Official Title of Study:

A Randomized, Multicenter, Open-Label, Phase 3 Study of Nivolumab plus Ipilimumab or Nivolumab in Combination with Oxaliplatin plus Fluoropyrimidine versus Oxaliplatin plus Fluoropyrimidine in Subjects with Previously Untreated Advanced or Metastatic Gastric or Gastroesophageal Junction Cancer
(CheckMate 649: CHECKpoint pathway and nivoluMab clinical Trial Evaluation 649)

NCT Number: NCT02872116

Document Date (Date in which document was last revised): 16-Sep-2019

Protocol Number: CA209649
IND Number: 126,406
Ex-US Non-IND
EUDRACT Number 2016-001018-76
Date: 04-May-2016
Revised Date 16-Sep-2019

CLINICAL PROTOCOL CA209649

A Randomized, Multicenter, Open-Label, Phase 3 Study of Nivolumab plus Ipilimumab or Nivolumab in Combination with Oxaliplatin plus Fluoropyrimidine versus Oxaliplatin plus Fluoropyrimidine in Subjects with Previously Untreated Advanced or Metastatic Gastric or Gastroesophageal Junction Cancer

(CheckMate 649: CHECKpoint pathway and nivoluMab clinical Trial Evaluation 649)

Revised Protocol Number: 09
Incorporates Amendment 29 and Administrative Letter 08

[redacted]

24-hr Emergency Telephone Number
USA: [redacted]
International: [redacted]

BRISTOL-MYERS SQUIBB RESEARCH AND DEVELOPMENT

3401 Princeton Pike
Lawrenceville, NJ 08648
Avenue de Finlande 4
B-1420 Braine-l'Alleud, Belgium

be added to this document is also confidential and proprietary to BMS and must be kept in confidence in the same manner as the contents of this document. Any person who receives this document without due authorization from BMS is requested to return it to BMS or promptly destroy it. All other rights reserved. References to BMS in this protocol may apply to partners to which BMS has transferred obligations, eg, a Contract Research Organization (CRO).

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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 09	16-Sep-2019	• Incorporates Amendment 29 and Administrative Letter 08.
Amendment 29	16-Sep-2019	• Based on the data from the Keynote 062 study, PFS and OS Kaplan-Meier curves separation observed delay, the timing of PFS and OS analyses are updated with minimum follow up 12 and 24 months. In addition, to reduce variability of efficacy results, PFS population was expanded to all randomized subjects with PD-L1 CPS ≥ 5. • Per Amendment 29, a 480 mg Q4W nivolumab dosing option for subjects who receive nivolumab alone after treatment with nivolumab in combination with ipilimumab or FOLFOX/XELOX is allowed.
Administrative Letter 08	13-Feb-2019	• Updates address, telephone and fax numbers of the Medical Monitor [redacted].
Revised Protocol 08	15-Nov-2018	• Incorporates Amendment 26
Amendment 26	15-Nov-2018	• Based on recent internal data, added approximately 356 subjects into randomization, in total of approximately 2005 subjects will be randomized to keep sample size for primary analyses of PFS and OS in PD-L1 CPS ≥5 subjects for nivolumab in combination with chemotherapy vs chemotherapy.
Revised Protocol 07	14-Sep-2018	Incorporates Amendment 23 and Administrative Letter 04.
Amendment 23	14-Sep-2018	Major Changes • Incorporates the combined positive score (CPS) for PD-L1 expression into CA209649; the primary population is now subjects with PD-L1expression ≥5 by CPS rather than by the tumor proportion score (TPS) for subjects with nivolumab in combination with oxaliplatin and fluoropyrimidine compared to oxaliplatin and fluoropyrimidine. • The planned analysis of overall survival (OS) for nivolumab plus ipilimumab arm is changed to a secondary objective. • Objective response rate (ORR) has been changed to a secondary endpoint. • The primary, secondary, and exploratory objectives have been updated to reflect changes in subject population definition. • Second disease progression (PFS2) and time to secondary subsequent therapy (TSST) have been added as exploratory analyses. Information on subsequent treatment will be collected during follow-up period. • Statistical assumptions and considerations revised to reflect changes in study population and revised objectives. • Biomarker sampling has been adjusted based on new knowledge in this area of clinical research.
Administrative Letter 04	18-Jun-2018	Corrects approximate number of total randomized subjects to 1649.
Revised Protocol 06	11-Jun-2018	Incorporates Amendment 20

Document	Date of Issue	Summary of Change
Amendment 20	11-Jun-2018	• Per recommendation of the Data Monitoring Committee (DMC), as of 05-June-2018, the nivolumab plus ipilimumab arm is now closed. Subjects randomized to this arm prior to or on 05-June-2018 will continue to receive treatment with study drugs per protocol, and the study data will remain blinded until planned primary analysis.
Revised Protocol 05	29-May-2018	Incorporates Amendment 19
Amendment 19	29-May-2018	• Added that randomization of an additional 300 subjects beyond the originally planned 1349 subjects across the 3 study arms will allow for more robust analysis of the treatment effect of nivolumab in combination with ipilimumab or chemotherapy across different PD-L1 cutoffs in 1L GC/GEJ cancer.
Revised Protocol 04	05-Jan-2018	Incorporates Amendment 17
Amendment 17	05-Jan-2018	• Change the primary population to all comers in nivolumab in combination with oxaliplatin and fluoropyrimidine, • Add ORR by Blinded Independent Central Review (BICR) and PFS by BICR as primary endpoints in the nivolumab in combination with oxaliplatin and fluoropyrimidine and oxaliplatin plus fluoropyrimidine arms. • Clarify distal esophageal adenocarcinoma is eligible in the inclusion criteria. • Removal of the 28 day screening window, amylase and lipase removal from mandatory tests, clarification of procedures • Correction of minor formatting and typographical errors
Revised Protocol 03	10-May-2017	Incorporates Amendment 13
Amendment 13	10-May-2017	• Modified inclusion value for albumin to 3.0 g/dL. • Added clarification for traditional Chinese medicines. • Clarified that PDL1 result must be evaluable in order to be randomized and that tumor sample must be submitted on positively charged slides if not sent as a tumor block. • Added instructions for the administration of nivolumab and chemotherapy when administered on the same day. • Specified that capecitabine should be taken with food. • Clarified that outcome research assessments schedule is independent of dosing schedule, and removed some wording that was leading to confusion regarding the safety visits schedule and treatment beyond disease progression.
Revised Protocol 02	07-Dec-2016	Incorporates Amendment(s) 08
Amendment 08	07-Dec-2016	• Added a new randomization arm, nivolumab-plus-chemotherapy (XELOX or FOLFOX) to the study • Added Blinded Independent Central Review (BICR) of tumor images

Document	Date of Issue	Summary of Change
		• Clarified some study procedures, including limiting the treatment period with nivolumab to 2 years • Added safety recommendations for subjects receiving capecitabine
Revised Protocol 01	20-Oct-2016	Incorporates Amendment(s) 07 and Administrative Letter 01
Amendment 07	20-Oct-2016	• Provided reference to the newly-updated Nivolumab Investigator Brochure Version 15 in order to ensure the latest safety information is available, including updated algorithms for the management of side effects and contraception language • Clarified some study inclusion/exclusion criteria and procedures • Provided additional guidance on the implementation of RECIST 1.1 criteria
Administrative Letter 01	02-Aug-2016	Clarified the protocol instructions regarding the administration of chemotherapy and biomarker sampling
Original Protocol	04-May-2016	Not applicable

SYNOPSIS

Clinical Protocol CA209649

Protocol Title: A Randomized, Multicenter, Open-Label, Phase 3 Study of Nivolumab plus Ipilimumab or Nivolumab in Combination with Oxaliplatin plus Fluoropyrimidine versus Oxaliplatin plus Fluoropyrimidine in Subjects with Previously Untreated Advanced or Metastatic Gastric or Gastroesophageal Junction Cancer

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

- Nivolumab+ipilimumab: nivolumab 1 mg/kg administered IV over 30 minutes followed by ipilimumab 3 mg/kg administered IV over 30 minutes on Day 1 of each treatment cycle every 3 weeks for 4 doses (Cycles 1 to 4), followed by nivolumab 240 mg administered IV over 30 minutes on Day 1 of each treatment cycle every 2 weeks (Cycle 5 and beyond). **Closed to enrollment as of 05-June-2018.**
- Nivolumab+XELOX: nivolumab 360 mg administered IV over 30 minutes on Day 1 of each treatment cycle, oxaliplatin 130 mg/m^2 administered IV on Day 1 of each treatment cycle and capecitabine 1000 mg/m^2 administered orally twice daily on Days 1 to 14 of each treatment cycle, every 3 weeks, or
- Nivolumab+FOLFOX: nivolumab 240 mg administered IV over 30 minutes on Day 1 of each treatment cycle, oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2 and fluorouracil 400 mg/m^2 administered IV on Day 1 of each treatment cycle, and fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours (or per local standard) daily on Days 1 and 2 of each treatment cycle, every 2 weeks, or
- XELOX: oxaliplatin 130 mg/m^2 administered IV on Day 1 of each treatment cycle and capecitabine 1000 mg/m^2 administered orally twice daily on Days 1 to 14 of each treatment cycle, every 3 weeks, or
- FOLFOX: oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2 and fluorouracil 400 mg/m^2 administered IV on Day 1 of each treatment cycle, and fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours (or per local standard) daily on Days 1 and 2 of each treatment cycle, every 2 weeks.

Study drugs will be administered until disease progression (PD) (unless treatment beyond PD is permitted, in nivolumab-plus-ipilimumab and nivolumab-plus-chemotherapy arms; see Section 4.5.1.6 of the protocol), unacceptable toxicity, withdrawal of consent, or other reasons of discontinuation specified in the protocol.

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.

Study Phase: Phase 3

Research Hypotheses: In subjects with advanced or metastatic GC or GEJ cancer with PD-L1 combined positive score (CPS) ≥ 5, the administration of nivolumab plus ipilimumab will improve OS compared to oxaliplatin plus fluoropyrimidine.

In subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥ 5, the administration of nivolumab in combination with oxaliplatin plus fluoropyrimidine will improve PFS, or OS compared to oxaliplatin plus fluoropyrimidine.

Objectives:

Primary Objectives

Nivolumab in combination with oxaliplatin plus fluoropyrimidine vs oxaliplatin plus fluoropyrimidine:

- To compare OS in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥ 5
- To compare PFS, as assessed by BICR in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥ 5

Secondary Objectives

Nivolumab plus ipilimumab vs oxaliplatin plus fluoropyrimidine:

- To compare OS in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥ 5 or in all randomized
- To evaluate OS in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥ 10 or 1
- To evaluate PFS, as assessed by BICR, in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥ 10, 5, 1 or all randomized subjects
- To evaluate ORR, as assessed by BICR, in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥ 10, 5, 1 or all randomized subjects
- To compare the time to symptom deterioration (TTSD) as assessed using the Gastric Cancer Subscale (GaCS) of the Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥ 5 or all randomized subjects.

Nivolumab in combination with oxaliplatin plus fluoropyrimidine vs oxaliplatin plus fluoropyrimidine:

- To compare OS in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥ 1 or all randomized subjects
- To evaluate OS in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥ 10
- To evaluate PFS, as assessed by BICR, in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥ 10, 1, or all randomized subjects
- To evaluate ORR, as assessed by BICR, in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥ 10, 5, 1, or all randomized subjects

Key Exploratory Objectives

Nivolumab in combination with oxaliplatin plus fluoropyrimidine vs oxaliplatin plus fluoropyrimidine:

- To assess TTSD using GaCS of FACT-Ga in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥ 5 or all randomized subjects

For both comparisons: Nivolumab in combination with oxaliplatin plus fluoropyrimidine vs oxaliplatin plus fluoropyrimidine and Nivolumab plus ipilimumab vs oxaliplatin plus fluoropyrimidine :

- To assess PFS and ORR, as assessed by the investigator in subjects with advanced or metastatic GC or GEJ cancer across PD-L1 CPS cut-offs
- To evaluate Duration of Response (DOR) as assessed by BICR and by investigator, in subjects with advanced or metastatic GC or GEJ
- To evaluate the durable response rate (objective response lasting continuously > 6 months) as assessed by BICR and by investigator, in subjects with advanced or metastatic GC or GEJ cancer.
- To evaluate at 18, 24, and 36 months survival rates in subjects with advanced or metastatic GC or GEJ cancer
- To evaluate second disease progression (PFS2) or time to second subsequent line therapy (TSST) in subjects with advanced or metastatic GC or GEJ cancers
- To assess PFS, ORR as assessed by either BICR or investigator, OS in subjects with advanced or metastatic GC or GEJ cancer across TPS cut-offs.
- To assess the overall safety and tolerability of nivolumab plus ipilimumab or nivolumab in combination with oxaliplatin plus fluoropyrimidine and oxaliplatin plus fluoropyrimidine in subjects with advanced or metastatic GC or GEJ cancer
- To explore potential biomarkers predictive of or associated with clinical efficacy (OS, PFS and ORR) and/or incidence of AEs of nivolumab plus ipilimumab or nivolumab in combination with oxaliplatin plus fluoropyrimidine including but not limited to microsatellite instability (MSI) status, tumor mutational burden

(TMB) [redacted] and inflammatory signatures in subjects with advanced or metastatic GC or GEJ cancer.

- To compare TTSD as assessed using GaCS of FACT-Ga in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥ 10, or 1.

More exploratory objectives are listed in the protocol.

Study Design:

This is a Phase 3, randomized, open-label, three-arm study of nivolumab plus ipilimumab or nivolumab in combination with oxaliplatin plus fluoropyrimidine versus oxaliplatin plus fluoropyrimidine in subjects with previously untreated advanced or metastatic GC or GEJ cancer. As of 05-June-2018, the nivolumab plus ipilimumab arm is closed to enrollment. Subjects randomized to this arm prior to or on 05-June-2018 will continue to receive treatment with study drugs per protocol and the study data will remain blinded for the planned primary analysis.

The original study design (before Amendment 08) had two arms. After signing the informed consent form, and upon confirmation of the subject's eligibility, subjects were randomized in an open-label fashion (1:1 ratio) to either the nivolumab-plus-ipilimumab arm or the chemotherapy (XELOX or FOLFOX) arm.

Amendment 08 added a new, nivolumab-plus-chemotherapy (XELOX or FOLFOX) arm. Approximately 1266 subjects were to be randomized in an open-label fashion (1:1:1 ratio) to nivolumab plus ipilimumab, nivolumab in combination with chemotherapy (XELOX or FOLFOX), or chemotherapy (XELOX or FOLFOX). Randomization will be stratified by TPS PD-L1 status (≥ 1% vs < 1% or indeterminate), region (Asia vs US vs Rest of World), ECOG performance status (0 vs 1), and chemotherapy regimen (XELOX vs FOLFOX). The study enroll subjects regardless PDL1 tumor expressing. During enrollment, the proportion of subjects with or without PD-L1 tumor expression will be monitored in pooled fashion, and may be re-assessed in case it does not reflect study assumptions (ie, subjects with PD-L1 tumor expression ≥ 1% is approximately 40% of all comers).

Amendment 19 added approximately 300 subjects to the study, in total approximately 1649 subjects will be randomized. The nivolumab plus ipilimumab arm was closed to enrollment as of 05-June-2018. Subjects randomized to treatment in this arm prior to or on 05-June-2018 will continue to receive treatment with study drugs per protocol, and the study data will remain blinded for the planned analysis. Per Amendment 20, subjects will be randomized in an open-label fashion (1:1) to either the nivolumab-plus-chemotherapy (XELOX or FOLFOX) or the chemotherapy arm (XELOX or FOLFOX).

Per Amendment 23, PD-L1 expression has incorporated CPS scoring for study analyses as described in detail in Section 1.1.13. However, the stratification factor of tumor proportion score (TPS) remains unchanged for consistency.

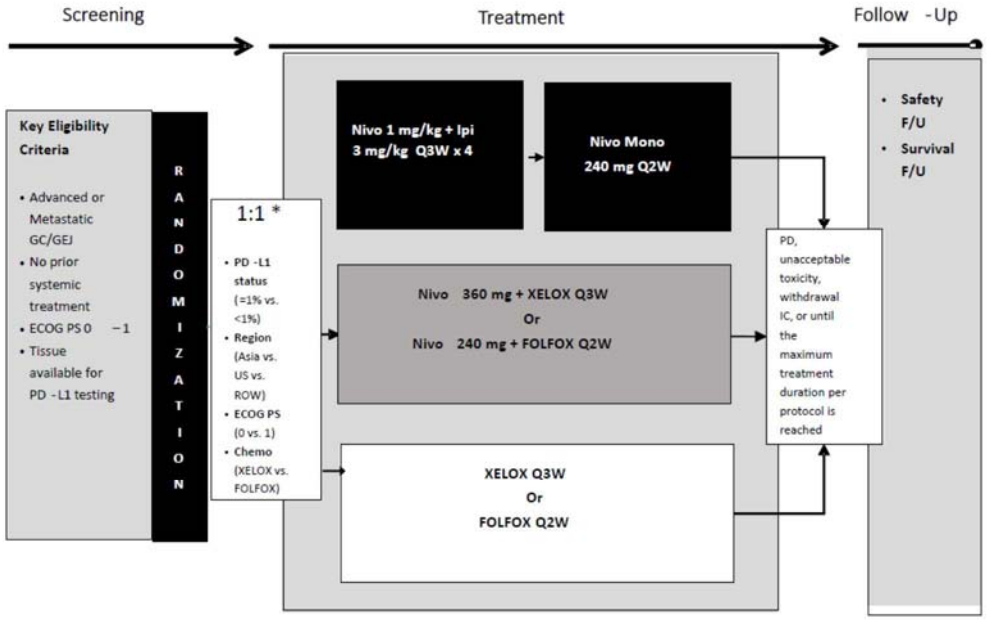
Amendment 26 is adding approximately 356 subjects to the study, and in total approximately 2005 subjects will be randomized. [redacted] Given the uncertainty about the CPS ≥ 5 prevalence, the sample size may need to be further adjusted based on the monitoring of the prevalence to keep sample size for the primary population.

The treatment will be given until PD (unless treatment beyond PD is permitted, in nivolumab-plus-ipilimumab and nivolumab-plus chemotherapy arms; see Section 4.5.1.6 of the protocol), unacceptable toxicity, or subject withdrawal of consent, whichever comes 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.

Per Amendment 29, a 480 mg Q4W nivolumab dosing option for subjects who receive nivolumab alone after treatment with nivolumab in combination with ipilimumab or FOLFOX/XELOX is allowed.

Study Schematic:



* Nivolumab + Ipilimumab arm is closed to enrollment as of 05-June-2018.

Study Population:

Subjects must meet all eligibility criteria. The key inclusion and exclusion criteria are as follows:

Key Inclusion Criteria:

a) All subjects must have inoperable, advanced, locally advanced or metastatic GC or GEJ or distal esophageal carcinoma and have histologically confirmed predominant adenocarcinoma.

b) Subject must be previously untreated with systemic treatment including HER 2 inhibitors given as primary therapy for advanced or metastatic disease.

c) Allowed Prior Therapies: Prior adjuvant or neoadjuvant chemotherapy, radiotherapy and/or chemoradiotherapy for GC or GEJ cancer are permitted as long as the last administration of the prior regimen (whichever was given last) occurred at least 6 months prior to randomization. Palliative radiotherapy is allowed and must be completed 2 weeks prior to randomization.

d) Subject must have at least one measurable lesion or evaluable disease by CT or MRI per RECIST 1.1 criteria.

e) ECOG performance status score of 0 or 1.

f) Tumor tissue must be provided for PD-L1 biomarker analyses prior to randomization.

Key Exclusion Criteria:

a) Known Her2 positive status

b) Subjects with untreated CNS metastases.

c) Subjects with ascites which cannot be controlled with appropriate interventions.

d) Subjects with > Grade 1 peripheral neuropathy.

e) Treatment with botanical preparations (eg herbal supplements or traditional Chinese medicines) intended to treat the disease under study within 2 weeks prior to randomization/treatment.

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

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

Study Drugs for CA209649		
Medication	**Potency**	**IP/Non-IP**
Nivolumab	10 mg/mL	IP
Ipilimumab	5 mg/mL	IP
Oxaliplatin	5 mg/mL	IP
Fluorouracil	50 mg/mL	IP
Leucovorin	50 mg/mL	IP
Capecitabine	150 mg and 500 mg tablets	IP

Study Assessments:

The primary endpoints of this study are OS and PFS (by BICR) in subjects with PD-L1 CPS ≥ 5 (nivolumab with oxaliplatin plus fluoropyrimidine vs oxaliplatin plus fluoropyrimidine).

Key secondary endpoints include: OS in subjects with PD-L1 CPS ≥ 5, ≥ 1 and in all randomized subjects and TTSD in subjects with PD-L1 CPS ≥ 5 or all randomized subjects (nivolumab plus ipilimumab vs oxaliplatin plus fluoropyrimidine) and OS with PD-L1 CPS ≥ 1 or all randomized subjects (nivolumab in combination with oxaliplatin plus fluoropyrimidine vs oxaliplatin plus fluoropyrimidine)**.** Other secondary and exploratory endpoints include ORR, DOR and DRR.

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) from first dose up to and including Week 48, and then every 12 weeks (± 7 days) thereafter, regardless of treatment schedule, until PD 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.

Statistical Considerations:

Sample Size Determination

Randomization Schema

The original study design (before Amendment 08) had 2 arms, with subjects being randomized in a 1:1 ratio to the nivolumab plus ipilimumab or to the oxaliplatin plus fluoropyrimidine arm (XELOX or FOLFOX; arm will be further referred to as chemotherapy arm). Amendment 08 added a new arm: nivolumab in combination with oxaliplatin plus fluoropyrimidine (XELOX or FOLFOX; arm will be further referred to as nivolumab plus chemotherapy arm). The IRT switched to a 1:1:1 randomization at all the participating sites when this third arm was ready to be opened on 27-Mar-2017. Up until that point, there were 83 subjects randomized in the 1:1 randomization to nivolumab plus ipilimumab and chemotherapy arm. In Amendment 08, it was planned to randomize 1266 subjects at 1:1:1 ratio to nivolumab plus ipilimumab, chemotherapy and nivolumab plus chemotherapy arms. The total number of subjects to be randomized was planned to be 1349.

Newly available internal and external data suggested a stronger predictability of PD-L1 CPS than TPS of immunotherapy treatment effects. However, uncertainty still exists of CPS at different cutoffs when extrapolated to

first line (1L) metastatic setting in GC and GEJ. To ensure sufficient sample size for evaluating the correlation of efficacy and different CPS cutoffs and to keep continuity of enrollment of the study, on 29-May-2018, Amendment 19 was approved to allow additional 300 subjects to be randomized under 1:1:1 ratio for a total sample size of 1566 to the 3 treatment arms.

Per DMC recommendation, randomization to the nivolumab plus ipilimumab arm was stopped on 05-June-2018. The subjects who were already randomized to treatment in this arm prior to or on 05-June-2018 continued to receive study treatment per protocol, and the study data remained blinded for the planned analysis. As such, the 1:1:1 randomization was carried through on 05-Jun-2018. These changes were implemented in Amendment 20. At this point, a total of 1098 subjects were randomized under 1:1:1 ratio. In addition there were 83 subjects randomized to nivolumab plus ipilimumab and to chemotherapy arms (prior to Amendment 08). Following Amendment 20, subjects were to be randomized in 1:1 ratio to either the nivolumab plus chemotherapy or the chemotherapy arm.

[redacted] Therefore, the enrollment was extended to ensure that the study was appropriately powered for PFS and OS primary endpoints in the CPS ≥ 5 population. To allow for this, Amendment 26 increased the total sample size from 1649 to approximately 2005. This resizing of the total population was to ensure that the sample size of the enriched population for the primary analyses (subjects with CPS ≥ 5) was the same as was specified in Amendment 23 to maintain the same power under the statistical assumptions as stated in Amendment 23.

