AST and bilirubin values	Revised to align with the nivolumab IB
Section 5.1, Table 5.1-1: Screening Procedural Outline - All Subjects (CA209648); Table 5.1-2: On-treatment Assessments - Subjects in Nivolumab 3 mg/kg and Ipilimumab 1 mg/kg - Arm A in CA209648; Table 5.1-3:On-Treatment Assessments - Subjects in Nivolumab 240 mg Combined with Fluorouracil plus Cisplatin - Arm B in CA209648; Table 5.1-4: On-Treatment Assessments - Subjects in Fluorouracil and Cisplatin (FP) - Arm C in CA209648; Table 5.1-5: Follow-Up Procedural Outline - All subjects (CA209648); 5.3.1: Screening Safety Assessments; 5.3.2: On-Treatment Safety Assessments	Amylase and lipase removed from laboratory tests	Amylase and Lipase elevations have been observed with nivolumab or nivolumab plus ipilimumab treatment. However very few subjects reported associated symptoms (eg, abdominal pain) or radiographic findings (eg, stranding) consistent with pancreatitis. Thus, there does not seem to be clinical significance to the elevated laboratory values and therefore there is no evidence suggesting that routine monitoring of amylase and lipase is required
Section 5.1, Table 5.1-1: Screening Procedural Outline - All Subjects (CA209648); 5.3.1: Screening Safety Assessments	Added a required serum follicle stimulating hormone, (FSH) level > 40 mIU/mL result for females under the age of 55 years to confirm menopause.	To be consistent with the instructions in Section 3.3.3.
Section 5.1, Table 5.1-2: On-treatment Assessments - Subjects in Nivolumab 3 mg/kg and Ipilimumab 1 mg/kg - Arm A in	Removed procedures in column for every 3 cycles (every 6 weeks)	To simplify the table (details are entered in the note column)

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
CA209648		
Section 5.1, Table 5.1-2: On-treatment Assessments - Subjects in Nivolumab 3 mg/kg and Ipilimumab 1 mg/kg - Arm A in CA209648; Table 5.1-3:On-Treatment Assessments - Subjects in Nivolumab 240 mg Combined with Fluorouracil plus Cisplatin - Arm B in CA209648; Table 5.1-4: On-Treatment Assessments - Subjects in Fluorouracil and Cisplatin (FP) - Arm C in CA209648	Outcomes research assessments FACT-E and EQ-5D to be assessed at set time points post cycle 1 d1 visit regardless of treatment schedule. PRO administrations not coinciding with another study assessment visit can be done via a phone contact. Health care resource utilization will be assessed at every dosing visit	Clarified schedule of PROs and health care assessment administration
Section 5.1, Table 5.1-3:On-Treatment Assessments - Subjects in Nivolumab 240 mg Combined with Fluorouracil plus Cisplatin - Arm B in CA209648; Table 5.1-4:On-Treatment Assessments - Subjects in Fluorouracil and Cisplatin (FP) - Arm C in CA209648	Removed all procedures in column for cycle 1 days 2-5 and removed procedure dispense study treatment from cycles 2 and beyond days 2-5	This is a correction to an error in the study protocol, no assessments have to be performed from D2 to D5 as the subject will not necessarily come to the hospital
Section 5.3.1: Screening Safety Assessments	Physical examinations added to screening assessments	Correction to be consistent with the table in Section 5.1
Section 5.3.4: Imaging Assessment for the Study	Added text to account for the collection of additional imaging that may demonstrate tumor response or progression for tumor assessment and subsequent submission to the BICR.	To be consistent with Section 4.5.6

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.6.1 Tumor Samples	Added text stating that tissue samples submitted be assessed for quality with an H&E stain and only participants who have met tissue quality thresholds be assigned study drug	To be consistent with the clarification made in Section 3.3.1 and 3.1.1
Section 8.5: Interim Analysis	Text removed regarding number of final events exceeding the number specified per protocol (250 deaths) and that final boundary would not be recalculated using updated information fraction at interim.	As the number of deaths is a random number, details regarding the final boundary in case number of final events exceeds 250 will be specified in a separate document.
Section 10 GLOSSARY OF TERMS	Added definitions for PD-L1 Evaluable Status and PD-L1 Indeterminate Status	To be consistent with the clarification made in Sections 3.3.1, 3.1.1, and 5.6.1
All	Updated End Note reference numbering throughout	Duplicates and unnecessary references removed
All	Minor formatting and typographical corrections	Clarifications to minor formatting and typographical corrections