The accrual was completed in May 2019 and in total 2032 subjects were randomized. It is estimated that 1582 subjects were concurrently randomized to nivolumab plus chemotherapy and to chemotherapy and that 815 subjects were concurrently randomized to nivolumab + ipilimumab and chemotherapy.

General Assumptions of Sample Size Determinations:

Primary Endpoints Family:

For the comparison of nivolumab plus chemotherapy vs chemotherapy both PFS and OS are primary endpoints.

Type I Error Splitting for Primary Endpoints Family:

For the purpose of sample size calculation, the family-wise error rate of 5% will be split as follows:

1. Comparison of PFS between nivolumab plus chemotherapy and chemotherapy in subjects with PD-L1 CPS ≥ 5, with alpha of 2%
2. Comparison of OS between nivolumab plus chemotherapy and chemotherapy in subjects with PD-L1 CPS ≥ 5, with alpha of 3%

Population for Primary Endpoints:

As mentioned in Section 1.1.13, the population for the primary endpoints will be all randomized subjects with PD-L1 CPS ≥ 5. For the design purpose, the prevalence was assumed to be 35% of all randomized subjects.

Sample Size: Nivolumab plus Chemotherapy vs Chemotherapy

Progression Free Survival

All concurrently randomized subjects to N+CT and CT arms with PD-L1 CPS ≥ 5 will be used for the PFS analysis. Given the delayed separation in the PFS distributions between pembrolizumab + chemotherapy and chemotherapy, the PFS analysis will be conducted after a minimum of 12 months follow-up after the last patient is randomized.

As such, the PFS analysis will be conducted after the following criteria are all met:

- CPS scoring by central laboratories is complete
- a minimum follow-up of 12 months

The HR is modelled as a 2-piece hazard ratio with a delayed effect between 3 and 6 months (a HR of 1 versus chemotherapy for the first 3 or 6 months) followed by a constant HR of 0.56. With 12 months minimum follow-up it

is expected that the number of events will range between 497 and 506 respectively and the power will range approximately between 99% and 60% with a Type I error of 2% (two-sided) (see Table 1 below).

The primary PFS analysis will be based on all the events observed at time of database lock.

Table 1: Summary of Sample Size Parameters and Schedule of Analyses for PFS (Nivolumab plus Chemotherapy vs Chemotherapy)

	3 months Delay	6 months Delay
# subjects with PD-L1 CPS ≥5[a]	554	554
Hypothesized delayed period	3	6
Hypothesized HR after delayed period	0.56	0.56
Hypothesized median in control arm	5.5 months	5.5 months
Significance level (2-sided)	0.02	0.02
Enrollment Period (from start of 1:1:1)	25.4 months	25.4 months
Minimum follow-up / Expected number of events[a,b,c]	12 months / 497	12 months / 506
Time of Analysis	37.4 months	37.4 months
Power[b]	99%	60%
Average HR[b]	0.66	0.8

[a] Based on 35% prevalence of PD-L1 CPS ≥ 5

[b] Results based on simulations.

[c] Number of events for the nivolumab plus chemotherapy vs. chemotherapy comparison in total.

Overall Survival

The interim analysis will be conducted after at least 12 months minimum follow-up, and the final analysis will be conducted after at least 24 months minimum follow-up.

With 24 months minimum follow-up at final analysis it is expected that 466 events will be observed. With an average HR of 0.74 modelled as a 2-piece hazard ratio, a delayed effect with a HR of 1 versus chemotherapy for the first 6 months followed by a constant HR of 0.65 the power will be approximately 85% with a Type I error of 3% (two-sided) (See Table 2).

Table 2: Summary of Sample Size Parameters and Schedule of Analyses for OS (Nivolumab plus Chemotherapy vs Chemotherapy)

# with PD-L1 CPS ≥ 5[a]	554
Hypothesized delayed period	6 months
Hypothesized HR after delayed period	0.65
Hypothesized median in control arm	11.1 months
Significance level (2-sided)	0.03
Enrollment Period (from start of 1:1:1)	25.4 months
INTERIM ANALYSIS #1 for OS	
Minimum follow-up/Expected number of events[a,b,c]	12 months/395
Time of analysis[d]	37.4 months
Significance level[e]	0.0164
Power	64%
FINAL ANALYSIS	
Minimum follow-up/Expected number of events[a,b,c]	24 months/466
Time of analysis[d]	49.4 months
Significance level	0.0252
Power[b]	85%
Average HR	0.74

[a] Based on a 35% prevalence of PD-L1 CPS ≥ 5.

[b] Results based on simulations

[c] Number of events for the nivolumab plus chemotherapy vs. chemotherapy comparison in total.

[d] After first patient randomized to nivolumab + chemotherapy or chemotherapy in 1:1:1 randomization.

[e] Significance levels will be calculated based on the actual number of deaths at each interim analysis

For the OS interim and final analyses, all the events reported in the database at time of database lock will be used for the primary analyses.

Primary Efficacy Measures

Overall survival (OS). 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 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 subsequent anti-cancer therapy. Subjects who did not have any on-study tumor assessments and did not die (or died after initiation of 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 prior to or on the initiation of the subsequent anti-cancer therapy.

Secondary Efficacy Measures

Time to Symptom Deterioration (TTSD) is defined as the time from randomization until a clinically meaningful decline from baseline in GaCS score. A clinically meaningful deterioration is defined as a reduction of 8.2 points in the GaCS score. Subjects who do not deteriorate will be censored at the time of their last GACS assessment. Subjects without baseline GaCS assessment will be censored on the randomization date. Those with baseline GaCS, who do not have any GaCS assessments after randomization will be censored on the day after randomization.

Objective Response Rate (ORR) as assessed by BICR is defined as the number of subjects with a best overall response (BOR) of CR or PR divided by the number of measurable subjects with target lesion at baseline. BOR is defined as the best response designation as determined by the BICR, recorded between the date of randomization and the date of objectively documented progression (per RECIST 1.1 as determined by the BICR) or the date of subsequent anti-cancer therapy, whichever occurs first. For subjects without documented progression or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination.

Efficacy Analyses

Strong Control Of Type I Error for Primary and Secondary endpoints

For design purposes, the alpha was split using Bonferroni method between the 2 primary endpoints:

1) Comparison of PFS between nivolumab plus chemotherapy and chemotherapy in subjects with PD-L1 CPS ≥ 5, with alpha of 2%
2) Comparison of OS between nivolumab plus chemotherapy and chemotherapy in subjects with PD-L1 CPS ≥ 5, with alpha of 3%

For analyses purposes of primary and key secondary endpoints the Bonferroni-based graphical approach. will be used and full details will be provided in the statistical analysis plan.

The alpha from the PFS of N+CT vs CT in PD-L1 CPS ≥ 5 testing will be carried to the testing of OS of N+I vs CT in PD-L1 CPS ≥ 5 analysis, should the PFS analysis be statistically significant. If OS of N+CT vs CT is significantly superior in subjects with PD-L1 CPS ≥ 5 then the inherited alpha will be shared equally to secondary endpoints of OS of N+CT vs CT in PD-L1 CPS ≥ 1 subjects and OS of N+I vs CT in PD-L1 CPS ≥ 5. The comparison of OS for N+I vs CT in PD-L1 CPS ≥ 5 may inherit alpha independently from the two primary endpoints and will be tested only once after 36 months of minimum follow-up. The alpha that will be allocated to the comparison of OS for N+I vs CT in PD-L1 CPS ≥ 5 will be 1.5%, 2% or 3.5% depending on the outcome of the primary endpoints for N+CT vs CT. The SAP will document the details of the actual alpha allocation to the secondary endpoints.

The timing of the efficacy analyses is described in Table 3.

Table 3: Timing of Analyses

	Endpoints		
Timing of Analysis	**PFS N+CT vs CT in all randomized subjects with PD-L1 CPS ≥ 5**	**OS N+CT vs CT in all randomized subjects with PD-L1 CPS ≥ 5**	**OS N+I vs CT in all randomized subjects with PD-L1 CPS ≥ 5**
12-month minimum FU	X	X (IA)	
24-month minimum FU[a]		X (FA)	X

[a] FU: follow-up. Twenty-four months minimum follow-up from last patient randomized to N+CT or CT, corresponds to approximately 36-month minimum follow-up for N+I vs CT.

TABLE OF CONTENTS

1 INTRODUCTION AND STUDY RATIONALE

CA209649 is a Phase 3, randomized, open-label study of nivolumab plus ipilimumab or nivolumab in combination with oxaliplatin plus fluoropyrimidine vs oxaliplatin plus fluoropyrimidine in subjects with previously untreated advanced or metastatic gastroesophageal junction (GEJ) or gastric cancer (GC). This study will determine if nivolumab plus ipilimumab improves overall survival (OS) vs the standard of care, oxaliplatin plus fluoropyrimidine, in subjects with GC/GEJ cancer with enriched PD-L1 expression by combined positive score (CPS); or whether nivolumab in combination with oxaliplatin plus fluoropyrimidine improves OS or PFS vs the standard of care, oxaliplatin plus fluoropyrimidine, in subjects with GC/GEJ cancer with enriched PD-LI expressing by CPS. Additional objectives include further characterization of efficacy, safety and tolerability, pharmacokinetics (PK), patient-reported outcomes, and potential predictive biomarkers of nivolumab in combination with ipilimumab or nivolumab in combination with oxaliplatin plus fluoropyrimidine in subjects with GC/GEJ whose tumors do or do not express PD-L1.

1.1 Study Rationale

1.1.1 Rationale for Investigating Advanced or Metastatic GC/GEJ in the First Line Setting

Gastric cancer is the 5th leading cancer and the 3rd leading cause of cancer-related deaths worldwide. The incidence of GC varies with different geographic regions, with over 70% of GCs occurring in developing countries.[1] Gastric cancer often presents as advanced disease upon diagnosis, comprising approximately 40% of newly diagnosed cases in the United States (US) and Europe, and approximately 20% in Japan and Korea, where early detection is common.[2]

Gastric cancer, including GEJ carcinoma, is a heterogeneous disease with several established risk factors, including environmental, genetic and behavioral risks. There has been a steady decline in GC mortality attributable to dietary and lifestyle changes worldwide[3] and to decreasing infection with *Helicobacter pylori,* which is considered the main cause in Asian countries.[4] However, the incidence of GEJ tumors and esophageal adenocarcinoma (EAC) has increased considerably due to increases in risk factors such as obesity and gastroesophageal reflux disease.[1]

Gastroesophageal junction cancer anatomically straddles the distal esophagus and proximal stomach; due to its location and given that, like GC, the majority of GEJ tumors are adenocarcinomas, GEJ tumors are frequently grouped together with GC. Adenocarcinoma is further classified into 2 distinct types: intestinal (well-differentiated) or diffuse (undifferentiated).[5]

Until optimal, tumor-specific treatment strategies are defined, advanced and metastatic GEJ cancer is treated and managed in a similar fashion to GC.[6,7] As current understanding of EAC's, are that they share similar disease and molecular characteristics[8] as GEJ and GC adenocarcinomas, EACs are managed and treated similar to those tumors per treatment guidelines and clinical practice.[9,10] Platinum compounds (oxaliplatin and cisplatin) and fluoropyrimidines (5-fluorouracil, capecitabine, and tegafur/gimeracil/oteracil potassium [S1]) are generally considered as first-line (1L), standard-of-care treatment options in metastatic GC and GEJ cancer across geographic

regions.[11,12,13] These platinum/fluoropyrimidine combinations are also generally accepted as active comparators in Phase 2 or Phase 3 randomized studies by health authorities worldwide. The different biological characteristics and treatment approaches among regions result in different survival outcomes, with median overall survival (mOS) durations of 12 to 14 months in Asian countries and 8 to 11 months in the US and Europe.[14,15,16.] While these cytotoxic agents are clinically active, with a 30% to 50% objective response rate (ORR) in the 1L GC treatment setting, this clinical activity is accompanied by high toxicity.[14,15,16,17] Grade 3/4 toxicities up to 77% have been reported for platinum doublets and > 80% for triplet regimens.[14,15,17,18] Hematological toxicity is the major problem; Grade 3/4 neutropenia has been reported in approximately 40% of patients treated with platinum doublets, and has increased to 82% when docetaxel was added on.[14,17,18] Renal toxicity and neuropathy are the main reasons for discontinuation of platinum treatment. Gastrointestinal complaints are also common.[14,15,17,18] In addition, despite ORRs of 30% to 50%, chemotherapy has resulted in few patients achieving complete response (CR); therefore, new treatment options are needed to improve survival and response as well as decrease toxicity in 1L GC/GEJ cancer.

In the past decade, multiple new investigational drugs with mainly molecular targets have been investigated in the 1L setting as add-ons to backbone platinum and fluoropyrimidine treatment. These agents, with the exception of trastuzumab, which targets the Her2-positive population,[19] have failed to show a survival benefit in randomized trials. The reasons include regional differences in efficacy, with the highest survival rate but smallest benefit noted in Asia and the shortest mOS but greatest benefit in Western countries.[14,18,19] Thus, a regional approach might be appropriate in 1L GC/GEJ treatment development, and this study will mainly focus on Western countries where great unmet medical needs are present.

1.1.2 Rationale for the Combined Targeting of PD-1 and CTLA-4 in Advanced or Metastatic GC/GEJ Cancer

Immunotherapeutic approaches have demonstrated clinical efficacy in several advanced cancer types, including melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC) and gastric cancer (GC).[20,21,22,23] Nivolumab (BMS-936558), a programmed cell death protein-1 (PD-1) antibody, and ipilimumab (BMS-734016), a cytotoxic T-cell lymphoma-4 (CTLA-4) antibody, are such immunotherapies that have been approved in the US, Europe, Japan and other countries.[24,25,26,27]

Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve antitumor activity.[28] In vitro combinations of nivolumab plus ipilimumab have increased 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.[28] 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 objective response rate 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. In this study, the combination of nivolumab and ipilimumab has demonstrated increased benefit compared to either ipilimumab or nivolumab monotherapies in subjects with advanced melanoma.[29]

In GC patients, tumors with PD-L1 expression have been reported to be associated with depth of muscle invasion, tumor size, and lymph node metastasis. The survival of patients with PD-L1 or PD-L2 expressing tumors is significantly worse than for those patients without PD-L1/PD-L2 expressing tumors. PD-L1 or PD-L2 expressing tumors have been reported in approximately 22% to 40% of GC and PD-L1 has been suggested as a prognostic marker.[30,31] More and more data of PD-L1 expression in GC has become available since this study was originally designed. These data suggest that PD-L1 is an independent prognosis factor while other data suggest that its use as prognosis factor may not be proven.[32,33,34,35,36]

The blockage of PD-1/PD-L1/PD-L2 might improve the survival of GC patients. Anti PD-1 and PD-L1 inhibitors (eg, nivolumab, pembrolizumab, and avelumab) have been investigated in GC treatment and have demonstrated anti-tumor activity.[37,38 39]

Treatment with pembrolizumab achieved a 33% ORR by investigator assessment and 22% by central data review in GC subjects with PD-L1 expressing tumors.[38] The 6-month progression-free survival (PFS) rate was 26% and median PFS was 1.9 months (95% CI: 1.8, 3.5). The 6-month OS rate was 66% and mOS was 11.4 months (95% CI: 5.7, NR). PD-L1 expressing tumors (cutoff 1%) were reported in 40% of GC patients in this study, which is consistent with previous reports.[38]

Preliminary data for second line (2L) and switching maintenance use of avelumab, an anti-PD-L1 IgG1 antibody, in advanced GC have been recently reported. The ORRs were 15% and 7.3%, the 6-month PFS rates were 19% and 34%, and the median PFS were 2.9 months and 3.5 months in avelumab as 2L and switching maintenance therapy, respectively.[39]

1.1.2.1 Previous Studies of Nivolumab and Ipilimumab in GC

In addition to studies performed in subjects with melanoma treated with nivolumab and/or ipilimumab, BMS has conducted two studies in the treatment of GC/GEJ cancer: CA184162 (ipilimumab alone) and CA209032 (nivolumab alone and in combination with ipilimumab).

CA184162 compared ipilimumab monotherapy 10 mg/kg (IV every 3 weeks x 4 doses, followed by ipilimumab 10 mg/kg IV every 12 weeks) to best supportive care (BSC) in subjects with unresectable locally advanced or metastatic GC/GEJ cancer who did not show evidence of disease progression following 1L or lead-in chemotherapy. A majority (88%) of subjects in the BSC arm continued to receive the fluoropyrimidine therapy that they had received during the lead-in period, ie, they were on active concomitant chemotherapy during the study.

A total of 114 subjects were randomized, 57 subjects to each group. The primary endpoint of the study was immune-related progression-free survival (irPFS) as per assessment of an Independent Review Committee (IRC). The endpoint was achieved at the time of interim analysis. At the interim analysis, the median irPFS in the ipilimumab and BSC groups were 2.92 months and 4.90 months, respectively. The rates of irPFS at 6 months in the ipilimumab and BSC groups were 22.3% and 38.5%, respectively. In the final analysis, the median OS (mOS) in the ipilimumab 10 mg/kg group and in the BSC group were 12.7 months [95% CI: 10.5, 18.9] and 12.1 months [95% CI: 9.3, Not Estimable], respectively. Hence, ipilimumab did not improve irPFS and OS compared to placebo in the 1L maintenance setting.[40]

CA209032 is an ongoing, open-label, multi-center Phase 1/2 study to investigate the safety and efficacy of nivolumab monotherapy or nivolumab plus ipilimumab combination therapy in multiple tumor types including GC/GEJ, and esophageal adenocarcinoma. The following dose cohorts enrolled subjects with GC/GEJ cancer who had previously received at least one prior therapy, and more than 80% of subjects received more than 2 prior therapies:

- N3 monotherapy cohort: nivolumab 3 mg/kg IV every 2 weeks (n = 59)
- N1+I3 cohort: nivolumab 1 mg/kg + ipilimumab 3 mg/kg, IV every 3 weeks x 4 doses, followed by nivolumab 3 mg/kg IV every 2 weeks (n = 49);
- N3+I1 cohort: nivolumab 3 mg/kg + ipilimumab 1 mg/kg, IV every 3 weeks x 4 doses, followed by nivolumab 3 mg/kg IV every 2 weeks (n = 52).

Table 1.1.2.1-1 summarizes the preliminary efficacy data obtained in CA209032.

Table 1.1.2.1-1:	**Clinical Activity of Nivolumab Monotherapy, and Nivolumab plus Ipilimumab Combination Therapy in Subjects with GC/GEJ Cancer (CA209032)**		
	N3 monotherapy N = 59	**N3+I1 N = 52**	**N1+I3 N = 49**
Population	**> 1L Prior therapy**		
Confirmed ORR, % (95% CI)	13.6 (6.0 - 25.0)	10.2 (3.4 - 22.2)	26.1 (14.3 - 41.1)
Duration of Response, mos. (95% CI)	7.1 (3.0 - 13.2)	NA (2.5 - NA)	5.6 (2.8 - NA)
PFS rate at 24 wks, % (95% CI)	17.7 (9.0 - 28.7)	8.8 (2.8 - 19.1)	23.9 (12.4 - 37.5)
Median PFS, mos (95% CI)	1.36 (1.25 - 1.51)	1.58 (1.38 - 2.6)	1.45 (1.25 - 3.94)
1-year OS rate, % (95% CI)	36 (21 - 51)	NA	34 (19 - 50)
Median OS, mos (95% CI)	5.03 (3.35 - 12.42)	4.83 (3.02 - 9.07)	6.87 (3.61 - NA)
Median length of follow-up, mos (range)	16.78 (1.86 - 24.79)	6.26 (1.07 - 13.28)	8.54 (0.93 - 12.40)

N3: nivolumab; 3 mg/kg; I1: ipilimumab, 1mg/kg; N1: nivolumab, 1 mg/kg: I3: ipilimumab, 3 mg/kg; ORR: objective response rate; PFS: progression-free survival; mOS: median overall survival; CI: confidence interval; 1L: first line.
Data base lock: Nov 2015

Table 1.1.2.1-2 presents preliminary data from CA209032 describing the clinical activity of nivolumab monotherapy and nivolumab-plus-ipilimumab combination therapy in subjects with GC/GEJ cancer by PD-L1 status at a 1% cutoff.

Clinical activity was observed in subjects with both PD-L1 expressing and non-expressing tumors, although there was a greater magnitude of efficacy in the subjects with PD-L1 expressing tumors with both nivolumab alone and in combination with ipilimumab.

Table 1.1.2.1-2:	**Clinical Activity of Nivolumab Monotherapy and in Combination with Ipilimumab in GC/GEJ Cancer by PD-L1 Status, Using 1% Cut Off, CA209032**					
	PD-L1	**ORR, % (n/N)**	**mDOR Mon (95% CI)**	**DCR % (n/N) CR/PR/SD**	**mPFS (mon)**	**mOS (mon)**
N3 Q2W	**≥ 1%**	26.7 (4/15)	7.1 (6.8 - 7.1)	33.3 (5/15)	1.33 (1.15 - 2.63)	3.35 (1.5 - 13)
N3 Q2W	**< 1%**	12 (3/25)	13.2 (3 - 13.2)	40 (10/25)	1.54 (1.22 - 2.79)	7.72 (3.3 - 16.1)

Table 1.1.2.1-2: Clinical Activity of Nivolumab Monotherapy and in Combination with Ipilimumab in GC/GEJ Cancer by PD-L1 Status, Using 1% Cut Off, CA209032						
	PD-L1	**ORR, % (n/N)**	**mDOR Mon (95% CI)**	**DCR % (n/N) CR/PR/SD**	**mPFS (mon)**	**mOS (mon)**
N1+I3	**≥ 1%**	44.4 (4/9)	NA (2.8 - NA)	55.5 (5/9)	4.37 (0.99 - NA)	NA (2.5 - NA)
N1+I3	**< 1%**	20.7 (6/29)	5.6 (2.7 - NA)	41.4 (12/29)	1.45 (1.18 - 3.94)	6.47 (3.09 - 9.79)
N3+I1	**≥ 1%**	27.3 (3/11)	NA (2.5 - NA)	36.4 (4/11)	1.38 (1.22 - 5.26)	7.23 (1.9 - NA)
N3+I1	**< 1%**	0 (0/27)	NA	37 (10/27)	1.58 (1.25 - 2.66)	4.37 (2.07 - 9.07)

ORR: Objective Response Rate; mDOR: median Duration of Response; DCR: Disease Control Rate; mPFS: median

The preliminary safety data from CA209032 indicates that 70% of subjects treated with nivolumab and 84% of those treated with N1+I3 had at least 1 AE. A total of 17% of subjects in the nivolumab group and 45% in the N1+I3 group had Grade 3/4 AEs. Serious AEs (SAEs) were reported in 69.5% of subjects in the nivolumab group and 87.8% in the N1+I3 group; SAEs in 45.8% of subjects in the nivolumab group and 34.7% in N1+I3 group were malignant neoplasm progressions. A total of 5% of subjects in the nivolumab group and 22% of subjects in the N1+I3 treatment group discontinued study drug due to AEs. In N1+I3 arm, Grade 3/4 AEs reported in > 5% of subjects were ALT increased (14%), diarrhea (12%), AST increased (10%), and adrenal insufficiency (8%). Those SAEs (except malignant neoplasm progression) of any grade of intensity reported in > 5% of subjects were diarrhoea (10%), ALT increased (10%), AST increased (8%), adrenal insufficiency (8%), pyrexia (8%), nausea (6%), colitis (6%), hyperglycaemia (6%), and fatigue (6%). These data are consistent with those of the Phase 3 melanoma study CA209067 where the same N1+I3 regimen was used.[37]

1.1.3 Rationale for Nivolumab-plus-Ipilimumab Treatment in 1L GC/GEJ Cancer Treatment

In evaluating trials targeting PD-1 or PD-L1 in GC/GEJ cancer, the following observations from CA209032 can be made regarding the potential of combination nivolumab-plus-ipilimumab therapy in 1L GC/GEJ treatment development:

- For nivolumab-plus-ipilimumab treatment, the N1+I3 cohort demonstrated a doubling of ORR compared to nivolumab monotherapy or the N3+I1 cohort and had an estimated ORR of 26% in all comers and 44% in subjects with PD-L1 expressing tumors. These results compare favorably to 1L SOC chemotherapy. The N1+I3 regimen was efficacious in both PD-L1 ≥ 1% and < 1% tumors, indicating a potential dose combination suitable for 1L evaluation in all comers.

- The safety profiles of nivolumab monotherapy and N1+I3 (Grade 3/4 AEs: 45%) were generally more favorable than that for platinum doublet chemotherapy (Grade 3/4 AEs: approximately 77%), with a different characteristic toxicity profile.
- For nivolumab monotherapy (3 mg/kg), the low ORR (12%) and mPFS (< 2 months) in heavily pre-treated GC/GEJ cancer did not compare favorably to standard 1L chemotherapy, where the ORR was 30% to 50% and mPFS was 4 to 6 months. Analysis by PD-L1 (≥ 1% vs < 1%) suggests that monotherapy development in a biomarker-selected population in the 1L setting may bring a limited survival benefit due to the low mOS (3.55 months) estimate even with a doubling of ORR (26%) in the subjects with PD-L1 ≥ 1% tumors.
- The activities of other monotherapy drugs targeting PD-1 or PD-L1 in subjects with PD-L1-expressing tumors or in an unselected population are consistent with nivolumab monotherapy results.[38,39] PD-L1 selected patients (ie, with PD-L1 expressing tumors) were reported with a mOS estimate of 11 months. However the single arm nature of the monotherapy trials and the mixing of regions (Asia and US/Europe) make these mOS estimates difficult to interpret when extrapolating to the 1L setting, even in a PD-L1 selected population.
- For ipilimumab monotherapy, the inferior ORR and mPFS compared to BSC (with 88% of subjects in BSC also receiving fluoropyrimidine) do not compare favorably to the ORR and mPFS with 1L platinum doublet chemotherapy and do not support monotherapy development in the 1L setting.

Thus, based on the aforementioned data, nivolumab 1 mg/kg with ipilimumab 3 mg/kg administered Q3W for a total of 4 doses followed by nivolumab 240 mg every 2 weeks (the rationale of nivolumab 240 mg is described in Section 1.1.4 below) will be used in this study as this combination regimen approach might bring greater clinical benefits than the SOC approach.

Due to the early closure of enrollment into the nivolumab plus ipilimumab arm per DMC recommendation (see Section 1.5) as specified in Amendment 19, the number of enrolled subjects in this treatment group is lower than the original planned sample size. As a result, the planned analysis of overall survival for this regimen is underpowered and is therefore changed to a secondary objective of the study per Amendment 23.

1.1.4 Rationale for Dose Selection of Nivolumab-plus-Ipilimumab Treatment

The nivolumab-plus-ipilimumab combination dosing regimen selected for evaluation in this study is N1+I3 administered every 3 weeks (Q3W) for 4 doses followed by nivolumab 240 mg administered every 2 weeks (Q2W) until end of treatment (EOT).

The combination dosing of N1+I3 was selected based on its better clinical activity vs N3+I1 demonstrated in the CA209032 study (Table 1.1.2.1-2). Similar to CA209032, following the administration of 4 doses of the combination with ipilimumab, nivolumab will be administered alone at a flat dose of 240 mg Q2W starting at Week 13 until EOT.

Nivolumab 240 mg Q2W was selected based on clinical data as well as modeling and simulation approaches using population pharmacokinetics (PPK) and exposure-response analyses of data from studies in 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 or 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. The PPK model previously developed using data from NSCLC subjects has recently been updated, using data from 1,544 subjects from 7 studies investigating nivolumab in the treatment of melanoma, NSCLC, and RCC. In this dataset, the median (minimum - maximum) weight was 77 kg (35 160 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 patient populations consisted of 1000 subjects per treatment arm randomly sampled from the aforementioned pooled database of cancer subjects. Because no differences in PK were noted across ethnicities and tumor types, these simulated melanoma and NSCLC data will be applicable to subjects with other tumor types. The simulated measures 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.

Nivolumab is safe and well tolerated up to the 10 mg/kg Q2W dose level. Adverse events have been broadly consistent across tumor types following monotherapy and have not demonstrated clear dose-response or exposure-response relationships. Additionally, the simulated median and 95th percentile interval of nivolumab summary exposures across body weight range (35 - 160 kg) are predicted to be maintained below the corresponding observed highest exposure experienced in nivolumab, ie, 95th percentile following nivolumab 10 mg/kg Q2W from clinical study CA209003. Thus, while subjects in the lower body weight ranges would have greater exposures than 80 kg subjects, the exposures are predicted to be within the range of observed exposures at doses (up to 10 mg/kg Q2W) used in the nivolumab clinical program, and are not considered to put subjects at increased risk. For subjects with greater body weights, the simulated ranges of exposures are also not expected to affect efficacy, because the exposures predicted following administration of a 240 mg Q2W are on the flat part of the exposure-response curves for previously investigated tumors, melanoma and NSCLC. Given the similarity of nivolumab PK across tumor types and the similar exposures predicted following administration of a 240 mg flat dose compared to 3 mg/kg, it is expected that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab. Collectively, these data support the use of the N1+I3 Q3W combination for 4 doses followed by nivolumab 240 mg Q2W until end of EOT in this study.

Per Amendment 29, a 480 mg Q4W nivolumab dosing option for subjects who receive nivolumab alone after treatment with nivolumab in combination with ipilimumab or FOLFOX/XELOX is allowed. As a treatment option, a 480 mg IV over 30-minutes Q4W nivolumab dosing regimen has been approved in US in subjects with advanced melanoma, SQ NSCLC, NSQ NSCLC, RCC, SCCHN, cHL and UC.[41] This option will benefit patients and treatment providers by increasing the time between clinic visits and reducing the scheduling burden on cancer treatment institutions, without compromising the established efficacy or safety of the currently approved regimens. In

comparing nivolumab 480 mg Q4W to 3 mg/kg Q2W, the geometric mean time-averaged concentration over the first 28 days (Cavgd28) was approximately 27% higher with 480 mg Q4W, whereas the geometric mean steady-state time-averaged concentration (Cavgss) for both dosing regimens was similar. Nivolumab geometric mean trough concentrations at Day 28 (Cmind28) and at steady-state (Cminss) were 22% and 16% lower, respectively, with 480 mg Q4W dosing. Conversely, geometric mean peak nivolumab concentrations after the first dose (Cmax1) and at steady-state (Cmaxss) were 111% and 43.4% higher, respectively, with 480 mg Q4W dosing, however these exposures are predicted to be lower than the exposure ranges observed at doses up to nivolumab 10 mg/kg Q2W used in the nivolumab clinical program. Extensive E-R analyses were conducted for OS, OR, and tumor growth dynamics to bridge efficacy of nivolumab 240 mg Q2W and 480 mg Q4W with the clinically evaluated 3 mg/kg Q2W dosing regimen. The primary exposure measure used in the analyses was Cavgd28 because it represents the relevant drug concentration over the entire duration of earlier dosing intervals from Q2W and Q4W regimens. The hazard ratios with nivolumab 240 mg Q2W or 480 mg Q4W were predicted to be similar to 3 mg/kg Q2W across multiple tumor types (melanoma, RCC, SQ and NSQ NSCLC). There were no differences in predicted response rate with nivolumab 240 mg Q2W or 480 mg Q4W compared to 3 mg/kg Q2W. There was also no apparent relationship between Cavgd28 and individual estimates of tumor growth rate. Key safety results from the interim safety population of CA209511 demonstrated that the safety profile of nivolumab 480 mg IV over 30 minutes Q4W is consistent with the established safety profile of nivolumab (3 mg/kg Q2W administered IV over 60 minutes) across multiple indications.[42] No new safety concerns were identified. Note that before 480 mg Q4W nivolumab flat dose in the CA209511 study, subjects had received 4 doses of nivolumab + ipilimumab (either 3 mg/kg of nivolumab + 1 mg/kg of ipilimumab or 1 mg/kg of nivolumab + 3 mg/kg of ipilimumab). These data support nivolumab 480 mg Q4W can be safely administrated in 1L GC/GEJ subjects.

1.1.5 Rationale for Nivolumab in Combination with Chemotherapy

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. Immunogenic chemotherapy such as oxaliplatin combination with immune checkpoint can trigger T-cell infiltration to tumor and provide additive or synergistic anti-tumor activity in-vivo, and expects to contribute for the durable anti-tumor responses.[43]

Nivolumab added to platinum doublet has been evaluated in chemotherapy-naive subjects with advanced NSCLC in a Phase 1/2 study CA209012.[44] Nivolumab 10 mg/kg was combined with gemcitabine + cisplatin and pemetrexed + cisplatin. Nivolumab 10 mg/kg, and 5 mg/kg, were combined with paclitaxel and carboplatin. The safety profile of nivolumab plus platinum-doublet chemotherapy reflected additive toxicities of the individual agents, which were manageable using established safety guidelines. The ORR of nivolumab and chemotherapy (33 - 47%) compared favorably to previously reported rates for the platinum-doublet chemotherapy alone (15 - 32%),

though the duration of responses was longer. Despite the small sample sizes of each cohort, the median survival (11.6 - 19.2 months) is promising compared to the histological platinum doublet therapy (8.1 - 10.3 months).[45,46,47,48,49] A confirmation Phase 3 study of nivolumab 360 mg flat dose plus platinum doublet chemotherapy in chemotherapy-naive NSCLC subjects is ongoing (CheckMate 227).

A Phase 2/3 study of nivolumab in combination with oxaliplatin and fluoropyrimidine in patients with chemotherapy-naive GC or GEJ in metastatic setting in Asia is ongoing. Part 1 includes 21 subjects who received nivolumab 360 mg in combination with S1 and oxaliplatin (SOX) every 3 weeks, and 19 subjects who received nivolumab 360 mg in combination with capecitabine and oxaliplatin (XELOX).[50] At a median of 8.3 months follow up, the ORR (by the investigator assessment) was 67% and 71% in nivolumab + SOX and nivolumab + XELOX, respectively. The disease control rate (DCR) was 86% and 82% in nivolumab + SOX and nivolumab + XELOX, respectively. The median duration of response (DOR) was not reached in subjects treated with nivolumab + SOX, and 5.8 months in subjects treated with nivolumab + XELOX. The median PFS by the investigator assessment is 9.9 months in subjects treated with nivolumab + SOX, and 7.1 months in subjects treated with nivolumab + XELOX. A total of 18/20 (90%) and 16/16 (100%) subjects evaluable for response in nivolumab + SOX and nivolumab + XELOX, respectively, experienced some tumor burden reduction, and the response were observed regardless of PDL1 expression status. There were no large differences between the central vs investigator assessment of responses and PFS. As of the date of data cut-off on Feb 2017, 11/21 (52%) and 7/18 (39%) subjects are still under treatment with nivolumab + SOX, or nivolumab + XELOX, respectively. The safety profile reflects the cumulative profiles of nivolumab and chemotherapy. All patients experienced at least 1 treatment-related AE of any grade. A total of 11/21 (52%) and 12/18 (67%) were Grade 3/4 AEs. The most common treatment-related AEs occurring in >10% were decreased neutrophil count (14%) in nivolumab + SOX, and peripheral sensory neuropathy (11%), decreased appetite (11%) and nausea (11%) in nivolumab + XELOX. No treatment-related deaths occurred in either treatment arm.

The preliminary safety data of pembrolizumab plus 5-FU and cisplatin in chemotherapy treatment-naive patients with advanced GC have been reported recently.[51] The safety profile also reflected additive toxicity of the individual agents with 72% experiencing Grade 3/4 treatment-related AE, and was also manageable. No treatment-related discontinuation attributed to pembrolizumab nor treatment-related deaths were reported.

Thus, these pre-clinical and clinical data suggest that nivolumab in combination with oxaliplatin and fluoropyrimidine is also expected to bring clinical benefits to advanced GC/GEJ patients with manageable safety.

In this nivolumab-plus-chemotherapy arm of the study, nivolumab 360 mg (for subjects assigned to nivolumab + XELOX) or nivolumab 240 mg (for subjects assigned to nivolumab + FOLFOX) will be administered as an IV infusion over 30 minutes every 3 weeks (Q3W) or every 2 weeks (Q2W), respectively. Nivolumab has been shown to be safe and well tolerated up to a dose level of nivolumab 10 mg/kg Q2W. As PPK analyses have shown that the PK of nivolumab are linear

over a dose range of 0.1 to 10 mg/kg with no differences observed in PK across ethnicities and tumor types, the PPK model was used to simulate exposures at different dosing regimens, including nivolumab 360 mg Q3W. The simulated steady-state average concentration (Cavgss) following administration of nivolumab 360 mg Q3W are expected to be similar to those following administration of nivolumab 240 mg Q2W and nivolumab 3 mg/kg Q2W administered to subjects weighing 80 kg. It should be noted that the steady-state peak concentrations (Cmaxss) following nivolumab 360 mg Q3W are predicted to be less than those following the administration of nivolumab 10 mg/kg Q2W providing sufficient safety margins. Finally, nivolumab 360 mg Q3W in combination with platinum-doublet chemotherapy dosing is currently being studied for the treatment of NSCLC in a Phase 3 study.

See Section 1.1.4, for the rationale for the 480 mg Q4W nivolumab dosing option for subjects who receive nivolumab alone after treatment with nivolumab in combination with chemotherapy.

1.1.5.1 Rationale for Primary Population in the Nivolumab in Combination with Chemotherapy

As described in Section 1.1.5, the ORRs of nivolumab in combination with oxaliplatin and fluoropyrimidines were 60-70%, comparing to historical data (30-50%) in the treatment naive GC/GEJ patients, a favorable clinical benefit can be expected in this combination. In addition, only 5 out of 38 PDL1 evaluable subjects was reported with PDL1 expressing tumors (PDL1 $\geq$ 1%). Although difficult to draw conclusion based on a small sample size, it is observed that the responses were independent from the PDL1 expressing status. Thus, considering all subjects are expected to benefit in the nivolumab in combination with chemotherapy, the primary population will be all comers.

Per Amendment 23, the primary population is changed to subjects with PDL1 CPS $\geq$ 5, as discussed in detail in Section 1.1.13.

1.1.5.2 Rationale for PFS as the Primary Endpoint in the Nivolumab in Combination with Chemotherapy Arm

PFS is a common efficacy endpoint, which helps to interpret the treatment effects when potential confounding effects are introduced by the subsequent therapies. As described in Section 1.1.5, both the ORR and PFS rates of nivolumab in combination with oxaliplatin and fluoropyrimidines are larger than the previously reported rates for chemotherapy treatment alone (ORR: 60-70% compared to 30-50%; PFS: 7-10 months compared to the previously reported 4-6 months).[14,15,16,17,18] As a high unmet medical need remains for patients with advanced and metastatic GC/GEJ, an effective new treatment option is urgently needed. The addition of PFS as surrogate survival-marker enables an earlier assessment of treatment effects than OS, which may allow early access for this significantly ill population.

Per Amendment 23, ORR has been changed to a secondary objective.

1.1.6 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).

Nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg over a long treatment duration. In subjects with advanced/metastatic clear cell RCC (CA209010 study), 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), 240 mg or 360 mg are 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-min infusion compared with that reported for patients with the 60-min infusion. Thus, it was shown that nivolumab can be safely infused over 30 minutes as a 3 mg/kg dose.

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.

1.1.7 Rationale for 2-year Nivolumab Treatment

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.[52] 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.[53]

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 (2) 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.[54] 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).[55]

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.[56]

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.[57]

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.[58]

Collectively, these data suggest that there is minimal if any benefit derived from continuing I-O treatment beyond two 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.

1.1.8 *Rationale for Including Both Subjects with PD-L1 and Non-PD-L1 Expressing Tumors in 1L GC/GEJ and Stratification by PD-L1 Expression*

Single-agent nivolumab in previously treated tumors, including squamous and non-squamous NSCLC, RCC and GC has demonstrated improved survival in subjects without preselection by PD-L1 tumor expression.[20,21,22,59] In GC/GEJ cancer, PD-L1 has been suggested as a prognostic marker.[30,31] however, recent data suggested PD-L1 expression might not be an independent poor prognostic factor.[32,33,34,35,36,80] Clinical data for the N1+I3 combination in Table 1.1.2.1-2 suggests that PD-L1 may also be predictive (eg, numerically higher ORR) as a therapy targeting PD-1 alone or in combination with CTLA-4, but also having activity in subjects whose tumors did not express PD-L1. In addition, in the CA209067 study, nivolumab combination with ipilimumab demonstrated clinical activity in subjects with advanced melanoma tumors which did not express PD-L1.[29] For these reasons, CA209649 will enroll subjects regardless of PD-L1 tumor expression, but stratify at the PD-L1 expression level of 1%, ie, subjects whose tumors express PD-L1 and those whose tumors do not, and have the primary analysis of OS in subjects with PD-L1 expressing tumors in N1+I3 versus chemotherapy.

In Study CA209012, 44 subjects with known PD-L1 expression received nivolumab combined with platinum doublet; the confirmed ORRs were 48% (11 of 23 subjects) and 43% (9 of 21 subjects) for subjects with ≥ 1% and < 1% PD-L1 expressing tumors, respectively.[44] [redacted] Like non-squamous NSCLC, nivolumab in combination with chemotherapy is expected to have anti-tumor activity in chemotherapy-naive adenocarcinoma GC/GEJ subjects both with PD-L1 and non-PD-L1 expressing tumors, and might be higher in PD-L1 expressing tumors. In Study Ono-4538-37, 5 out 38 subjects with ≥ 1% PD-L1 expressing tumors received nivolumab combined with oxaliplatin and fluoropyrimidines, 4 of these 5 subjects achieved PR which is numerically higher than all comers (68%) in treatment naive GC/GEJ

subjects.[50] As descripted in Section 1.1.5.2, the anti-tumor response observed regardless the PDL1 expressing status subjects will be enrolled regardless of PD-L1 tumor expression in the nivolumab in combination with chemotherapy arm, with stratification by PD-L1 expression level of 1%.

As described above, PD-L1 is considered a potential predictive biomarker for immunotherapy in multiple tumor types, and the optimal cut-off and testing methods to determine PD-L1 expression are still evolving and under investigation. However, a significantly higher treatment effect was observed with immunotherapy in high PD-L1 expressing population of treatment naïve NSCLC[60] A similar finding of improved efficacy with immunotherapy using a higher PD-L1 cut-off was also reported in GC.[61,62] The most recent data in 2L advanced GC/GEJ cancer from Keynote 61 suggested a higher treatment effect in patients with higher PD-L1 expression (CPS 10) vs lower PD-L1 expression (CPS1), with HR 0.64 vs HR 0.82.[62]

The CPS scoring has been incorporated for the PD-L1 expression evaluation in CA209649 study in Amendment 23, as discussed in detail in Section 1.1.13.

1.1.9 Rationale for Choice of Comparator

Platinum compounds (oxaliplatin and cisplatin) and fluoropyrimidines (fluorouracil, capecitabine, and S1) are generally considered as the standard-of-care, 1L treatment options of choice across geographic regions.[11,12,13, 63] Concerning fluoropyrimidines, Asian investigators prefer S1 because of its better survival rates, tolerability, and convenience of oral administration. However, S1 is not approved in the US. Thus, this study will not include S1, but, rather, capecitabine or fluorouracil, which are the most frequently administered fluoropyrimidines in the US and Europe, and also available in Asia. The investigator can choose either capecitabine or fluorouracil, based on local standards.

The NCCN guideline suggests the 2-drug chemotherapy as the preferred regimen in the 1L setting; the 3-drug regimen, due to its toxicity profile, should be considered only for use in patients with good performance statuses.[11] In addition, the triplet regimen is not common in Asia due to its high toxicity profile.[13] Thus the comparator selected in this study is only the platinum doublet regimen.

Cisplatin has been the most frequently administered platinum in GC treatment. Since the REAL-2 study demonstrated an oxaliplatin-based regimen to be non-inferior to cisplatin with a favorable safety profile,[15] oxaliplatin combinations with fluoropyrimidines have been studied in multiple Phase 2 and 3 trials, and showed similar efficacy trends across regions.[16,64,65,66] A meta-analysis comparing oxaliplatin-based and cisplatin-based regimens showed that oxaliplatin was associated with significant improvements in PFS (HR 0.88, 95% CI: 0.80 - 0.98) and OS (HR 0.88, 95% CI: 0.78 - 0.99), with fewer AEs of neutropenia, anemia, alopecia and thromboembolic events, but more neurotoxicity and diarrhea.[67] As a result, oxaliplatin has become one of the major backbone platinum compounds in the 1L setting.

A Phase 3 trial in esophageal/gastric/GEJ cancers comparing the FOLFOX regimen (5-fluorouracil plus leucovorin and oxaliplatin) vs FLP (5-fluorouracil plus leucovorin and cisplatin) showed no statistically significant differences between the 2 treatments, but favored the FOLFOX arm vs the

FLP arm in terms of median PFS (the primary endpoint, 5.7 months vs 3.9 months), response rate (35% versus 25%), and median survival (10.7 months vs 8.8 months). FOLFOX was associated with significantly less nausea and vomiting, fatigue, renal toxicity and alopecia, but more Grade 3/4 sensory neuropathy than FLP.[64]

A similar survival outcome with XELOX (capecitabine plus oxaliplatin) was demonstrated in Phase 2 studies;[68] in addition, the convenience of the XELOX regimen (oral capecitabine every 2 weeks plus an oxaliplatin IV infusion in a 3-week cycle) has favored increased implementation of this regimen in clinical practice globally.

Based on these observations, the oxaliplatin-based regimens FOLFOX and XELOX are considered to be reasonable comparators in this Phase 3 study, and the investigators can choose either regimen per their local standard.

1.1.10 Rationale for Adding Chemotherapy Regimen as Stratification Factor

In this study, the stratification factors are PD-L1 status, region and ECOG performance status. As described in Section 1.1.8, the antitumor activity has been observed in subjects with and without PD-L1 expressing tumors, and a greater response observed in the GC/GEJ and non-squamous NSCLC with nivolumab in combination with ipilimumab or chemotherapy. In Section 1.1.1, the different regional survival outcomes have been reported in GC/GEJ multi-Phase 3 studies, and performance status is known as an important parameter for predicting the survival in advanced GC.[69] Thus, these 3 factors have been selected as stratification factors.

Chemotherapy effectively treats cancer in part by facilitating an immune response to the tumor when given at the standard dose and schedule. This immunomodulatory effect is dependent on the drug itself, its dose and its schedule in relation to an immune-based intervention.[70] The antitumor activity differs depending on the cytotoxic agents given in combination with the immunocheckpoint agents.[43] Thus, the chemotherapy regimen has newly been added as a stratification factor in this study, to avoid a potential imbalance of different treatment effects of nivolumab when combined with XELOX or FOLFOX.

1.1.11 Rationale for Open-Label Design

The treatment schedule for administering the nivolumab combination with ipilimumab will be every 3 weeks for 4 doses followed by nivolumab monotherapy every 2 weeks. Administration of the control arm FOLFOX will be every 2 weeks and XELOX will be every 3 weeks. Administration of the nivolumab in combination with FOLFOX will be every 2 weeks, and XELOX will be every 3 weeks, to align with the schedule of the backbone therapies. These different dosing schedules and unique and characteristic drug-related AEs (eg, neuropathy with platinum doublets and immune AEs with nivolumab combined with ipilimumab) make blinding impractical. In addition, the correct management of frequent AEs such as diarrhea might require a process of unblinding which may delay appropriate supportive care for management of AEs (anti-diarrheals for chemotherapy-induced diarrhea and immune suppression for diarrhea associated with immune-mediated agents). Thus, this study is designed as an open-label trial.

1.1.12 Rationale for Permitting Continued Treatment in Select Cases of Progressive Disease for Subjects in the Nivolumab Plus Ipilimumab and Nivolumab in Combination with Chemotherapy Arms

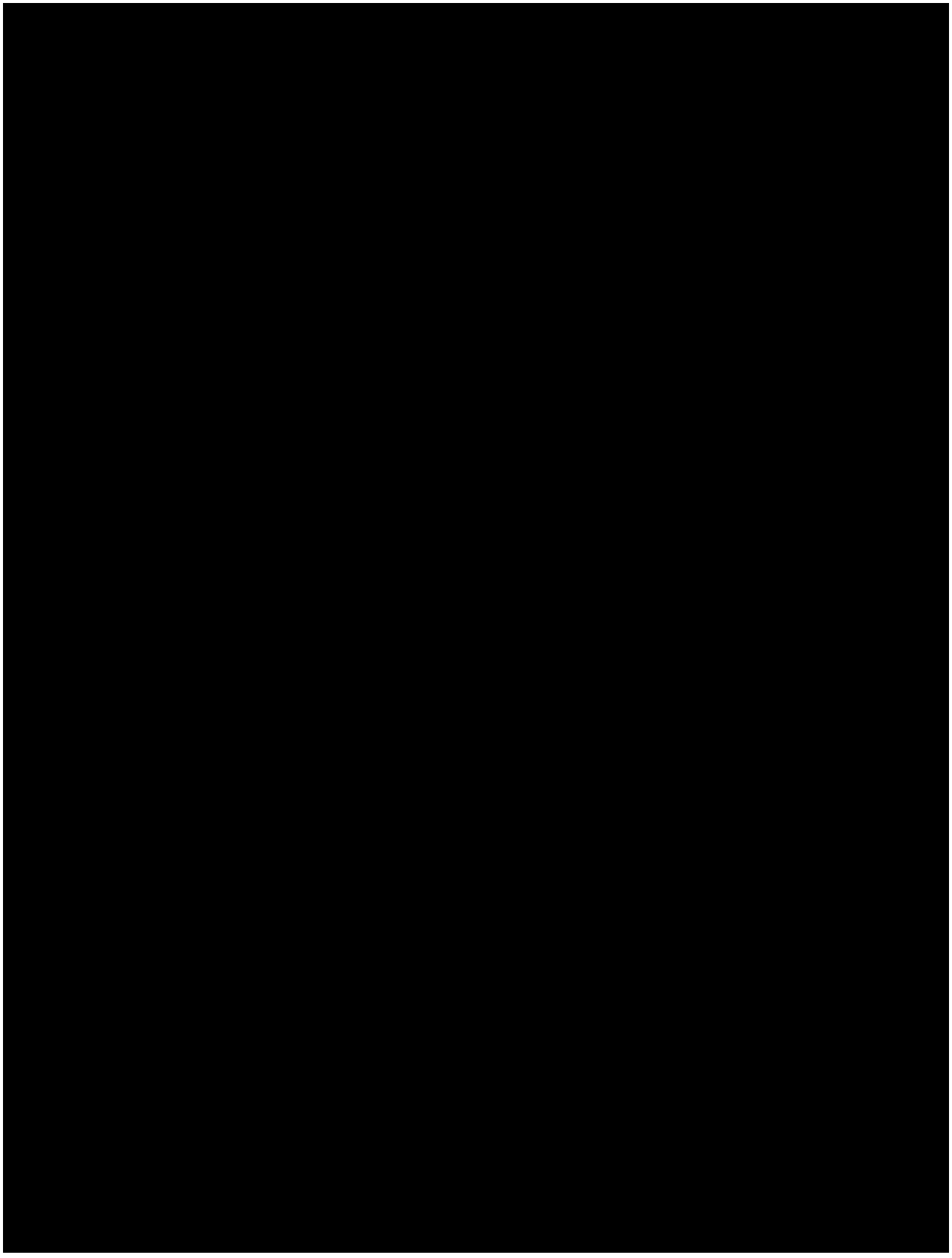
Accumulating clinical evidence indicates some subjects treated with immune system stimulating agents may develop progression of disease (by conventional response criteria) before demonstrating clinical objective responses and/or stable disease. This phenomenon was observed in approximately 10% of subjects in the Phase 1 study of nivolumab and also with ipilimumab monotherapy.[71] Two hypotheses have been put forth to explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease, leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. Therefore subjects will be allowed to continue study therapy after initial investigator-assessed RECIST 1.1-defined progression if they are assessed to be deriving clinical benefit and tolerating study drug (Section 4.5.1.6). Such subjects must discontinue study therapy upon evidence of further progression.

1.1.13 Rationale for incorporation of CPS for PD-L1 expression evaluation and changing primary population to subjects with PD-L1 CPS ≥ 5

Combined positive score (CPS) is defined as the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.[72] CPS is a composite score that incorporates both tumor and tumor-associated immune cell (TAIC) PD-L1 expression, whereas tumor proportion score (TPS) or tumor PD-L1 only reflects the percentage of tumor cells that are positive for PD-L1 expression.

CPS appears to be a good predictor for response in gastric cancer with checkpoint inhibitors. In Keynote-059 Cohort 1, patients with advanced gastric cancer who had received ≥2 lines of prior chemotherapy were treated with pembrolizumab monotherapy (n=257). Pembrolizumab showed promising clinical activity with antitumor response significantly associated with CPS (P= 0.002) but not TPS (P= 0.224) at CPS/TPS 1 cut-off. The odds ratio between the PD-L1 positive and negative populations had increased from 1.4 for TPS 1 to 2.8 for CPS 1, indicating the better predictive value of CPS compared to TPS.[73] In Keynote-061, which evaluated pembrolizumab vs. paclitaxel in 2L GC/GEJC, pembrolizumab did not improve overall survival or progression free survival in patients whose CPS ≥1; however the HRs of OS were 1.20, 0.82 and 0.64 in the CPS<1, CPS≥1 and CPS≥10 populations respectively, demonstrating a trend of increased efficacy with increasing CPS cutoffs.[74]

[redacted]



The prevalence of CPS decreases with increasing CPS cut-offs. In the KEYNOTE 61 study, the prevalence was up to 67% at CPS≥1, and up to 18% at CPS ≥10.[74] In KEYNOTE 59 study, the prevalence of CPS ≥1 was 58% in 3L GC/GEJ(N=259) and 64% in 1L GC/GEJ(N=25)[73].[75]

[redacted]

While TPS was originally used to define the PD-L1 expressing population in the original protocol, the observed prevalence of PD-L1 ≥ 1% by TPS based on aggregate data is much lower than the original assumption of 40% used in this study impacting the study power and current study sample size. More importantly, based on accumulating clinical data, CPS seems to better predict response than TPS and able to better select patients for treatment with checkpoint inhibitors in gastric cancer. Thus, CPS ≥ 5 will now be used to define the primary population for this study in order to achieve promising clinical benefit in a relatively biomarker enriched population. [redacted] Therefore, a conservative prevalence of 35% prevalence will be assumed for CPS ≥ 5 in this study in order to ensure sufficient sample size for the primary analysis. In addition, the study will also evaluate the efficacy across different CPS cut-offs eg, CPS10, CPS1 as well as all randomized population in secondary and exploratory objectives.

[redacted] Therefore, the enrolment will be extended to ensure that the study is appropriately powered for PFS and OS primary endpoints in the CPS ≥ 5 population. To allow for this, the total sample size will be increased from 1649 to approximately 2005. This resizing of the total population will ensure that the sample size of the enriched population for the primary analyses (subjects with CPS ≥ 5) is the same as is specified in Amendment 23, and will maintain the same power under the statistical assumptions as stated in Amendment 23.

The current estimation of 27% prevalence of CPS ≥ 5 may still change when more data are available. Close monitoring of the prevalence in a blinded fashion is ongoing and the final sample size of all randomized subjects may be adjusted accordingly to ensure sufficient power for the primary analyses.

1.1.14 Rationale for Statistical Analyses Update in Amendment 29

Per amendment 23, the primary population changed to subjects with PD-L1 expression by CPS ≥ 5, and the PD-L1 CPS scoring process started for all randomized subjects. In March 2019, it was determined that additional scoring of a significant number of samples was needed. The expected completion of PD-L1 CPS scoring was delayed and is now projected to be completed approximately 6 months or later after the completion of enrollment. Amendment 29 documents the corresponding changes to the statistical analysis timing and power estimation of PFS and OS (see Section 8).

Early in June 2019, the final analyses of the 1L GC phase 3 Keynote-062 study were disclosed at the ASCO meeting.[76] The study included 3 arms: pembrolizumab monotherapy (Pem), pembrolizumab plus chemotherapy (Pem+CT) and chemotherapy (CT). Chemotherapy backbone used fluoropyrimidine and cisplatin. The study primary objectives to demonstrate non-inferiority for Pem vs CT and superiority for Pem+CT vs CT. For the comparison of Pem vs CT, the study met the non-inferiority of OS in CPS ≥ 1 with HR 0.91. In the subgroup analysis among subjects with CPS ≥ 10, OS improvement has been seen with HR 0.69, however it did not meet the pre-specified statistical significance. A detriment of OS Kaplan-Meier (KM) curves has been observed for approximately the first 12 months and 9 months in subjects with CPS ≥ 1 and CPS ≥ 10, respectively. For the comparison of Pem+CT vs CT, the study did not meet the primary endpoints of PFS and OS in Pem+CT vs CT, at either CPS ≥ 1 or CPS ≥ 10. The HR for OS was 0.85 in both subjects with CPS ≥ 1 and CPS ≥ 10. Approximately 6-month delayed separation of KM curves was also observed for both CPS ≥ 1 and CPS ≥ 10. The observed HR for PFS in CPS ≥ 1 vs CPS ≥ 10 were 0.84 and 0.73, respectively, demonstrating an enrichment by higher cutoff of CPS. Similar to the OS KM curves, a delayed separation of PFS KM curves also observed in subjects with CPS ≥ 1 vs CPS ≥ 10. In the summary, the Keynote-062 data suggested that sufficient follow-up for I-O alone or in combination with chemotherapy will be needed in order to fully capture long-term treatment effect.

1.2 Research Hypotheses

In subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥ 5, the administration of nivolumab plus ipilimumab will improve OS compared to oxaliplatin plus fluoropyrimidine.

In subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥ 5, the administration of nivolumab in combination with oxaliplatin plus fluoropyrimidine will improve PFS or OS compared to oxaliplatin plus fluoropyrimidine.

1.3 Objectives

1.3.1 Primary Objectives

Nivolumab in combination with oxaliplatin plus fluoropyrimidine vs oxaliplatin plus fluoropyrimidine:

- To compare OS in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥ 5
- To compare PFS, as assessed by BICR in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥ 5.

1.3.2 Secondary Objectives

Nivolumab plus ipilimumab vs oxaliplatin plus fluoropyrimidine:

- To compare OS in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥ 5 or in all randomized
- To evaluate OS in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥ 10 or 1

- To evaluate PFS, as assessed by BICR, in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥ 10, 5, 1 or all randomized subjects
- To evaluate ORR, as assessed by BICR, in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥ 10, 5, 1 or all randomized subjects
- To compare the time to symptom deterioration (TTSD) as assessed using the Gastric Cancer Subscale (GaCS) of the Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥ 5 or all randomized subjects.

Nivolumab in combination with oxaliplatin plus fluoropyrimidine vs oxaliplatin plus fluoropyrimidine:

- To compare OS in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥ 1 or all randomized subjects
- To evaluate OS in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥10
- To evaluate PFS, as assessed by BICR, in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥10, 1 or all randomized subjects
- To evaluate ORR, as assessed by BICR, in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥10, 5, 1, or all randomized subjects

1.3.3 Exploratory Objectives

Nivolumab in combination with oxaliplatin plus fluoropyrimidine vs oxaliplatin plus fluoropyrimidine:

- To assess TTSD as assessed using GaCS of FACT-Ga in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS ≥ 5 or all randomized subjects

For both comparisons: Nivolumab in combination with oxaliplatin plus fluoropyrimidine vs oxaliplatin plus fluoropyrimidine and Nivolumab plus ipilimumab vs oxaliplatin plus fluoropyrimidine:

- To assess PFS and ORR, as assessed by the investigator in subjects with advanced or metastatic GC or GEJ cancer across CPS cut-offs
- To evaluate Duration of Response (DOR) as assessed by BICR and by investigator, in subjects with advanced or metastatic GC or GEJ cancer
- To evaluate the durable response rate (objective response lasting continuously > 6 months) as assessed by BICR and by investigator, in subjects with advanced or metastatic GC or GEJ cancer
- To evaluate at 18-month, 24-month, and 36-month survival rates in subjects with advanced or metastatic GC or GEJ cancer
- To evaluate second disease progression (PFS2) or time to second subsequent line therapy (TSST) in subjects with advanced or metastatic GC or GEJ cancers

- To assess PFS, ORR as assessed by either BICR or investigator, OS in subjects with advanced or metastatic GC or GEJ cancer across TPS cut-offs.
- To assess the overall safety and tolerability of nivolumab plus ipilimumab or nivolumab in combination with oxaliplatin plus fluoropyrimidine and oxaliplatin plus fluoropyrimidine in subjects with advanced or metastatic GC or GEJ cancer
- To explore potential biomarkers predictive of or associated with clinical efficacy (OS, PFS and ORR) and/or incidence of AEs of nivolumab plus ipilimumab or nivolumab in combination with oxaliplatin plus fluoropyrimidine including but not limited to microsatellite instability (MSI) status, tumor mutational burden (TMB) [redacted] and inflammatory signatures in subjects with advanced or metastatic GC or GEJ cancer.

[redacted]

- To characterize the pharmacokinetics (PK) of nivolumab and ipilimumab and nivolumab in combination with oxaliplatin plus fluoropyrimidine and explore exposure-response relationships with respect to safety and efficacy
- To characterize the immunogenicity (IMG) of nivolumab and ipilimumab and nivolumab in combination with oxaliplatin plus fluoropyrimidine when administered in combination to subjects with advanced or metastatic GC or GEJ cancer
- To assess TTSD as assessed using GaCS of FACT-Ga in subjects with advanced or metastatic GC or GEJ cancer with PD-L1 CPS $\geq$ 10 or 1
- To assess changes from baseline in the subject's overall health status using the 3-level version of the EQ-5D (EQ-5D-3L) index and visual analog scale (EQ-VAS) of nivolumab plus ipilimumab or nivolumab in combination with oxaliplatin plus fluoropyrimidine vs oxaliplatin plus fluoropyrimidine in subjects with advanced or metastatic GC or GEJ cancer
- To assess the subject's cancer-related quality of life using the FACT-Ga questionnaire and selected components, including the GaCS and 7-item version of the FACT-General (FACT-G7) of nivolumab plus ipilimumab or nivolumab in combination with oxaliplatin plus fluoropyrimidine vs oxaliplatin plus fluoropyrimidine in subjects with advanced or metastatic GC or GEJ cancer.

1.4 Product Development Background

1.4.1 Mechanism of Action

1.4.1.1 Nivolumab

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 responses.[77,78,79] 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.[80] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA.[81] 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.[82] 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 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 cytotoxic T-cell lymphocyte associated protein 4 (CTLA-4). 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 cytomegalovirus (CMV) re-stimulation assay with human peripheral blood mononuclear cells (PBMCs), the effect of nivolumab on antigen-specific recall response indicates that nivolumab augments 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 results in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[83]

1.4.1.2 Ipilimumab

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.[84,85]

Ipilimumab (BMS-734016) 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 antigen-presenting cells (APCs), with subsequent blockade of the inhibitory modulation of T-cell activation promoted by the CTLA-4/B7 interaction.

1.4.2 Summary of Clinical Pharmacology

1.4.2.1 Nivolumab

The PK of nivolumab were studied in subjects over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. The geometric mean (% CV%) clearance (CL) was 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) was 8.0 L (30.4%), and geometric mean elimination half-life (t1/2) was 26.7 days

(101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3-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 CL of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1. Although ECOG status, baseline glomerular filtration rate (GFR), albumin and body weight had an effect on nivolumab CL, the effect was not clinically meaningful. When nivolumab is administered in combination with ipilimumab, the CL of nivolumab was increased by 24%, whereas there was no effect on the CL 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 1.1.4). Additional details are provided in the nivolumab investigator brochure (IB).[86]

1.4.2.2 Ipilimumab

The PPK of ipilimumab was studied in 785 subjects (3200 serum concentrations) with advanced melanoma in 4 Phase 2 studies (CA184004, CA184007, CA184008, and CA184022),[87] 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 those 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 t1/2 and Vss of ipilimumab calculated from the model were 15.4 days and 7.47 L, respectively, which are consistent with those determined by noncompartmental analysis. Volume of the central compartment (Vc) and peripheral compartment were found to be 4.35 L and 3.28 L, respectively, suggesting that ipilimumab first distributes into the plasma volume and, subsequently, into extracellular fluid space. The CL and Vc of ipilimumab were found to increase with increase in body weight. However, there was no significant increase in exposure with increase in body weight when dosed on a mg/kg basis, supporting dosing of ipilimumab based on a weight-normalized regimen. The PK of ipilimumab is not affected by age, gender, race, immunogenicity (anti-drug antibody [ADA] status), concomitant use of chemotherapy, prior therapy, body weight, 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 or moderate renal impairment, the CLs of ipilimumab were 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 CLs of ipilimumab in subjects with mild or moderate hepatic impairment was similar to those of subjects with normal hepatic function.

Additional details are provided in the ipilimumab IB.[88]

1.4.3 Safety Summary

The overall safety experience with nivolumab, as monotherapy or in combination with other therapeutics, is based on experience in approximately 12,300 subjects treated to date. Extensive details on the safety profile of nivolumab, including results from other clinical studies, are available in the nivolumab IB, and will not be repeated herein.

Overall, the safety profile of nivolumab alone or in combination with other therapeutic agents such as ipilimumab or chemotherapy is manageable and generally consistent across completed and ongoing clinical trials, with no 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. Results to date suggest that the safety profile of nivolumab/ipilimumab combination therapy and nivolumab in combination with chemotherapy is consistent with the mechanisms of action of nivolumab and ipilimumab. The nature of the AEs is similar to that observed with either agent used as monotherapy; however, both frequency and severity of most AEs are increased with the combination.

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. For additional material, see the nivolumab IB.

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 advanced or metastatic GC and GEJ cancer present a great unmet need. Preliminary results from CA209032, in which nivolumab monotherapy and nivolumab-plus-ipilimumab treatments were administered to heavily pretreated subjects with advanced/metastatic GC and GEJ cancers, demonstrated clinical activity in subjects whose tumors did or did not express PD-L1; better results were obtained in subjects with PD-L1 expressing (PD-L1+) tumors. In addition, in various other tumor types, nivolumab alone and in combination with ipilimumab demonstrated clinical benefits independent or dependent of PD-L1 expressing status.[20,21,22,39] Preliminary data from NSCLC study suggests that nivolumab in combination with platinum doublet has additive anti-tumor activity in subjects regardless of PD-L1 expression, but numerically higher ORR observed in non-squamous NSCLC.[44] Based on this clinical experience, CA209649 will enroll patients regardless of PD-L1 status, but the efficacy analyses will be conducted first in the population with PD-L1 expressing tumors and then in the population of all comers in N1+I3 comparison. Preliminary data from ONO-4538-37 suggested that nivolumab in combination with oxaliplatin and fluoropyrimidine had the promising clinical activity (60-70% ORR) in treatment-

naive advanced/metastatic GC/GEJ subject regardless PDL1 expressing status. As the majority of all comer subjects are expected to benefit from nivolumab in combination with chemotherapy, the primary efficacy analysis will focus on all comers in this comparison.

The safety profile of nivolumab combined with ipilimumab in GC/GEJ cancer from CA209032, as measured by total and Grade 3/4 AEs, is comparable to that of a 1L platinum doublet. In the Ono-4538-37 study, the safety profile of nivolumab combined with oxaliplatin and fluoropyrimidine reflects the additive toxicity of nivolumab monotherapy and chemotherapy, and no new safety signal identified. The safety profile of this nivolumab-plus-ipilimumab combination or nivolumab is characterized by immune-related toxicities, such as diarrhea, rash, pneumonitis, liver toxicity, and endocrinopathies. These events were mostly low grade and manageable with the use of corticosteroids. The ongoing external studies of PD-L1 inhibitors in combination with chemotherapy in treatment-naive advanced GC/GEJ subjects suggest that this combination is tolerable and manageable, no new safety signals being detected. The safety profile of the combination used in CA209649 in GC and GEJ cancer is consistent with that reported in subjects with previously untreated melanoma.

To ensure an ongoing favorable risk/benefit assessment for subjects enrolled in CA209649, a DMC will be utilized to monitor the safety and clinical activity of the treatments throughout the conduct of the trial.

At a regularly scheduled DMC meeting [redacted], the DMC recommended stopping further enrollment to the nivolumab plus ipilimumab treatment arm due to an observed increased early death rate in this arm as well as increased toxicity rate. The DMC also recommended that current subjects who are already in the nivolumab plus ipilimumab arm should continue as planned per protocol, as should enrollment to the other two arms (nivolumab combined with chemotherapy and chemotherapy alone).

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 form 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 the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation, etc) that is likely to affect, to a significant degree one or more of the following: (1) the physical, safety or mental integrity of one or more subjects/participants: (2) the scientific value of the trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP Regulation(s) or Trial protocol(s).

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/participants recruitment materials (e.g., 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/participants 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/participants 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/participants, 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 (i.e., 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/participants, 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/participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects'/participants' signed ICF and, in the US, the subjects'/participants' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

Subjects/participants unable to give their written consent (e.g., stroke or subjects/participants 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/participants are the most important considerations and should prevail over interests of science and society.

After DMC recommendation [redacted], any subject enrolled and awaiting randomization before 05-June-2018 must be verbally re-consented to indicate their awareness of the closure of the nivolumab and ipilimumab arm with randomization now 1:1 to nivolumab plus chemotherapy versus chemotherapy only. These subjects will need to be re-consented once the revised IRB-approved ICF is available. Subjects currently on study will need to be re-consented with the updated IRB-approved ICF at their next scheduled visit.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a Phase 3, randomized, open-label, three-arm study of nivolumab plus ipilimumab or nivolumab in combination with oxaliplatin plus fluoropyrimidine vs oxaliplatin plus fluoropyrimidine in subjects with previously untreated advanced or metastatic GC or GEJ cancer. The nivolumab plus ipilimumab arm is closed to enrollment as of 05-June-2018. Subjects enrolled in this arm prior to 05-June-2018 will continue to receive treatment with study drugs per protocol and the study data will remain blinded for the planned primary analysis.

The study will enroll subjects regardless the PD L1 expressing tumors.

The original study design (before Amendment 08) had two arms. After signing the informed consent form, and upon confirmation of the subject's eligibility, subjects were randomized in an open-label fashion (1:1 ratio) to either the nivolumab-plus-ipilimumab arm or the chemotherapy (XELOX or FOLFOX) arm.

Amendment 08 added a new, nivolumab-plus-chemotherapy (XELOX or FOLFOX) arm. The IRT switched to a 1:1:1 randomization at all the study participating sites.

Amendment 19 added approximately 300 subjects to the study; in total approximately 1649 subjects will be randomized. The nivolumab plus ipilimumab arm was closed to enrollment as of 05-June-2018. Subjects randomized to treatment in this arm prior to 05-June-2018 will continue to receive treatment with study drugs per protocol, and the study data will remain blinded for the planned primary analysis. Per Amendment 20, subjects will be randomized in an open-label fashion (1:1) to either the nivolumab-plus-chemotherapy (XELOX or FOLFOX) or the chemotherapy arm (XELOX or FOLFOX):

- Nivolumab-plus-Ipilimumab Arm: nivolumab 1 mg/kg administered IV over 30 minutes followed by ipilimumab 3 mg/kg administered IV over 30 minutes on Day 1 of each treatment cycle every 3 weeks for 4 doses (Cycles 1 to 4), followed by nivolumab 240 mg administered IV over 30 minutes on Day 1 of each treatment cycle every 2 weeks (Cycle 5 and beyond). Arm is closed to enrollment as of 05-June-2018.
- Nivolumab-plus-Chemotherapy Arm (XELOX or FOLFOX):

Nivolumab plus XELOX	**Nivolumab plus FOLFOX**
Nivolumab 360 mg IV over 30 minutes on Day 1 of each treatment cycle, every 3 weeks + Oxaliplatin 130 mg/m^2 IV on Day 1 of each treatment cycle + capecitabine 1000 mg/m^2 orally twice daily (ie, 1000 mg/m^2 in the morning and 1000 mg/m^2 in the evening) on Days 1 to 14 of each treatment cycle, every 3 weeks	Nivolumab 240 mg IV over 30 minutes on Day 1 of each treatment cycle, every 2 weeks + Oxaliplatin 85 mg/m^2 + leucovorin 400 mg/m^2 + fluorouracil 400 mg/m^2 IV on Day 1 of each treatment cycle, and fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours (or per local standard) daily on Days 1 and 2 of each treatment cycle, every 2 weeks

or

- Chemotherapy Arm (XELOX or FOLFOX) :

XELOX	FOLFOX
Oxaliplatin 130 mg/m^2 IV on Day 1 of each treatment cycle + capecitabine 1000 mg/m^2 orally twice daily (ie, 1000 mg/m^2 in the morning and 1000 mg/m^2 in the evening) on Days 1 to 14 of each treatment cycle, every 3 weeks	Oxaliplatin 85 mg/m^2 + leucovorin 400 mg/m^2 + fluorouracil 400 mg/m^2 IV on Day 1 of each treatment cycle, and fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours (or per local standard) daily on Days 1 and 2 of each treatment cycle, every 2 weeks

Amendment 26 added approximately 356 subjects to the study; in total approximately 2005 subjects will be randomized. However, given the uncertainty about the CPS ≥ 5 prevalence, the sample size may need to be further adjusted based on the monitoring of the prevalence to keep sample size for the primary population.

The treatment will be given until disease progression (PD) (unless treatment beyond progression is permitted, in nivolumab-plus-ipilimumab and nivolumab-plus-chemotherapy arms; see Section 4.5.1.6), unacceptable toxicity, maximum 24 months treatment duration or subject withdrawal of consent, whichever comes first.

Based on investigator judgment of benefit/risk, nivolumab 480 mg flat dose Q4W (IV over 30 minutes on Day 1 of each treatment cycle, Q4W) can be used as an option for those subjects who receive nivolumab treatment alone. For subjects in nivolumab-plus-chemotherapy arm, a 480 mg Q4W nivolumab treatment regimen will be permitted when all chemotherapy is discontinued and nivolumab is continued alone. Subjects must be in the study for a minimum of 6 months from Cycle 1, Day 1 before switching to 480 mg Q4W nivolumab.

Chemotherapy will be given as per the study dosing schedule.

Stratification factors:

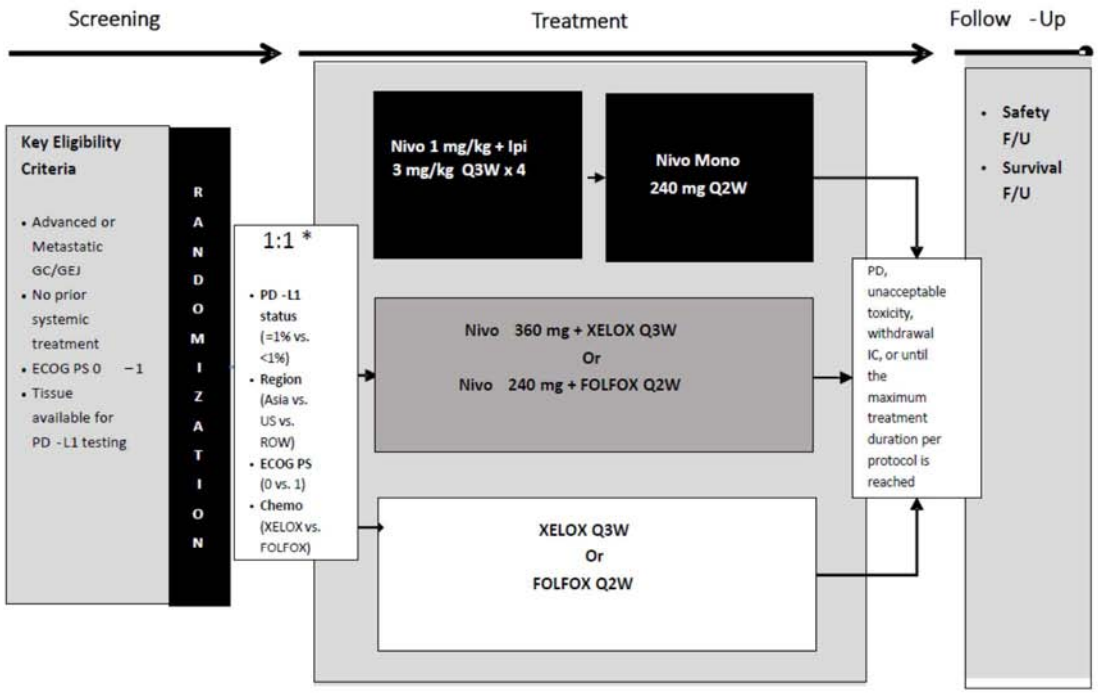
1) PD-L1 status (≥ 1% vs < 1% [including indeterminate])*
2) Region (Asia vs US vs Rest of world [ROW])
3) ECOG performance status (0 vs 1).
4) Chemotherapy (XELOX vs FOLFOX)

* During enrollment, the proportion of subjects with or without PD-L1 tumor expression will be monitored in pooled fashion, and may be re-assessed in case it does not reflect study assumptions (ie, subjects with PD-L1 tumor expression ≥ 1% is approximately 40% of all comers).

Per Amendment 23, PD-L1 expression has incorporated CPS scoring for the analysis. However, the stratification factor of tumor proportion score (TPS) remains unchanged for consistency.

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

Figure 3.1-1: Study Design Schematic



* Nivolumab + Ipilimumab arm is closed to enrollment as of 05-June-2018.

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 form (ICF).
- Subject is enrolled using the Interactive Response Technology (IRT) system.
- The choice of chemotherapy regimen XELOX or FOLFOX must be decided before contacting the IRT system for randomization.
- 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, 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 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.

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

- Begins after contacting the IRT system for randomization.
- Per Amendment 20, subjects will be randomized in an open-label fashion (1:1) to either the nivolumab-plus-chemotherapy (XELOX or FOLFOX) or the chemotherapy arm (XELOX or FOLFOX).
- Administration of study treatment is to begin within 3 calendar days of randomization.
- The treatment phase ends when the subject is discontinued from study therapy (ie, PD, unacceptable toxicity, maximum 2 year treatment of nivolumab, or subject withdrawal of consent).
- Adverse event assessments should be documented at each clinic visit and Women of Child-bearing Potential (WOCBP) must have a pregnancy test every 4 weeks (± 7 days).
- Treated subjects will be evaluated for tumor assessments every 6 weeks (± 7 days) up to and including Week 48, then every 12 weeks (± 7 days) thereafter.
- Biomarker sampling will follow the protocol-defined schedule [redacted].
- Patient-reported questionnaires EQ-5D-3L and FACT-Ga will be collected every 6 weeks.

Nivolumab-plus-Ipilimumab Arm: Closed to enrollment as of 05-June-2018.

- On the day of infusion, 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 4.5.1.6.
- PK and IMG sampling data will be collected as indicated in Table 5.5-1.

Nivolumab-plus-Chemotherapy (XELOX or FOLFOX) Arm:

- On the day of infusion, nivolumab is to be administered first. The administration procedures of chemotherapy will follow local standards.
- Nivolumab is allowed to be administrated alone in case the chemotherapy has to be discontinued due to toxicity. Chemotherapy alone is also allowed to be administered in doublet or monotherapy in case nivolumab has to be discontinued due to unacceptable toxicity.
- Nivolumab 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 4.5.1.6. Chemotherapy alone is not allowed to treat beyond progression.
- PK and IMG sampling data will be collected as indicated in Table 5.5-2 (Nivolumab with XELOX) and Table 5.5-3 (Nivolumab with FOLFOX).
- No cross-over is allowed between XELOX and FOLFOX.

Chemotherapy Arm (XELOX or FOLFOX)

- The administration procedures will follow the local standards.
- No cross-over is allowed between XELOX and FOLFOX.

Study assessment data are to be collected as outlined in Table 5.1-2 (on-treatment assessments, nivolumab-plus-ipilimumab), Table 5.1-3 (on-treatment assessments, nivolumab-plus-chemotherapy), and Table 5.1-4 (on-treatment assessments, chemotherapy).

3.1.3 Follow-up Phase

- Begins when the decision is made to discontinue a subject from study therapy.
- After completion of the first 2 follow-up (FU) visits (30 days [± 7 days] from last dose and 84 days [± 7 days] from FU1), subjects will be followed by clinic visit or phone contact every 3 months (± 14 days) or more frequently as needed for survival status and subsequent anti-cancer therapy.
- Subjects who discontinue treatment for reasons other than PD will continue to have tumor assessments (until PD) every 6 weeks (± 7 days) up to and including Week 48, then every 12 weeks (± 7 days) thereafter.
- Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All toxicities will be documented for a minimum of 100 days after the last dose of study drug.
- Patient-reported questionnaires EQ-5D-3L, GaCS from the FACT-Ga, and the FACT-G7 will be collected every 3 months (± 14 days) via phone contact or in-person visit.
- The biomarker sampling will continue as per protocol defined schedule [redacted].

Study follow-up assessment data are to be collected as outlined in Table 5.1-5.

The start of the trial is defined as the first visit for the 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, participants who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study treatment for the maximum treatment duration allowed by the study protocol. Study treatment 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 study is terminated due to safety concerns, b) development is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives, c) the subject can obtain medication from a government sponsored or private health program.

3.3 Study Population

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

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

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

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

2. Target Population

a) All subjects must have inoperable, advanced or metastatic GC or GEJ or distal esophageal carcinoma and have histologically confirmed predominant adenocarcinoma. The documentation of GEJ involvement can include biopsy, endoscopy, or imaging.

b) Subject must be previously untreated with systemic treatment (including HER 2 inhibitors) given as primary therapy for advanced or metastatic disease.

c) Allowed Prior Therapies: Prior adjuvant or neoadjuvant chemotherapy, radiotherapy and/or chemoradiotherapy for GC or GEJ cancer are permitted as long as the last administration of the last regimen (whichever was given last) occurred at least 6 months prior to randomization. Palliative radiotherapy is allowed and must be completed 2 weeks prior to randomization.

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

e) ECOG performance status score of 0 or 1 (Appendix 3).

f) Tumor tissue must be provided for biomarker analyses. 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. Subjects with non-evaluable results will not be allowed to be randomized. Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections, with an associated pathology report, must be submitted for biomarker evaluation prior to randomization. The 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.

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

h) Screening laboratory values must meet the following criteria:

i) WBC ≥ 2000/uL

ii) Neutrophils ≥ 1500/uL

iii) Platelets ≥ 100 x 10^3/uL

iv) Hemoglobin ≥ 9.0 g/dL

v) Serum albumin ≥ 3.0 g/dL

vi) Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance > 50 mL/min (using the Cockcroft-Gault formula)

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

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

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

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

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

Note: For subjects with hemoglobin ≥ 8.0 g/dL, blood transfusion is allowed and must be completed at least 72 hours prior to randomization. The repeated hemoglobin value ≥ 9.0 g/dL must be verified prior to randomization.

3. Age and Reproductive Status

a) Males and Females, ≥ 18 years of age

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

c) 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).

d) 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 and fetal protection 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.

e) WOCBP randomized to the chemotherapy arm must agree to follow instructions for method(s) of contraception for a period of 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo at least 5 half-lives. WOCBP randomized to the chemotherapy arm should use an adequate method to avoid pregnancy for approximately 4.5 months (ie, 30 days plus 98 days) after the last dose of investigational drug.

f) Males randomized to the chemotherapy arm and who are sexually active with WOCBP must agree to follow instructions for methods of contraception for a period of 90 days (duration of sperm turnover) plus the time required for the investigational drug to undergo at least 5 half-lives. Males randomized to the chemotherapy arm and who are sexually active with WOCBP should use an adequate method to avoid pregnancy for approximately 6 months (ie, 90 days plus 98 days) after the last dose of investigational drug. In addition, male subjects must be willing to refrain from sperm donation during this time.

g) Azoospermic males are exempt from contraceptive requirements unless the potential exists for fetal toxicity due to study drug being present in seminal fluid, even if the subject has undergone a successful vasectomy or if the partner is pregnant. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, but still must undergo pregnancy testing as described in this section.

h) Women must not be breastfeeding.

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 and when applicable, the potential of fetal toxicity occurring due to transmission of study drug, present in seminal fluid, to a developing fetus, even if the subject has undergone a successful vasectomy or if the partner is pregnant. 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

1. Target Disease Exceptions

a) Known Her2 positive status

b) Subjects with untreated known CNS metastases. Subjects are eligible if CNS metastases are adequately treated and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to randomization. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization.

c) Subjects with ascites which cannot be controlled with appropriate interventions.

2. Medical History and Concurrent Diseases

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

b) Subjects with active, known, or suspected autoimmune disease. Subjects with Type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, or 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.

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

d) 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.

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

f) Subjects with > Grade 1 peripheral neuropathy.

g) 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.

h) 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.

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

j) Subjects who have received a live/attenuated vaccine within 30 days of first treatment (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]).

3. Physical and Laboratory Test Findings

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

4. Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components

b) Any contraindications to any of the study drugs of the chemotherapy regimen (XELOX or FOLFOX) selected by the investigator. Investigators should refer to local package insert of the chemotherapy drugs.

5. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated. (Note: under certain specific circumstances and only in countries where local regulations permit, 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.

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

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

3.3.3 Women of Childbearing Potential

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) 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 3.4.2)
- Any concurrent anti-neoplastic therapy (ie, surgery, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of GC/GEJ).
- Any botanical preparation (eg herbal supplements or traditional Chinese medicines) intended to treat the disease under study. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.
- 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.

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 need anticoagulation treatment due to concomitant cardiovascular disease should be monitored closely, a maintenance of INR > 2 is recommended.

Subjects who are administered concomitantly capecitabine and oral coumarin-derivative anticoagulant therapy such as warfarin should have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose. Subjects who are administered capecitabine and other sensitive CYP2C9 substrate or a CYP2C9 substrate with narrow therapeutic index should be closely monitored for toxicity.

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.

3.5 Discontinuation of Subjects following any Treatment with Study Drug

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

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness. (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- Toxicity as specified in Sections 4.5.1.5 and 4.7
- Disease progression assessed by RECIST 1.1 criteria, unless the subject meets criteria for treatment beyond progression.

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 (e.g., 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, if local regulations allow. If, for whatever reason, the pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended), following approvals of participant /sponsor /IRB/EC, as applicable.

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

BMS may request that survival data be collected on all treated/randomized subjects outside of the protocol defined window (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 Investigational [Medicinal] Products (IPs/IMPs) consisting of the following:

- Nivolumab Solution for Injection
- Ipilimumab Solution for Injection
- Oxaliplatin Concentrate for Solution for Infusion
- Fluorouracil Solution for Injection
- Leucovorin (Folinic Acid) Solution for Injection
- Capecitabine tablets

The study drugs are described in Table 4-1.

Table 4-1: Study Drugs for CA209649

Product Description / Class and Dose 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/4 vials per carton. Clear to opalescent, colorless to pale yellow liquid. May contain particles.	2° to 8°C. Protect from light and freezing.
Oxaliplatin Concentrate for Solution for Infusion[b,c]	100 mg (5 mg/mL)	IP	Open label	Clear, colorless solution (20 mL/ vial), 1 vial/carton	Do not store above 25°C. Do not refrigerate or freeze. Store vial in outer carton. Protect from light.
Capecitabine[b,c]	150 mg and 500 mg tablets	IP	Open label	Wallet/blister card containing 10, 20, or 30 tablets	Do not store above 30°C.
Fluorouracil Solution for Injection[b,c]	2500 mg (50 mg/ mL)	IP	Open label	Clear, colorless or almost colorless solution. 50 mL/vial (1 vial/carton)	Do not store above 25°C. Do not refrigerate or freeze. Store in outer carton. Protect from light.
Leucovorin (folinic acid) Solution for Injection[b,c]	400 mg (50 mg/mL)	IP	Open label	8 mL/vial (1 or 4 vials/carton)	2° to 8°C. Store in original container. Protect from light.

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

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

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

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, Oxaliplatin solution for injection, Capecitabine tablets, Fluorouracil solution for injection, and Leucovorin solution for injection (Table 4-1).

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.

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 BMS should be contacted 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, oxaliplatin, fluorouracil, leucovorin, and capecitabine.

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 ICF must be assigned a subject number in the IRT.

Specific instructions for using the IRT 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 (the required tumor tissue received and evaluable result obtained by the central laboratory) 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: Asia vs US 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] is entered by the central laboratory vendor into the IRT and both the site and the BMS study team remain blinded to the result)
- Chemotherapy regimen: XELOX vs FOLFOX.

The original study design (before Amendment 08) had 2 arms. Subjects meeting all eligibility criteria were randomized in an open-label fashion (1:1 ratio) to either the nivolumab-plus-ipilimumab arm or the chemotherapy (XELOX or FOLFOX) arm.

Starting with Amendment 08, subjects meeting all eligibility criteria will be randomized in a 1:1:1 ratio to either the nivolumab-plus-ipilimumab arm, the nivolumab-plus-chemotherapy (XELOX or FOLFOX) arm, or the chemotherapy (XELOX or FOLFOX) arm. The nivolumab plus ipilimumab arm was closed to enrollment as of 05-June-2018. Subjects randomized to treatment in this arm prior to or on 05-June-2018 will continue to receive treatment with study drugs per protocol, and the study data will remain blinded for the planned primary analysis. Per Amendment 20, subjects will be randomized in an open-label fashion (1:1) to either the nivolumab-plus-chemotherapy (XELOX or FOLFOX) or the chemotherapy arm (XELOX or FOLFOX).

Randomization will be stratified by the following factors:

- PD-L1 expression level (≥ 1% vs < 1% or indeterminate)*
- Region: Asia vs US vs rest of world
- ECOG performance status: 0 vs 1
- Chemotherapy regimen (XELOX vs FOLFOX)

*During enrollment, the proportion of subjects with or without PD-L1 tumor expression will be monitored in pooled fashion, and may be re-assessed in case it does not reflect study assumptions (ie, subjects with PD-L1 tumor expression ≥ 1% is approximately 40% 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 Nivolumab and Ipilimumab Dosing

The nivolumab plus ipilimumab arm was closed to enrollment as of 05-June-2018. Subjects randomized to treatment in this arm prior to or on 05-June-2018 will continue to receive treatment with study drugs per protocol, and the study data will remain blinded until planned primary analysis.

4.5.1.1 Nivolumab and Ipilimumab Dose and Schedule

Subjects randomized to the nivolumab-plus-ipilimumab arm should receive nivolumab 1 mg/kg administered IV over 30 minutes followed by ipilimumab 3 mg/kg administered IV over 30 minutes on Day 1 of each treatment cycle every 3 weeks for 4 doses (Cycles 1 to 4), followed by nivolumab 240 mg administered IV over 30 minutes on Day 1 of each treatment cycle every 2 weeks (Cycle 5 and beyond) until PD (unless treatment beyond PD is permitted; see Section 4.5.1.6), unacceptable toxicity, withdrawal of consent, 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 and ipilimumab. From Amendment 29, subjects treated in the nivolumab 240 mg Q2W have an option to switch nivolumab 480 mg Q4W, the nivolumab 480 mg should be given 2 weeks following the last administration of nivolumab 240 mg dose.

Table 4.5.1.1-1: Dose Schedule of Nivolumab and Ipilimumab

Treatment Group	Drug Name	Cycle 1 (Week 1)	Cycle 2 (Week 4)[a]	Cycle 3 (Week 7)[a]	Cycle 4 (Week 10)[a]	Cycle 5 (Week13) till EOT (Q2 weeks)[b]
Nivolumab +Ipilimumab	Nivolumab 1 mg/kg	Day 1	Day 1	Day 1	Day 1	-
	Ipilimumab 3 mg/kg	Day 1	Day 1	Day 1	Day 1	-
Nivolumab	Nivolumab 240 mg	-	-	-	-	Day 1

[a] Cycles 2 to 4: Subsequent nivolumab and ipilimumab doses may be administered within 3 days before or after the scheduled date if necessary. Subjects may be dosed no less than 18 days between doses.

[b] Cycle 5 till EOT: Nivolumab may be administered up to 2 days before or 3 days after the scheduled date if necessary. Subjects may be dosed no less than 12 days between doses.

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 to the nearest milligram per institutional standard.

When study drugs (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 drug and will start after the infusion line has been flushed, filters changed and the patient has been observed to ensure no infusion reaction has occurred. The time between infusions is expected to be approximately 30 minutes but may be more or less depending on the situation.

There will be no dose escalations or reductions of nivolumab and ipilimumab allowed. Subjects may be dosed no less than 18 days from the previous dose during Q3W cycles (Cycles 1 to 4) and no less than 12 days from the previous dose during Q2W cycles (Cycles 5 and beyond). Pre-medications are not recommended for the first dose of nivolumab.

The treatment with nivolumab will be given for up to 24 months in the absence of disease progression or unacceptable toxicity.

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 4.5.1.8.

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

For further information related to nivolumab and ipilimumab preparation and dosing, please refer to the pharmacy manual.

4.5.1.2 Dose Delay Criteria for Nivolumab and/or Ipilimumab Therapy

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, AST, ALT and/or Total Bilirubin abnormalities
- Any Grade 3 skin, drug-related AE
- Any Grade 3 drug-related laboratory abnormality (excluding AST, ALT or Total Bilirubin), with the following exceptions for lymphopenia, and asymptomatic amylase or lipase abnormalities:
  - Grade 3 lymphopenia does not require dose delay
  - 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 receiving ipilimumab in combination with nivolumab 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 and/or nivolumab).

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.

4.5.1.3 Dose Reductions for Nivolumab or Ipilimumab Therapy

There will be no dose reductions for nivolumab or ipilimumab.

4.5.1.4 Criteria for Resuming Treatment for Nivolumab or Ipilimumab

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 4.5.1.5) 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 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor.
- Participants who received systemic corticosteroids for the management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled timepoint per protocol. However, if the treatment is delayed past the scheduled timepoint per protocol, the scheduled study treatment administration will be delayed, but not skipped, until dosing resumes. In particular, this is to ensure that subjects will receive 4 administrations of combined nivolumab and ipilimumab treatment if toxicity allows.

If dose delay is necessary for subjects during Week 1 - 12, 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 19 days must elapse between the replacement dose of ipilimumab and the administration of the next dose of nivolumab combined with ipilimumab.

If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in Section 4.5.1.5.

4.5.1.5 Criteria for Nivolumab and/or Ipilimumab Treatment Discontinuation

Treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, diarrhea, colitis, neurologic toxicity, drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related diarrhea, colitis, neurologic toxicity, myocarditis, uveitis, pneumonitis, 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 adrenal insufficiency requires discontinuation regardless of control with hormone replacement (note: Hospitalization for diagnostic workup of adrenal insufficiency without severe symptoms should not be considered a Grade 3 event)
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN
- *In most cases of Grade 3 AST or ALT elevation, study drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.
- Any Grade 4 drug-related 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
  - Grade 4 drug-related endocrinopathy AEs, such as hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:

  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor.
- 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.

Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks from the previous dose, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.

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.

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 240 mg every 2 weeks.

If a subject in any of the nivolumab/ipilimumab combination arms 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.

4.5.1.6 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[89]

Subjects treated with nivolumab alone or in combination with ipilimumab or chemotherapy will be permitted to continue their 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 treatment (alone or in combination with ipilimumab or chemotherapy). 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 plus ipilimumab or nivolumab.

If the investigator feels that the subject treated with nivolumab (alone or in combination with ipilimumab or chemotherapy) continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to Table 5.1-2.

For the subjects who continue treatment 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. 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 treatment (alone or in combination with ipilimumab or chemotherapy) 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.

4.5.1.7 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 are considered I-O agents 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
- Myocarditis

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

4.5.1.8 Treatment of Nivolumab- or Ipilimumab-Related Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, they are 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 nivolumab or ipilimumab 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 Grades 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.

4.5.2 Nivolumab plus Chemotherapy Arm

4.5.2.1 Nivolumab plus Chemotherapy Arm Dosing Schedule

Subjects randomized to the nivolumab-plus-chemotherapy arm should receive either nivolumab 360 mg plus XELOX or nivolumab 240 mg plus FOLFOX.

- Subjects assigned to nivolumab plus-XELOX will receive nivolumab 360 mg administered IV over 30 minutes and oxaliplatin 130 mg/m^2 administered IV on Day 1 of each treatment cycle every 3 weeks, and capecitabine 1000 mg/m^2 administered orally twice daily (ie, 1000 mg/m^2 in the morning and 1000 mg/m^2 in the evening) on Days 1 to 14 of each treatment cycle every 3 weeks (see Table 4.5.2.1-1). Dosing windows for subsequent XELOX doses should adhere to recommendations in the prescribing information or local standards, where indicated.
- Premedication is not usually required in the first cycle. For subsequent cycles, adequate premedication may be administrated per local standard.
- Capecitabine should be taken with food.

Table 4.5.2.1-1: Dose Schedule of Nivolumab-plus-XELOX

Treatment group	Drug name	Cycle 1 (Week 1)	Cycle 2 (Week 4)	Cycle 3 (Week 7)	Cycle 4 (Week 10)	Cycle 5 (Week 13) till EOT (Q3 weeks)
Nivolumab-plus-XELOX	Nivolumab 360 mg	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**
	Oxaliplatin 130 mg/m^2	Day 1	Day 1	Day 1	Day 1	Day 1
	Capecitabine 1000 mg/m^2 twice daily	Days 1 to 14	Days 1 to 14	Days 1 to 14	Days 1 to 14	Days 1 to 14

- Subjects assigned to nivolumab-plus-FOLFOX will receive nivolumab 240 mg administered IV over 30 minutes and oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 400 mg/m^2 administered IV on Day 1 of each treatment cycle every 2 weeks, and fluorouracil

1200 mg/m^2 IV continuous infusion over 24 hours daily or per local standard on Days 1 and 2 of each treatment cycle every 2 weeks (see Table 4.5.2.1-2). Dosing windows for subsequent FOLFOX doses should adhere to recommendations in the prescribing information or local standards, where indicated.
Premedication is not usually required in the first cycle. For subsequent cycles, adequate premedication may be administrated per local standard.

Table 4.5.2.1-2: Dose Schedule of Nivolumab-plus-FOLFOX

Treatment group	Drug name	Cycle 1 (Week 1)	Cycle 2 (Week 3)	Cycle 3 (Week 5)	Cycle 4 (Week 7)	Cycle 5 (Week 9) till EOT (Q2 weeks)
Nivolumab-plus-FOLFOX	Nivolumab 240 mg	Day 1	Day 1	Day 1	Day 1	Day 1
	Oxaliplatin 85 mg/m^2	Day 1	Day 1	Day 1	Day 1	Day 1
	Leucovorin 400 mg/m^2	Day 1	Day 1	Day 1	Day 1	Day 1
	Fluorouracil 400 mg/m^2	Day 1	Day 1	Day 1	Day 1	Day 1
	Fluorouracil 1200 mg/m^2	Days 1 & 2	Days 1 & 2	Days 1 & 2	Days 1 & 2	Days 1 & 2

- No cross-over will be allowed between XELOX and FOLFOX in this study.

When study drugs (nivolumab and chemotherapy) 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 chemotherapy infusion(s). The second infusion will always be the chemotherapy study drug(s) and will start after the infusion line has been flushed, filters changed and the patient has been observed to ensure no infusion reaction has occurred. The time between infusions is expected to be approximately 30 minutes but may be more or less depending on the situation.

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.

4.5.2.2 Dose Modification Criteria for Nivolumab-plus-Chemotherapy

Dose modification criteria for the combination regimen should follow the respective individual dose modification criteria of each component. For chemotherapy, it is allowed to follow local standard or local package insert recommendations.

Dosing for all drugs should be delayed/interrupted if any criteria in Sections 4.5.1.2 (for nivolumab) or Sections 4.6.2.2 (for XELOX) and 4.6.2.3 (for FOLFOX.) are met.

Dose reduction of nivolumab are not permitted. Dose reduction for chemotherapy is permitted according to local standard or local package insert. See also Sections 4.6.2.2 for XELOX and 4.6.2.3 for FOLFOX.

Subjects may resume dosing when resuming criteria for BOTH nivolumab (Section 4.5.1.4) and chemotherapy (Section 4.6.2.2 for XELOX and Section 4.6.2.3 for FOLFOX) are met. That is, nivolumab and chemotherapy must be administered together until treatment discontinuation. It is allowed to administer either nivolumab or chemotherapy doublet or single drug alone if the other(s) are delayed or discontinued due to toxicity which is not overlapping for nivolumab and chemotherapy, judging by the treating investigator if it is the best interest in the subjects.

The assessments for discontinuation of nivolumab and/or chemotherapy should be made separately. Nivolumab discontinuation criteria are detailed in Section 4.5.1.5, and chemotherapy discontinuation criteria are detailed in Sections 4.6.2.2 (for XELOX) and 4.6.2.3 (for FOLFOX). Continuation of nivolumab alone when chemotherapy has been discontinued due to toxicity is permitted. Chemotherapy doublet or single drug is allowed to continue if the discontinuation criteria for nivolumab is met.

From Amendment 29, nivolumab 480 mg Q4W is permitted when all chemotherapy components are discontinued and nivolumab is continued alone. Subjects must be in the study for a minimum of 6 months from Cycle 1, Day 1 before switching to 480 mg Q4W nivolumab. Nivolumab 480 mg should be given 2 weeks or 3 weeks following the last administration of nivolumab 240 mg Q2W or 360 mg Q3W, respectively.

Subjects treated with nivolumab-plus-chemotherapy will be permitted to continue nivolumab treatment beyond initial RECIST 1.1-defined PD, assessed by the investigator, as long as they meet the criteria described in Section 4.5.1.6. The management of nivolumab-related adverse events and infusion reactions should follow instructions listed in Section4.5.1.7 and 4.5.1.8.

4.6 Chemotherapy Arm Dosing

4.6.1 Oxaliplatin-Plus-Fluoropyrimidine Dose and Schedule

Subjects randomized to the chemotherapy arm should receive either XELOX or FOLFOX:

- Subjects assigned to XELOX will receive oxaliplatin 130 mg/m^2 administered IV on Day 1 of each treatment cycle and capecitabine 1000 mg/m^2 administered orally twice daily (ie, 1000 mg/m^2 in the morning and 1000 mg/m^2 in the evening) on Days 1 to 14 of each treatment cycle, every 3 weeks (see Table 4.6.1-1). Dosing windows for subsequent XELOX doses should adhere to recommendations in the current prescribing information or local standards, where indicated.
  Premedication is not usually required in the first cycle. For subsequent cycles, adequate premedication may be administrated per local standard.
  Capecitabine should be taken with food.

Table 4.6.1-1: Dose Schedule of XELOX						
Treatment group	**Drug name**	**Cycle 1 (Week 1)**	**Cycle 2 (Week 4)**	**Cycle 3 (Week 7)**	**Cycle 4 (Week 10)**	**Cycle 5 (Week 13) till EOT (Q3 weeks)**
XELOX	Capecitabine 1000 mg/m^2 twice daily	Days 1 to 14	Days 1 to 14	Days 1 to 14	Days 1 to 14	Days 1 to 14
	Oxaliplatin 130 mg/m^2	Day 1	Day 1	Day 1	Day 1	Day 1

- Subjects assigned to FOLFOX will receive oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 400 mg/m^2 administered IV on Day 1 of each treatment cycle, and fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours daily or per local standard on Days 1 and 2 of each treatment cycle, every 2 weeks (see Table 4.6.1-2). Dosing windows for subsequent FOLFOX doses should adhere to recommendations in the prescribing information or local standards, where indicated.

  Premedication is not usually required in the first cycle. For subsequent cycles, adequate premedication may be administrated per local standard.

Table 4.6.1-2: Dose Schedule of FOLFOX						
Treatment group	**Drug name**	**Cycle 1 (Week 1)**	**Cycle 2 (Week 3)**	**Cycle 3 (Week 5)**	**Cycle 4 (Week 7)**	**Cycle 5 (Week 9) till EOT (Q2 weeks)**
FOLFOX	Oxaliplatin 85 mg/m^2	Day 1	Day 1	Day 1	Day 1	Day 1
	Leucovorin 400 mg/m^2	Day 1	Day 1	Day 1	Day 1	Day 1
	Fluorouracil 400 mg/m^2	Day 1	Day 1	Day 1	Day 1	Day 1
	Fluorouracil 1200 mg/m^2	Days 1 & 2	Days 1 & 2	Days 1 & 2	Days 1 & 2	Days 1 & 2

- No cross-over will be allowed between XELOX and FOLFOX in this study.

4.6.2 Dose Modification Criteria for Oxaliplatin-Plus-Fluoropyrimidine Treatment

Dose modifications of oxaliplatin, capecitabine, leucovorin, and fluorouracil are permitted according to local standards or local package inserts.

4.6.2.1 General Guidance for Dose Modification for Chemotherapy

- Treatment for the first cycle should only commence if all the inclusion criteria are met and the subject has been enrolled. For subsequent cycles, dose delay/modification is permitted per local standard or as described in Section 4.6.2.2 and Section 4.6.2.3.
- Doses of any study drug omitted for toxicity are not replaced or restored; instead, the patient should resume the planned treatment cycles. Supportive care (for example, colony-stimulating factors [CSFs], blood and blood products, etc. can be administered in accordance with the latest American Society of Clinical Oncology (ASCO) or other equivalent guidelines.
- Dose modification, for non-serious and non-life-threatening toxicities like alopecia, altered taste or nail changes may not be required and the final decision is left to the discretion of the treating investigator.
- In situations where concomitant toxicities of varying severity exist, dose modification will be tailored for the toxicity with highest CTCAE grading.
- If there is a delay or modification in administration of study drug(s) due to toxicity, treatment with the other study agent(s) should continue as scheduled. If clinically appropriate, the investigator can delay all treatment components up to a maximum of 7 days to allow synchronized administration of all agents.

If toxicity related to any component of chemotherapy does not resolve in the same treatment cycle, the administration of that component can be delayed up to 6 weeks. If the toxicity does not resolve within 6 weeks, that component will be discontinued unless it is determined by the treating investigator that the patient might benefit from continuation of the component.

4.6.2.2 Dose Modification Criteria for XELOX

Capecitabine

Toxicity due to capecitabine administration may be managed by symptomatic treatment and/or treatment interruption or dose reduction. Dose modifications of capecitabine are presented in Table 4.6.2.2-1. Once the dose has been reduced, it should not be increased at a later time. For those toxicities considered by the treating physician to be unlikely to become serious or life-threatening, eg alopecia, altered taste, or nail changes, treatment can be continued at the same dose without reduction or interruption. Subjects taking capecitabine should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs. Doses of capecitabine omitted for toxicity are not replaced.

Table 4.6.2.2-1: Recommended Dose Modifications of Capecitabine

Toxicity[a]	During a course of therapy	Dose adjuvant for next treatments (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
1st appearance	Interrupt until resolved to Grade 0 1	100% (1000 mg/m^2)
2nd appearance		75% (750 mg/m^2)
3rd appearance		50% (500 mg/m^2)
4th appearance	Discontinue treatment permanently	-
Grade 3		
1st appearance	Interrupt until resolved to Grade 0 1	75% (750 mg/m^2)
2nd appearance		50% (500 mg/m^2)
3rd appearance	Discontinue treatment permanently	-
Grade 4		
1st appearance	Discontinue treatment permanently or, if physician deems it to be in the patient's best interest to continue, interrupt until resolved to Grade 0 - 1	50% (500 mg/m^2)

[a] According to the National Cancer Institute of Canada Clinical Trial Group (NCIC CTG) Common Toxicity Criteria (version 1) or the Common Terminology Criteria for Adverse Events (CTCAE) of the Cancer Therapy Evaluation Program, US National Cancer Institute, version 4.0.

Oxaliplatin

Dose Modifications for Neurotoxicity

- For Grade 2 peripheral sensory neuropathy (moderate paresthesia or dysesthesia), or limiting instrumental activities of daily living, skip oxaliplatin. When toxicity resolves to ≤ Grade 1, resume oxaliplatin to 75% of initial dose. If oxaliplatin is skipped for 4 weeks (2 consecutive doses) for neurologic toxicity, discontinue oxaliplatin.
- For Grade 3 or greater peripheral sensory neuropathy (severe paresthesia or dysesthesia), or limiting self-care activities of daily living), discontinue oxaliplatin.

Dose Modifications for Subjects with Renal Impairment

- For normal renal function or mild to moderate renal impairment (CrCl > 50 mL/min), the full dose of oxaliplatin can be administered.
- For severe renal impairment, the oxaliplatin dose should be reduced to 75% of initial dose.

Dose Modifications for Subjects with Hematological Toxicity

- For Grade 2 or Grade 3 thrombocytopenia, oxaliplatin should be reduced to 75% of initial dose. For Grade 4 thrombocytopenia, the dose should be reduced to 50% of initial dose.
- For Grade 3 or Grade 4 neutropenia or febrile neutropenia, the oxaliplatin dose should be reduced to 75% of initial dose.

4.6.2.3 Dose Modification Criteria for FOLFOX

Recommended dose modifications of FOLFOX are provided in Table 4.6.2.3-1 and Table 4.6.2.3-2.

Table 4.6.2.3-1: Recommended Dose Modifications of FOLFOX

Drug	Starting Dose	Dose Modification	
		Dose Level - 1	Dose Level - 2
Oxaliplatin	85 mg/m^2	70 mg/m^2	50 mg/m^2
5-FU	Bolus 5-FU: 400 mg/m^2 Leucovorin: 400 mg/m^2 Infusion 5-FU: 2400 mg/m^2/48 hours	Bolus 5-FU: 300 mg/m^2 Leucovorin: 300 mg/m^2 Infusion 5-FU: 2000 mg/m^2/48 hours	Bolus 5-FU: 200 mg/m^2 Leucovorin: 200 mg/m^2 Infusion 5-FU: 1600 mg/m^2/48 hours

5-FU: 5-fluorouracil

Table 4.6.2.3-2: Dose Modifications of FOLFOX

Toxicity	Definition	During a course of therapy	Dose adjustment for next treatments
Neutropenia	Grade 3 or greater	Interrupt until resolved to Grade 2	Dose level -1 *If treatment delayed for 4 consecutive weeks, discontinue all treatment
Thrombocytopenia	Grade 2	Interrupt until resolved to Grade 1	Dose level -1 *If Grade 2 persists > 7 days, oxaliplatin reduced by 2 dose levels when platelets improve to Grade 1
	Grade 3	Interrupt until resolved to Grade 1	Dose level -1 *If Grade 3 persists > 7 days, oxaliplatin reduced by 2 dose levels when platelets improve to Grade 1
	Grade 4	Interrupt until resolved to Grade 1	Dose level -2 *If Grade 4 persists > 7 days, oxaliplatin reduced by 2 dose levels when platelets improve to Grade 1
Neurologic toxicity	Grade 2 peripheral sensory neuropathy	Interrupt until resolved to Grade 1	Oxaliplatin dose -1 Continue 5-FU and leucovorin *If oxaliplatin delayed for neurologic toxicity for 4 consecutive weeks, discontinue oxaliplatin, continue 5-FU and leucovorin
	Grade 3 or greater peripheral sensory neuropathy	Discontinue oxaliplatin	Continue 5-FU and leucovorin
Gastrointestinal toxicities	Grade 2 or greater diarrhea	Interrupt until resolved to Grade 1	Dose level -1 If dose delayed for diarrhea for 4 consecutive weeks, discontinue all treatment

For toxicities not listed above, dose modifications are permitted per local standards.

Subjects may also discontinue oxaliplatin following multiple cycles if, in the investigator's judgment, cumulative toxicity is likely to increase over time and become problematic.

4.7 Criteria for Oxaliplatin-plus-Fluoropyrimidine Discontinuation

Except where specified below, both chemotherapy drugs in the platinum doublet chemotherapy regimen should be discontinued for any of the following:

- Any Grade ≥ 4 peripheral neuropathy requires discontinuation of oxaliplatin.
- In case of persistent Grade 3 paraesthesia, oxaliplatin should be discontinued.

- Any Grade ≥ 3 mucocutaneous reaction possibly attributable to capecitabine or leucovorin requires permanent discontinuation.
- Grade ≥ 3 drug-related thrombocytopenia associated with clinically significant bleeding
- Any drug-related liver function test (LFT) abnormality that meets the following criteria requires discontinuation:
  - AST or ALT > 5-10 x upper limit of normal (ULN) for > 2 weeks
  - AST or ALT > 10 x ULN
  - Total bilirubin > 5 x ULN
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any oxaliplatin-related decrease in creatinine clearance to < 30 mL/min (using the Cockroft Gault formula) requires discontinuation of oxaliplatin.
- Any drug-related AE which recurs after 2 prior dose reductions for the same drug-related AE 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 Grade 4 drug-related AE which the investigator deems is inappropriate to be managed by dose reduction(s) requires discontinuation of the drug(s) felt to be causing the event. The drug not felt to be related to the event may be continued.
- If any toxicity does not resolve within 42 days, that component will be discontinued unless it is determined by the treating investigator that the subject might benefit from continuation of the component.

For toxicities that are not listed above, the treating investigators can decide to discontinue any individual chemotherapy agent or all chemotherapy agents if it is not the best interest in the subject per the local standards.

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

4.8 Blinding/Unblinding

Not applicable.

4.9 Treatment Compliance

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

4.10 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 (e.g., 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 SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, i.e., 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.

4.11 Retained Samples for Bioavailability/Bioequivalence/Biocomparability

Not applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline - All Subjects (CA209649)

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. 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 formalin-fixed, paraffin-embedded [FFPE] tissue block or minimum 20 positively charged slides*) must be available within 6 months prior to randomization and sent to a central laboratory for biomarker analysis. PDL1 status must be assessed prior to randomization. Tissue must be a core needle biopsy, excisional biopsy, 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 20 slides are not obtainable, discuss with Sponsor.
Safety Assessments		
Physical Examination	X	Within 14 days prior to randomization.
Physical Measurements	X	Include Height, Weight and BSA. Within 14 days prior to randomization.
Vital Signs	X	Obtain vital signs at the screening visit and within 72 hours prior to first dose. Including BP, heart rate, and temperature.

Table 5.1-1: Screening Procedural Outline - All Subjects (CA209649)		
Procedure	**Screening Visit**	**Notes**
Performance Status (ECOG)	X	Within 14 days prior to randomization. See protocol Appendix 3.
Assessment of Signs and Symptoms	X	Within 14 days prior to randomization.
Serious Adverse Event (SAE) Assessment	X	After informed consent is signed.
Review of concomitant medications	X	Within 28 days prior to randomization.
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, total bilirubin, blood urea nitrogen (BUN) or serum urea level, creatinine, Ca, Na, K, Cl, fasting glucose and albumin within 14 days prior to randomization. Endocrine panel (TSH, Free T4, Free T3; Total T3/T4 are acceptable if Free T3/T4 are not available), Hep B/C (HBV 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 drug.
Efficacy Assessment		
Baseline Tumor Imaging Assessment	X	CT/MRI scan of chest, 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 contact	X	The IRT must be contacted for subject number assignment at the time informed consent is obtained.

Table 5.1-2: On-Treatment Assessments - Subjects in Nivolumab-plus-Ipilimumab Arm (CA209649)				
Procedure	**Cycle 1 Day 1 (3-week cycle) C1D1**	**Cycles 2 - 4 (Every 3 weeks) on Day 1**	**Cycle 5 and beyond (Every 2 weeks) on Day 1[a]**	**Note *Treatment till PD, unacceptable toxicity, withdraw from IC**
Safety Assessments				
Physical Examination	X	X	X	To be performed within 72 hours of dosing.
Vital Signs	X	X	X	Obtain vital signs within 72 hours prior to dose. Including BP, heart rate, and temperature.
Weight and ECOG Performance Status	X	X	X	Within 72 hours of dosing. See protocol Appendix 3 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	-
Laboratory Tests	See Note	See Note	See Note	Within 72 hours prior to each dose through Week 23 visit and every alternate dose thereafter. Include CBC w/differential, ALT, AST, total bilirubin, BUN or serum urea level, creatinine, Ca, Na, K, Cl, LDH and glucose. TSH (with reflexive Free T4 and Free T3; Total T3/T4 are acceptable if Free T3/T4 are not available) every 6 weeks (± 7 days) starting at C1D1. 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	See Note	Serum or urine within 24 hours prior to the initial administration of study drug and then every 4 weeks (± 7 days) regardless of dose delays; if collected with a dosing visit, then obtain within 24 hours prior to administration of study drug: urine or serum.

Table 5.1-2: On-Treatment Assessments - Subjects in Nivolumab-plus-Ipilimumab Arm (CA209649)				
Procedure	**Cycle 1 Day 1 (3-week cycle) C1D1**	**Cycles 2 - 4 (Every 3 weeks) on Day 1**	**Cycle 5 and beyond (Every 2 weeks) on Day 1[a]**	**Note** ***Treatment till PD, unacceptable toxicity, withdraw from IC**
PK and Immunogenicity Sampling				
PK samples	See Table 5.5-1 for details regarding specific sample timing.			
Immunogenicity blood sample	See Table 5.5-1 for details regarding specific sample timing.			
Efficacy Assessments				
Tumor Imaging Assessment		See Note	See Note	CT/MRI scan of chest, abdomen, pelvis, and any clinically indicated sites. 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 PD is permitted; see Section 4.5.1.6), or the subject withdraws consent, whichever comes first. Subjects who discontinue study treatment for reasons other than PD will continue to have tumor assessments until their disease progresses or they withdraw consent. Use same imaging method as was used at screening/baseline
Collection of biomarker sampling	[redacted]			
Outcomes Research Assessments				
FACT-Ga	X	See Note	See Note	Assessed every 6 weeks (± 3 days) from C1D1, regardless of treatment schedule; if administered on a dosing day, assessment should take place prior to any other study procedures.
EQ-5D-3L	X			
Health Care Resource Utilization	X	X	X	

Table 5.1-2: On-Treatment Assessments - Subjects in Nivolumab-plus-Ipilimumab Arm (CA209649)				
Procedure	**Cycle 1 Day 1 (3-week cycle) C1D1**	**Cycles 2 - 4 (Every 3 weeks) on Day 1**	**Cycle 5 and beyond (Every 2 weeks) on Day 1[a]**	**Note *Treatment till PD, unacceptable toxicity, withdraw from IC**
Study Drug				
Randomization	X			Contact IRT for randomization Note: Randomization to the nivolumab plus ipilimumab arm was closed as of 05-June-2018
Dispense Study Treatment	X	X	X	First dose to be administered within 3 calendar days after randomization. See Table 4.5.1.1-1. Cycles 2 - 4: subsequent nivolumab and ipilimumab doses may be administered within 3 days before or after the scheduled date if necessary. Subjects may be dosed no less than 18 days between doses. Cycle 5 till EOT: nivolumab 240 mg may be administered up to 2 days before or 3 days after the scheduled date if necessary. Subjects may be dosed no less than 12 days between doses. Nivolumab 480 mg should be given 2 weeks following the last administration of nivolumab 240 mg. Nivolumab 480 mg may be administered up to 3 days before or 3 days after the scheduled date, if necessary. Subjects may be dosed no less than 25 days between doses. Vials may be assigned through IRT up to 3 calendar days prior to every dose date.

[a] For subjects receiving nivolumab 480 mg Q4W alone, schedule of study procedures will be aligned with dosing visits (every 4 weeks on Day 1). Laboratory test should be done prior each dose. TSH (with reflexive Free T4 and Free T3; Total T3/T4 are acceptable if Free T3/T4 are not available) is acceptable to perform at alternative dose.

Table 5.1-3:	**On-Treatment Assessments - Subjects in Nivolumab-plus-Chemotherapy (XELOX or FOLFOX) Arm (CA209649)**			
Procedure	**Nivolumab-plus-XELOX and Nivolumab-plus-FOLFOX Cycle 1 Day 1 (C1D1)**	**Nivolumab-plus-XELOX Cycle 2 and beyond (Every 3 weeks) on Day 1**	**Nivolumab-plus-FOLFOX Cycle 2 and beyond (Every 2 weeks) on Day 1[a]**	**Note** ***Treatment till PD, unacceptable toxicity, withdraw from IC**
Safety Assessments				
Targeted Physical Examination	X	X	X	To be performed within 72 hours of dosing.
Vital Signs	X	X	X	Obtain vital signs within 72 hours prior to dose. Including BP, heart rate and temperature.
Weight, BSA and ECOG Performance Status	X	X	X	Within 72 hours of dosing. See protocol Appendix 3 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	-
Laboratory Tests	See Note	See Note	See Note	Nivolumab + XELOX: Within 72 hours prior to each dose. Nivolumab + FOLFOX: Within 72 hours prior to each dose through Week 23 and every alternate dose thereafter. Include CBC w/differential, ALT, AST, total bilirubin, BUN or serum urea level, creatinine, Ca, Na, K, Cl, LDH and glucose. TSH (with reflexive Free T4 and Free T3; Total T3/T4 are acceptable if Free T3/T4 are not available) every 6 weeks (± 7 days) starting at C1D1. 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-plus-Chemotherapy (XELOX or FOLFOX) Arm (CA209649)**			
Procedure	**Nivolumab-plus-XELOX and Nivolumab-plus-FOLFOX Cycle 1 Day 1 (C1D1)**	**Nivolumab-plus-XELOX Cycle 2 and beyond (Every 3 weeks) on Day 1**	**Nivolumab-plus-FOLFOX Cycle 2 and beyond (Every 2 weeks) on Day 1[a]**	**Note** ***Treatment till PD, unacceptable toxicity, withdraw from IC**
Pregnancy Test (WOCBP only)	X	See Note	See Note	Serum or urine within 24 hours prior to the initial administration of study drug and then every 4 weeks (± 7 days) regardless of dose delays; if collected with a dosing visit, then obtain within 24 hours prior to administration of study drug: urine or serum.
PK and Immunogenicity Sampling				
PK samples	See Table 5.5-2 and Table 5.5-3 for details regarding specific sample timing.			
Immunogenicity blood sample	See Table 5.5-2 and Table 5.5-3 for details regarding specific sample timing.			

Table 5.1-3: On-Treatment Assessments - Subjects in Nivolumab-plus-Chemotherapy (XELOX or FOLFOX) Arm (CA209649)

Procedure	Nivolumab-plus-XELOX and Nivolumab-plus-FOLFOX Cycle 1 Day 1 (C1D1)	Nivolumab-plus-XELOX Cycle 2 and beyond (Every 3 weeks) on Day 1	Nivolumab-plus-FOLFOX Cycle 2 and beyond (Every 2 weeks) on Day 1[a]	Note *Treatment till PD, unacceptable toxicity, withdraw from IC
Efficacy Assessments				
Tumor Imaging Assessment		See Note	See Note	CT/MRI scan of chest, abdomen, pelvis, and any clinically indicated sites. 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 PD is permitted; see Section 4.5.1.6), or the subject withdraws consent, whichever comes first. Subjects who discontinue study treatment for reasons other than PD will continue to have tumor assessments until their disease progresses or they withdraw consent. Use same imaging method as was used at screening/baseline
Collection of biomarker sampling data	[redacted]			
Outcomes Research Assessments				
FACT-Ga	X	See Note	See Note	Assessed every 6 weeks (± 3 days) from C1D1, regardless of treatment schedule; if administered on a dosing day, assessment should take place prior to any other study procedures.
EQ-5D-3L	X			
Health Care Resource Utilization	X	X	X	

Table 5.1-3:	**On-Treatment Assessments - Subjects in Nivolumab-plus-Chemotherapy (XELOX or FOLFOX) Arm (CA209649)**			
Procedure	**Nivolumab-plus-XELOX and Nivolumab-plus-FOLFOX Cycle 1 Day 1 (C1D1)**	**Nivolumab-plus-XELOX Cycle 2 and beyond (Every 3 weeks) on Day 1**	**Nivolumab-plus-FOLFOX Cycle 2 and beyond (Every 2 weeks) on Day 1[a]**	**Note** ***Treatment till PD, unacceptable toxicity, withdraw from IC**
Study Drug				
Randomization	X			Contact IRT for randomization
Dispense Study Treatment	X	X	X	First dose to be administered within 3 calendar days after randomization. Nivolumab and chemotherapy (XELOX or FOLFOX) should be administered on the same day. • Nivolumab dose schedule: in the nivolumab-plus-XELOX arm (every-3-week dosing), nivolumab may be administered within 3 days before or after the scheduled date if necessary, but subjects may be dosed no less than 18 days between doses; in the nivolumab-plus-FOLFOX arm (every-2-week dosing), nivolumab may be administered up to 2 days before or 3 days after the scheduled date if necessary, but subjects may be dosed no less than 12 days between doses. Nivolumab 480 mg should be given 2 weeks following the last administration of 240 mg, or 3 weeks following the last administration of 360 mg. Nivolumab 480 mg may be administered up to 3 days before or 3 days after

Table 5.1-3:	**On-Treatment Assessments - Subjects in Nivolumab-plus-Chemotherapy (XELOX or FOLFOX) Arm (CA209649)**			
Procedure	**Nivolumab-plus-XELOX and Nivolumab-plus-FOLFOX Cycle 1 Day 1 (C1D1)**	**Nivolumab-plus-XELOX Cycle 2 and beyond (Every 3 weeks) on Day 1**	**Nivolumab-plus-FOLFOX Cycle 2 and beyond (Every 2 weeks) on Day 1[a]**	**Note** ***Treatment till PD, unacceptable toxicity, withdraw from IC**
				the scheduled date, if necessary. Subjects may be dosed no less than 25 days between doses. • XELOX dose schedule: see Table 4.6.1-1. Subsequent XELOX doses may be administered within dosing windows per package insert or local standard. • FOLFOX dose schedule: see Table 4.6.1-2. Subsequent FOLFOX doses may be administered within dosing windows per package insert or local standard. Vials may be assigned up to 3 calendar days prior to every dose date.

[a] For subjects in nivo-plus-chemotherapy arm, a 480 mg Q4W nivolumab treatment regimen will be permitted when all chemotherapy is discontinued and nivolumab is continued alone, subjects in this arm must be in the study for a minimum of 6 months from Cycle 1, Day 1 before switching to 480 mg Q4W nivolumab. For subjects receiving nivolumab 480 mg Q4W alone, schedule of study procedures will be aligned with dosing visits (every 4 weeks on Day 1). Laboratory test should be done prior each dose. TSH (with reflexive Free T4 and Free T3; Total T3/T4 are acceptable if Free T3/T4 are not available) is acceptable to perform at alternative dose.

Table 5.1-4: On-Treatment Assessments - Subjects in Chemotherapy (XELOX or FOLFOX) Arm (CA209649)				
Procedure	**XELOX and FOLFOX Cycle 1 Day 1 (C1D1)**	**XELOX Cycle 2 and beyond (Every 3 weeks) on Day 1**	**FOLFOX Cycle 2 and beyond (Every 2 weeks) on Day 1**	**Note** ***Treatment till PD, unacceptable toxicity, withdraw from IC**
Safety Assessments				
Targeted Physical Examination	X	X	X	To be performed within 72 hours of dosing.
Vital Signs	X	X	X	Obtain vital signs within 72 hours prior to dose. Including BP, heart rate and temperature.
Weight, BSA and ECOG Performance Status	X	X	X	Within 72 hours of dosing. See protocol Appendix 3 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	-
Laboratory Tests	See Note	See Note	See Note	XELOX: Within 72 hours prior to each dose. FOLFOX: Within 72 hours prior to each dose through Week 23 and every alternate dose thereafter. Include CBC w/differential, ALT, AST, total bilirubin, BUN or serum urea level, creatinine, Ca, Na, K, Cl, LDH and glucose. 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	See Note	Serum or urine within 24 hours prior to the initial administration of study drug and then every 4 weeks (± 7 days) regardless of dose delays; if collected with a dosing visit, then obtain within 24 hours prior to administration of study drug: urine or serum.

Table 5.1-4: On-Treatment Assessments - Subjects in Chemotherapy (XELOX or FOLFOX) Arm (CA209649)				
Procedure	**XELOX and FOLFOX Cycle 1 Day 1 (C1D1)**	**XELOX Cycle 2 and beyond (Every 3 weeks) on Day 1**	**FOLFOX Cycle 2 and beyond (Every 2 weeks) on Day 1**	**Note** ***Treatment till PD, unacceptable toxicity, withdraw from IC**
Efficacy Assessments				
Tumor Imaging Assessment		See Note	See Note	CT/MRI scan of chest, abdomen, pelvis, and any clinically indicated sites. 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 or the subject withdraws consent, whichever comes first. Subjects who discontinue study treatment for reasons other than PD will continue to have tumor assessments until their disease progresses or they withdraw consent. Use same imaging method as was used at screening/baseline
Collection of biomarker sampling data	[redacted]			
Outcomes Research Assessments				
FACT-Ga	X	See Note	See Note	Assessed every 6 weeks (± 3 days) from C1D1, regardless of treatment schedule; if administered on a dosing day, assessment should take place prior to any other study procedures.
EQ-5D-3L	X			
Health Care Resource Utilization	X	X	X	

Table 5.1-4: On-Treatment Assessments - Subjects in Chemotherapy (XELOX or FOLFOX) Arm (CA209649)				
Procedure	**XELOX and FOLFOX Cycle 1 Day 1 (C1D1)**	**XELOX Cycle 2 and beyond (Every 3 weeks) on Day 1**	**FOLFOX Cycle 2 and beyond (Every 2 weeks) on Day 1**	**Note** ***Treatment till PD, unacceptable toxicity, withdraw from IC**
Study Drug				
Randomization	X			Contact IRT for randomization
Dispense Study Treatment	X	X	X	First dose to be administered within 3 calendar days after randomization. XELOX dose schedule: see Table 4.6.1-1. Subsequent XELOX doses may be administered within dosing windows per package insert or local standard. FOLFOX dose schedule: see Table 4.6.1-2. Subsequent FOLFOX doses may be administered within dosing windows per package insert or local standard. Vials may be assigned up to 3 calendar days prior to every dose date.

Table 5.1-5: Follow-Up Procedural Outline - All Subjects (CA209649)			
Procedure	**Follow-up Visits 1 and 2 FU1: 30 days (± 7 days) after last dose FU2: 84 days (± 7 days) after FU1**	**Survival Follow-Up Visits every 3 months (± 14 days) from FU2**	**Notes**
Safety Assessments			
Physical Examination	X		
Adverse Events Assessment	X		Assessed using NCI CTCAE v.4
Review of Subsequent Cancer Therapy	X	X	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 above information will be also collected during survival follow up period
Review of Concomitant Medications	X		
Laboratory Tests	See Note		Include CBC w/differential, ALT, AST, total bilirubin, BUN or serum urea level, creatinine, Ca, Na, K, Cl, LDH and glucose. If there are ongoing AE, monthly lab tests will be conducted till FU2.
Pregnancy Test (WOCBP only)	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 drug for reasons other than PD, follow-up scans should be performed every 6 weeks (± 7 days) up to and including Week 48, then every 12 weeks (± 7 days) until PD, lost to follow-up, or withdrawal of consent. Radiographic assessments should not be delayed until follow-up visits 1 & 2.

Table 5.1-5: Follow-Up Procedural Outline - All Subjects (CA209649)			
Procedure	**Follow-up Visits 1 and 2 FU1: 30 days (± 7 days) after last dose FU2: 84 days (± 7 days) after FU1**	**Survival Follow-Up Visits every 3 months (± 14 days) from FU2**	**Notes**
			CT/MRI scan of chest, abdomen, pelvis, and any clinically indicated sites. Use same imaging method as was used at screening/baseline.
Outcomes Research Assessments			
GaCS from the FACT-Ga	X	See Note	Every 3 months (± 14 days) after FU2, via a phone contact or in-person visit.
FACT-G7	X		
EQ-5D-3L	X		
Health Care Resource Utilization	X		
Collection of biomarker sampling	[redacted]		
Subject Status			
Survival status	X	X	Every 3 months (± 14 days) or more frequently as needed after FU2, may be accomplished by in-person visit or phone contact.

5.1.1 Retesting During Screening or Lead-in Period

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

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

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

5.2 Study Materials

- NCI CTCAE version 4
- Nivolumab IB
- Ipilimumab IB
- Pharmacy Binder
- Laboratory manuals for collection and handling of blood (including biomarker and immunogenicity) and tissue specimens
- Site manual for operation of IRT system, including enrollment/randomization worksheets
- Site manual for imaging process and requirements
- Manual for entry of local laboratory data
- Serious Adverse Events (or eSAE) case report form pages
- Subject Questionnaires: FACT-Ga (GaCS, FACT-G7), EQ-5D-3L
- Pregnancy Surveillance Forms
- RECIST 1.1 pocket guide.

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, ECG, and assessment of signs and symptoms. Vital signs (blood pressure [BP], heart rate and temperature) will be obtained at the screening visit and within 72 hours prior to first dose.

Screening local laboratory assessments should be done within 14 days prior to randomization and are to include: CBC with differential, chemistry panel including LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Na, K, Cl, LDH, fasting glucose and albumin. The endocrine panel including TSH, free T3, and free T4 (Total T3/T4 are acceptable if Free T3/T4 are not available). Hep B/C testing (HBV HBsAG, HCV antibody or HCV RNA) should be done within 28 days prior to randomization.

Pregnancy tests for WOCBP must be performed at the screening visit and within 24 hours prior to the initial administration of study drug.

Tumor tissue samples, recent or archival, must be available within 6 months prior to randomization and sent to a central laboratory for PD-L1 status and biomarker analysis. See Section 3.1.1 for details.

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

5.3.2 On-Treatment Safety Assessments

Subjects will be evaluated for safety if they have received any study drug. Adverse event (AEs and SAEs) 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 dosing: CBC with differential, LFTs (ALT, AST, total bilirubin), BUN or serum urea level, creatinine, Ca, Na, K, Cl, LDH and glucose.

Thyroid function testing (TSH with reflexive fT3 and fT4; Total T3/T4 are acceptable if Free T3/T4 are not available) is to be done every 6 weeks (± 7 days) starting at C1D1 (every 3 cycles for subjects receiving nivolumab at 240 mg Q2W and every 2 cycles for subjects receiving nivolumab at 360 mg Q3W or 480 mg Q4W).

On-treatment pregnancy tests should be performed as per the schedule in Table 5.1-2, Table 5.1-3, and Table 5.1-4.

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, or fever) consistent with possible pulmonary AEs, 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 described in Table 5.1-5. A physical examination will be performed at follow-up visits FU1 and FU2. Laboratory and pregnancy tests will be performed as described in Table 5.1-5.

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.

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, utilizing CT or MRI. In addition to chest, abdomen, and pelvis, clinically indicated sites as determined by the treating investigator should be assessed 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 (unless treatment beyond PD is permitted; see Section 4.5.1.6), or the subject withdraws consent, whichever comes first. Subjects who discontinue study treatment for reasons other than PD will continue to have tumor assessments until their disease progresses or they withdraw consent.

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, and 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 (Appendix 4). Correction: the Verification of Response stated in the Appendix 4.1.2 should be confirmation of PR and CR is required ≥ 4 weeks to ensure that the responses identified are not the result of measurement error.

All radiologic imaging from this study will be transmitted to a centralized imaging core laboratory for Blinded Independent Central Review (BICR).

5.4.1 Independent Review of Progression

The clinical management of subjects during the study will be based upon local radiologic tumor measurements. 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.

If clinically acceptable, subsequent therapy should begin only after RECIST 1.1 progression has been assessed by BICR. Subjects who start palliative local therapy or subsequent therapy without prior assessment of RECIST 1.1 progression by central review, the BICR 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 BICR must be requested. Tumor assessments may be discontinued when the independent radiologist assesses 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.

Details of the Independent Review of Progression process 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 and nivolumab-plus-chemotherapy arms at the time points indicated in Table 5.5-1, Table 5.5-2, and Table 5.5-3. 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.

Table 5.5-1: Pharmacokinetic and Immunogenicity Sampling Schedule for the Nivolumab + Ipilimumab Arm followed for Nivolumab monotherapy 240 mg every 2 weeks or 480 mg every 4 weeks

Study Cycle/Day Cycles 1 - 4 = every 3 weeks Cycle 5 and beyond = 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	Ipilimumab PK Blood Sample	Ipilimumab IMG Blood Sample
Cycle 1 Day 1	Predose[a]	00:00	X	X	X	X

Table 5.5-1: Pharmacokinetic and Immunogenicity Sampling Schedule for the Nivolumab + Ipilimumab Arm followed for Nivolumab monotherapy 240 mg every 2 weeks or 480 mg every 4 weeks

Study Cycle/Day Cycles 1 - 4 = every 3 weeks Cycle 5 and beyond = 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	Ipilimumab PK Blood Sample	Ipilimumab IMG Blood Sample
Cycle 2 Day 1	Predose[a]	00:00	X	X	X	X
Cycle 4 Day 1	Predose[a]	00:00	X	X	X	X
Cycle 5 Day 1	Predose[a]	00:00	X	X	X	X
Cycle 11 Day 1	Predose[a]	00:00	X	X	X	X
Cycle 17 Day 1	Predose[a]	00:00	X	X		
Cycle 23 Day 1	Predose[a]	00:00	X	X		
Cycle 35 Day 1	Predose[a]	00:00	X	X		
Cycle 47 Day 1	Predose[a]	00:00	X	X		

[a] All predose samples should be taken just prior to the start of nivolumab infusion (preferably within 30 minutes).

Table 5.5-2: Pharmacokinetic and Immunogenicity Sampling Schedule for the Nivolumab + Chemotherapy Arm - Q3W Dosing with XELOX

Study Cycle/Day Nivolumab + XELOX= every 3 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]	00:00	X	X
Cycle 2 Day 1	Predose[a]	00:00	X	X
Cycle 5 Day 1	Predose[a]	00:00	X	X
Cycle 11 Day 1	Predose[a]	00:00	X	X
Cycle 17 Day 1	Predose[a]	00:00	X	X
Cycle 25 Day 1	Predose[a]	00:00	X	X
Cycle 33 Day 1	Predose[a]	00:00	X	X

[a] All predose samples should be taken just prior to the start of nivolumab infusion (preferably within 30 minutes). If nivolumab is discontinued, then PK and IMG samples should be collected for the next 2 cycles scheduled for PK/IMG sampling following discontinuation.

Table 5.5-3: Pharmacokinetic and Immunogenicity Sampling Schedule for the Nivolumab + Chemotherapy Arm - Q2W Dosing with FOLFOX

Study Cycle/Day Nivolumab + FOLFOX= 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]	00:00	X	X
Cycle 2 Day 1	Predose[a]	00:00	X	X
Cycle 3 Day 1	Predose[a]	00:00	X	X
Cycle 7 Day 1	Predose[a]	00:00	X	X
Cycle 9 Day 1	Predose[a]	00:00	X	X
Cycle 17 Day 1	Predose[a]	00:00	X	X
Cycle 25 Day 1	Predose[a]	00:00	X	X
Cycle 37 Day 1	Predose[a]	00:00	X	X
Cycle 49 Day 1	Predose[a]	00:00	X	X

[a] All predose samples should be taken just prior to the start of nivolumab infusion (preferably within 30 minutes). If nivolumab is discontinued, then PK and IMG samples should be collected for the next 2 cycles scheduled for PK/IMG sampling following discontinuation.

5.5.1 Pharmacokinetic and Immunogenicity Collection and Processing

Pharmacokinetic samples will be analyzed for nivolumab/ipilimumab by a validated ligand binding assay. Immunogenicity samples will be analyzed for anti-nivolumab antibodies/anti-ipilimumab antibodies by a validated IMG assay; samples may also be analyzed for neutralizing antibodies by a validated method. Serum samples may be analyzed by an exploratory method that measures ADAs for technology exploration purposes; exploratory results will not be reported. Serum samples designated for PK or biomarker assessments may also be used for IMG analysis if required (eg, insufficient volume for complete IMG assessment or to follow up on suspected IMG-related AE).

Designated staff of Bristol-Myers Squibb Research & Development may be unblinded (obtain the randomization codes) prior to database lock to facilitate the bioanalytical analysis of pharmacokinetic samples and immunogenicity. A bioanalytical scientist in the Bioanalytical Sciences department of Bristol-Myers Squibb Research & Development (or a designee in the

external central bioanalytical laboratory) will be unblinded to (may obtain) the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples.

5.6 Biomarker Assessments

Peripheral blood and tumor tissue will be collected prior to therapy. Peripheral blood samples will also be collected at selected timepoints on treatment, up to 5 days prior to dosing. 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 (e.g., if an event occurs between biomarker sampling and dosing that prevents dosing from taking place). A detailed description of each assay system is described below. [redacted]

[redacted]

5.6.1 Tumor Samples

Tumor specimens will be obtained from consenting subjects prior to treatment to characterize immune cell populations and expression of selected tumor markers. Tumor tissue (block or slides) must be available for submission prior to randomization. In situations where on-treatment biopsies or surgeries are performed, tumor samples should be sent for central pathology reading.

[redacted]

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.

Biopsy samples from resections should be fixed in 10% neutral-buffered formalin for 24 to 48 hours prior to paraffin embedding. Tumor tissue samples should not be shipped in formalin as the temperature and length of fixation cannot be controlled during shipping.

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

Sample shipments should include a completed requisition form containing collection date, collection method, primary/metastatic, site, fixation conditions, and a copy of the pathology report, if available.

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.

[redacted]

5.6.1.7 Microsatellite Instability Testing

MSI-H (Microsatellite Instability-High) in tumors refers to changes in 2 or more of the 5 National Cancer Institute-recommended panels of microsatellite markers in tumor tissue compared to a reference whole blood sample (baseline SNP collection). The original (1997) Bethesda guidelines proposed a panel of 5 microsatellite markers for the uniform analysis of MSI in hereditary nonpolyposis colorectal cancer (HNPCC). This panel, which is referred to as the Bethesda Panel, included 2 mononucleotide (BAT-25 and BAT-26) and 3 dinucleotide (D5S346, D2S123, and D17S250) repeats.[90] Individual testing sites may utilize a slightly different panel of markers incorporating alternative mononucleotide or dinucleotide markers. Regardless of the panel of markers, samples with instability in 2 or more of these markers are defined as MSI-High (MSI-H), whereas those with one unstable marker are designated as MSI-Low (MSI-L). Samples with no detectable alterations are MSI-stable (MSS).

Alternative assay platforms could also be used for MSI testing.

5.7 Outcomes Research Assessments

Subjects will be asked to complete the EQ-5D-3L and FACT-Ga before any clinical activities are performed during the treatment and follow-up phases. Questionnaires will be provided in the subject's preferred language, if available. Table 5.1-2, Table 5.1-3, Table 5.1-4, and Table 5.1-5 provide information regarding the timing of patient-reported outcomes assessments.

Subjects' reports of general health status will be measured using the EQ-5D-3L. The EQ-5D-3L 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-3L. Altogether, the instrument describes 35 to 243 health states. Empirically derived weights can be applied to an individual's

responses to the EQ-5D-3L 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-3L 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-Ga questionnaire and selected components, including the FACT-G7 and GaCS, will be used to assess the effects of underlying disease and its treatment on health-related quality of life (HRQoL) for patients.

As a generic cancer-related core, the FACT-Ga 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 HRQoL in cancer patients.

In addition to the FACT-G, The FACT-Ga includes a 19-item disease-specific GaCS that assesses additional disease specific symptoms and impacts relating to pain, reflux, dysphagia, eating difficulties, tiredness, weakness, interference, and difficulty planning. Each FACT-Ga item is rated on a five-point scale ranging from 0 (not at all) to 4 (very much).

Scores for the PWB, FWB, SWB, and EWB subscales can be combined to produce a FACT-G total score, which provides an overall indicant of generic HRQoL. The FACT-G and GaCS scores, can be combined to produce a total score for the FACT-Ga, which provides a composite measure of general and targeted HRQoL. Higher scores indicate better HRQoL. The full FACT-Ga 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 GaCS and FACT-G7 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 Other Assessments

Not applicable.

6 ADVERSE EVENTS

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

temporally associated with the use of study drug, whether or not considered related to the study drug.

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

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

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

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. Care should be taken not to introduce bias when collecting AE and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known adverse events, when appropriate for the program or protocol.

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

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

6.1 Serious Adverse Events

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

A ***Serious Adverse Event (SAE)*** is defined as 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.

Pregnancy, Section 6.4, and potential drug induced liver injury (DILI), Section 6.6, must follow the same transmission timing and processes to BMS as used for SAEs. (See Section 6.1.1 for reporting pregnancies).

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

EVALUATING AES AND SAES

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

6.1.1 Serious Adverse Event Collection and Reporting

Section 5.6.1 in the nivolumab and ipilimumab IBs presents 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, information on 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 from the time of signing the consent, including those thought to be associated with protocol-specified procedures 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 BMS (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 required 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. When paper forms are used, the original paper forms are to remain on site. 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.

Follow-up of AEs and SAEs

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

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

All SAEs must be followed to resolution or stabilization.

BMS will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

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

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.

Information on 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),
- AND
- Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
- AND
- No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

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

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

An independent Data Monitoring Committee (DMC) will be utilized. A DMC will be established to provide oversight of safety and efficacy considerations in CA209649. 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, nivolumab plus ipilimumab and nivolumab plus chemotherapy. 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.

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

As of 05-June-2018, the nivolumab plus ipilimumab arm was closed to enrollment based on the DMC recommendation. Subjects randomized to treatment in this arm prior to or on 05-June-2018 will continue to receive treatment with study drugs per protocol, and the study data will remain blinded until planned primary analysis.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

8.1.1 Randomization Schema

The original study design (before Amendment 08) had 2 arms, with subjects being randomized in a 1:1 ratio to the nivolumab plus ipilimumab or to the oxaliplatin plus fluoropyrimidine arm (XELOX or FOLFOX; arm will be further referred to as chemotherapy arm). Amendment 08 added a new arm: nivolumab in combination with oxaliplatin plus fluoropyrimidine (XELOX or FOLFOX; arm will be further referred to as nivolumab plus chemotherapy arm). The IRT switched to a 1:1:1 randomization at all the participating sites when this third arm was ready to be opened on 27-Mar-2017. Up until that point, there were 83 subjects randomized in the 1:1 randomization to nivolumab plus ipilimumab and chemotherapy arm. In Amendment 08, it was planned to randomize 1266 subjects at 1:1:1 ratio to nivolumab plus ipilimumab, chemotherapy and nivolumab plus chemotherapy arms. The total number of subjects to be randomized was planned to be 1349.

Newly available internal and external data suggested a stronger predictability of PD-L1 CPS than TPS of immunotherapy treatment effects (See Section 1.1.13). However, uncertainty still exists of CPS at different cutoffs when extrapolated to first line (1L) metastatic setting in GC and GEJ. To ensure sufficient sample size for evaluating the correlation of efficacy and different CPS cutoffs and to keep continuity of enrollment of the study, on 29-May-2018, Amendment 19 was approved to allow additional 300 subjects to be randomized under 1:1:1 ratio for a total sample size of 1566 to the 3 treatment arms.

Per DMC recommendation, randomization to the nivolumab plus ipilimumab arm was stopped on 05-June-2018. The subjects who were already randomized to treatment in this arm prior to or on 05-June-2018 continued to receive study treatment per protocol, and the study data remained blinded for the planned analysis (see Section 1.5). As such, the 1:1:1 randomization was carried through on 05-Jun-2018. These changes were implemented in Amendment 20. At this point, a total of 1098 subjects were randomized under 1:1:1 ratio. In addition there were 83 subjects randomized to nivolumab plus ipilimumab and to chemotherapy arms (prior to Amendment 08). Following

Amendment 20, subjects were to be randomized in 1:1 ratio to either the nivolumab plus chemotherapy or the chemotherapy arm.

[redacted] Therefore, the enrollment was extended to ensure that the study was appropriately powered for PFS and OS primary endpoints in the CPS ≥ 5 population. To allow for this, Amendment 26 increased the total sample size from 1649 to approximately 2005. This resizing of the total population was to ensure that the sample size of the enriched population for the primary analyses (subjects with CPS ≥ 5) was the same as was specified in Amendment 23 to maintain the same power under the statistical assumptions as stated in Amendment 23.

The accrual was completed in May 2019 and in total 2032 subjects were randomized. It is estimated that 1582 subjects were concurrently randomized to nivolumab plus chemotherapy and to chemotherapy and that 815 subjects were concurrently randomized to nivolumab + ipilimumab and chemotherapy (see Section 8.1.3).

Table 8.1.1-1 presents the randomization schema and sample size.

Table 8.1.1-1: Randomization Allocation and Sample Size

Protocol Periods	Randomization allocation	Number of Randomized Subjects Current/ Cumulative
First patient randomized - Amendment 8	1:1 (Nivolumab +Ipilimumab : Chemotherapy)	83/83
Amendment 08 - Amendment 20	1:1:1 (Nivolumab + Ipilimumab : Chemotherapy: Nivolumab + Chemotherapy)	1098/1181
Amendment 20 to amendment 26	1:1 (Chemotherapy : Nivolumab + Chemotherapy)	468/1649
Amendment 26 to the end of enrollment	1:1 (Chemotherapy : Nivolumab + Chemotherapy)	383/2032

8.1.2 Changes of Statistical Analyses and Timing of Analyses in Amendment 29

Per protocol Amendment 23 (November 2018), the primary population of both primary endpoints PFS and OS was changed to randomized subjects with PD-L1 CPS ≥ 5 and the PD-L1 CPS scoring process started for subjects already randomized in the study to date. In March 2019, the need for additional steps for the PD-L1 CPS scoring process was established (see Section 1.1.14) and consequently the expected completion date of PD-L1 CPS scoring will be delayed and is now projected to complete approximately 6 months or later after the completion of enrollment.

As discussed in Section 1.1.14, recent data in 1L GC Phase 3 study suggested a longer delay of separation of KM curves of I-O+ chemo vs chemo for PFS and OS[76]. These data suggested that a

longer follow-up would warrant the full capture of the treatment effect for the primary endpoints of PFS and OS in the N+CT vs CT.

Considering the delay of completion of PD-L1 CPS scoring, and the need to have longer minimum follow-up for PFS and OS to ensure data maturity, Amendment 29 documents the changes on the timing of PFS and OS analyses from event driven to time driven. In addition, Amendment 29 specifically, documents the changes of the primary population of PFS.

The primary analysis of PFS in all randomized subjects with PD-L1 CPS ≥ 5 will be conducted after a 12-month minimum follow-up (from the date last patient was concurrently randomized to N+CT or CT). The primary analysis of OS in all randomized subjects with PD-L1 CPS ≥ 5 includes one interim and final analysis. The interim analysis will be conducted after 12-month minimum follow-up along with the primary PFS analysis. The final OS analysis will be conducted after a 24-month minimum follow-up, ie, 12 months after the OS interim analyses.

The analysis of OS in N+I vs CT in all randomized subjects with PD-L1 CPS ≥ 5 will be conducted at approximately 36-month minimum follow-up (after the last patient was randomized to N+I or CT). This analysis will be at the time of the final analysis of N+CT vs CT.

The timing of the efficacy analyses is described in Table 8.1.2-1.

Table 8.1.2-1: Timing of Analyses

	Endpoints		
Timing of Analysis	**PFS N+CT vs CT in all randomized subjects with PD-L1 CPS ≥ 5**	**OS N+CT vs CT in all randomized subjects with PD-L1 CPS ≥ 5**	**OS N+I vs CT in all randomized subjects with PD-L1 CPS ≥ 5**
12-month minimum FU	X	X (IA)	
24-month minimum FU[a]		X (FA)	X

[a] FU: follow-up. Twenty-four months minimum follow-up from last patient randomized to N+CT or CT, corresponds to 36-month minimum follow-up for N+I vs CT.

For the primary analyses of the endpoints stated above, all events observed in the locked database will be used.

As of May 2019, study enrollment has been completed. Therefore in Amendment 29, the total sample size is fixed; however, the sample size for the primary population (subjects with PD-L1 CPS ≥ 5) remains unknown as CPS scoring is still ongoing. While BMS has no knowledge of the actual prevalence of CPS ≥ 5 in this study, the prevalence is assumed to be 35% consistent with sample size and power calculations in Amendment 23. Sections 8.1.4 and 8.1.5 are updated to reflect design characteristics for time driven analyses and using 35% prevalence for PD-L1 CPS ≥ 5. Once the PD-L1 CPS scoring is completed and data is available, the actual prevalence of PD-L1 CPS ≥ 5 will be assessed in pooled blinded fashion for all randomized subjects in this study.

The power statement of the primary endpoints of PFS and OS will be updated using the actual prevalence and documented in the final SAP prior to first database lock for efficacy analysis.

8.1.3 General Assumptions of Sample Size Determinations

Primary Endpoints Family:

For the comparison of nivolumab plus chemotherapy vs chemotherapy both PFS and OS are primary endpoints.

Type I Error Splitting for Primary Endpoints Family:

For sample size calculation purpose, the family-wise error rate of 5% will be split as follows:

1. Comparison of PFS between nivolumab plus chemotherapy and chemotherapy in subjects with PD-L1 CPS ≥ 5, with alpha of 2%
2. Comparison of OS between nivolumab plus chemotherapy and chemotherapy in subjects with PD-L1 CPS ≥ 5, with alpha of 3%

Population for Primary Endpoints:

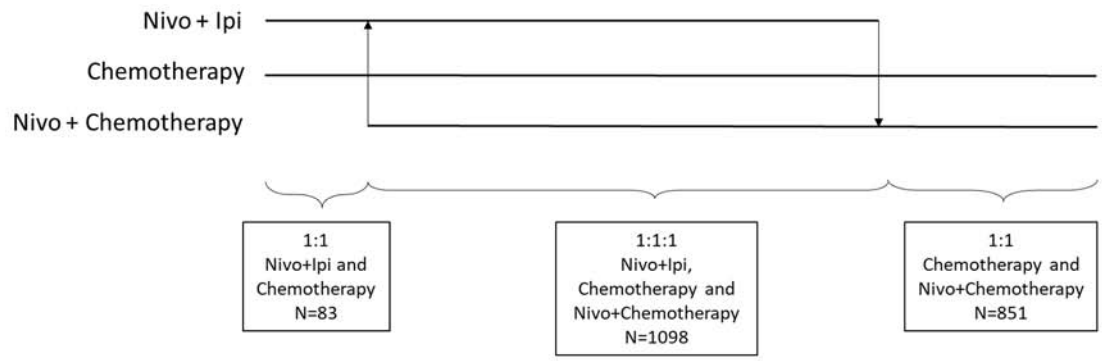
As mentioned in Section 1.1.13 the population for the primary endpoints will be all randomized subjects with PD-L1 CPS ≥ 5. For the design purpose, the prevalence was assumed to be 35% of all randomized subjects.

Concurrently Randomized

For the comparison of nivolumab plus chemotherapy and chemotherapy only subjects who were randomized to those 2 arms concurrently will be used. This means subjects randomized to chemotherapy before the nivolumab plus chemotherapy arm was introduced will not be included in the analysis of this comparison.

For the comparison of nivolumab + ipilimumab and chemotherapy only subjects who were randomized to those 2 arms concurrently will be used. This means subjects randomized to chemotherapy after the closure of nivolumab plus ipilimumab randomization will not be included in the analysis of this comparison.

Figure 8.1.3-1: Randomization Schema



Assumptions for Control Arm of Chemotherapy:

In previous protocol versions (up to amendment 20), PD-L1≥ 1% per TPS was assumed as negative prognostic factor (ie the median OS for chemotherapy was assumed to be smaller for subjects with tumor PD-L1≥1% per TPS than for all randomized subjects). However, for PD-L1 CPS, recent data does not suggest such a negative prognostic effect for chemotherapy.[62] Therefore, in Amendment 23, the OS and PFS distributions for the chemotherapy arm are assumed to be the same regardless of CPS cutoffs, eg, in PD-L1 CPS ≥ 5 and in all randomized subjects.

The PFS and OS data from the external data[14,18,91] were considered the most relevant to the studied chemotherapy arm (control). Therefore, the chemotherapy arm is assumed to have a 4-piece exponential distribution with a median PFS of 5.5 months (see Figure 8.1.3-2) and a 4-piece exponential distribution with a median OS of 11.1 months (see Figure 8.1.3-3).

Figure 8.1.3-2: PFS for Chemotherapy from External Data and Assumed Distribution for Chemotherapy

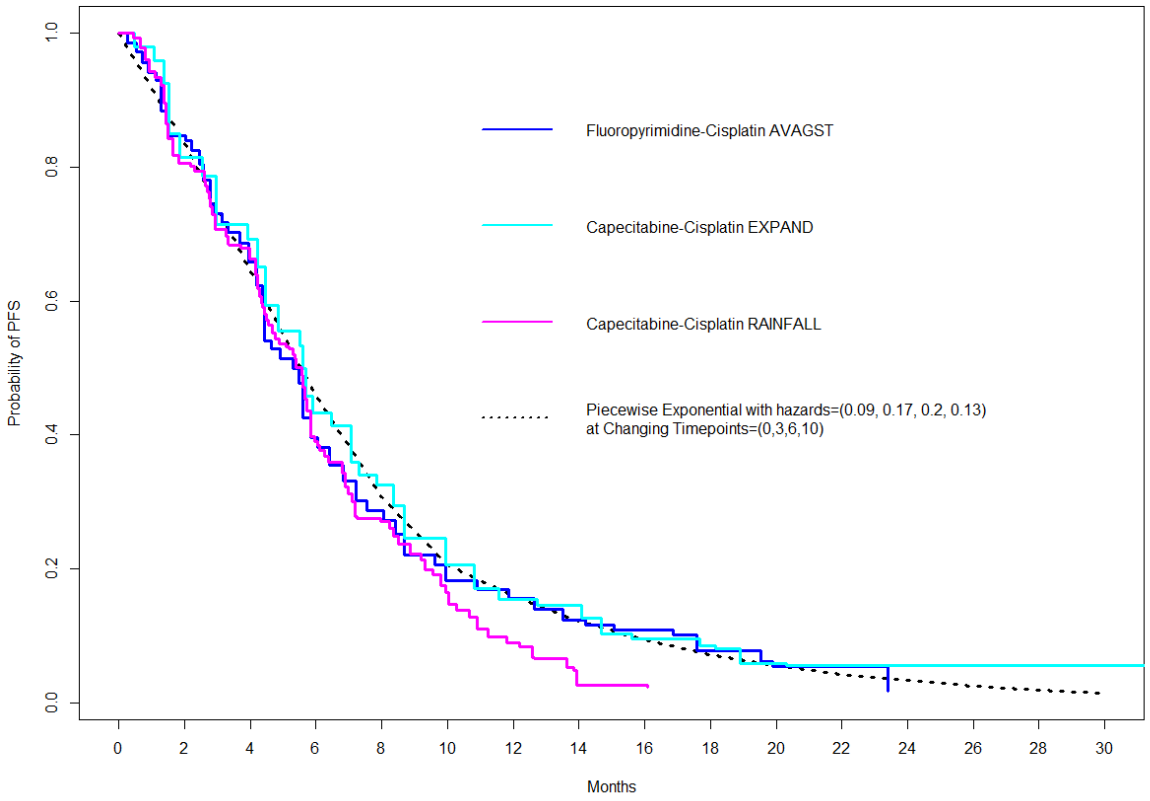
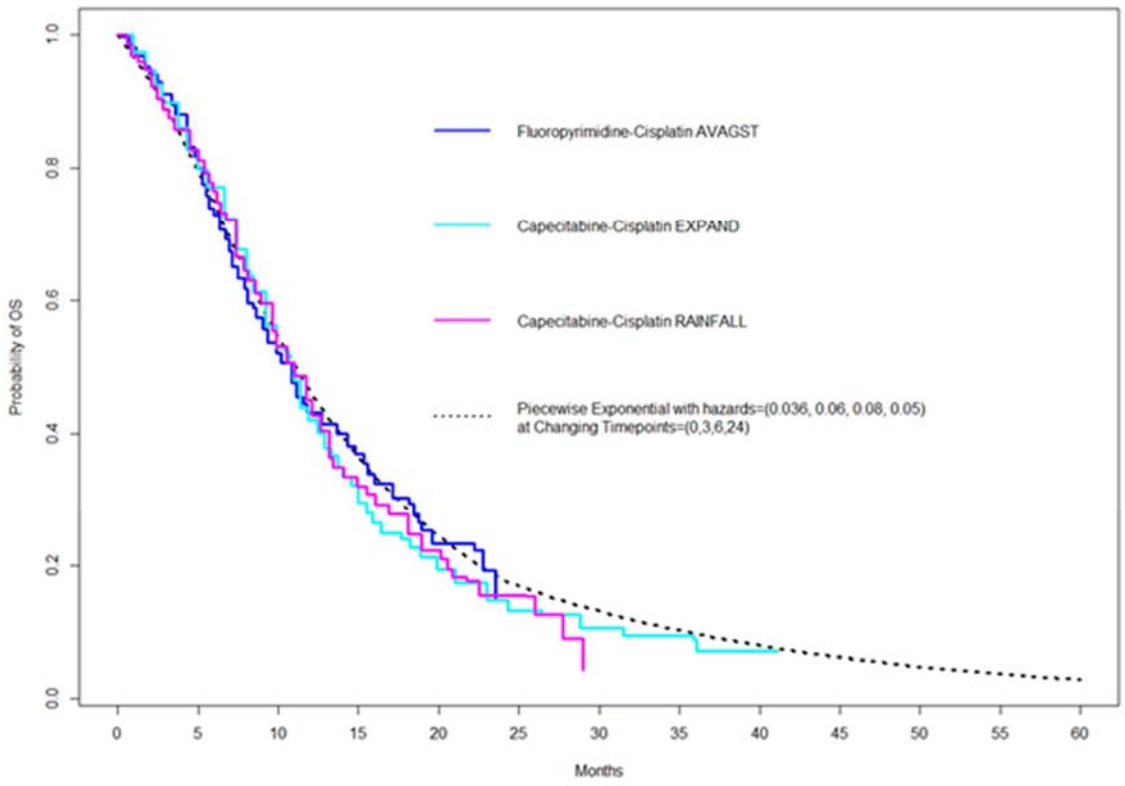


Figure 8.1.3-3: OS for Chemotherapy from External Data and Assumed Distribution for Chemotherapy



Statistical Software for Sample Size Calculation

Sample size calculations of the primary endpoints were based on simulations in EAST 6.4.1.

8.1.4 Sample Size: Nivolumab plus Chemotherapy vs Chemotherapy

Progression Free Survival

All concurrently randomized subjects to N+CT and CT arms with PD-L1 CPS ≥ 5 will be used for the PFS analysis. Given the delayed separation in the PFS distributions between pembrolizumab + chemotherapy and chemotherapy,[76] the PFS analysis will be conducted after a minimum of 12 months follow-up after the last patient is randomized.

As such, the PFS analysis will be conducted after the following criteria are all met:

- CPS scoring by central laboratories is complete
- a minimum follow-up of 12 months

Based on the observed delay in the PFS KM curved of Pem+CT vs. CT, the HR is modelled as a 2-piece hazard ratio with a delayed effect between 3 and 6 months (a HR of 1 versus chemotherapy for the first 3 or 6 months) followed by a constant HR of 0.56 (see Table 8.1.4-1). With 12 months

minimum follow-up it is expected that the number of events will range between 497 and 506 respectively and the power will range approximately between 99% and 60% with a Type I error of 2% (two-sided) (See Table 8.1.4-2).

The primary PFS analysis will be based on all the events observed at time of database lock.

Table 8.1.4-1: Assumed PFS Hazard Rates and Hazard Ratios (Nivolumab plus Chemotherapy vs Chemotherapy)

Periods	Hazard Rates for Chemotherapy	Hazard Ratios (3 months delay)	Hazard Ratios (6 months delay)s
0-3 months	0.09	1	1
3-6 months	0.17	0.56	1
6-10 months	0.2	0.56	0.56
> 10 months	0.13	0.56	0.56

Table 8.1.4-2: Summary of Sample Size Parameters and Schedule of Analyses for PFS (Nivolumab plus Chemotherapy vs Chemotherapy)

	3 months Delay	6 months Delay
# subjects with PD-L1 CPS ≥5[a]	554	554
Hypothesized delayed period	3	6
Hypothesized HR after delayed period	0.56	0.56
Hypothesized median in control arm	5.5 months	5.5 months
Significance level (2-sided)	0.02	0.02
Enrollment Period (from start of 1:1:1)	25.4 months	25.4 months
Minimum follow-up / Expected number of events[a,b,c]	12 months / 497	12 months / 506
Time of Analysis	37.4 months	37.4 months
Power[b]	99%	60%
Average HR[b]	0.66	0.8

[a] Based on 35% prevalence of PD-L1 CPS≥5

[b] Results based on simulations.

[c] Number of events for the nivolumab plus chemotherapy vs. chemotherapy comparison in total.

Overall Survival

A delayed separation of at least 6 months between the OS distribution of pembrolizumab + chemotherapy and chemotherapy was observed.[76] To fully capture the treatment effect, the interim and final analyses of OS will be conducted after a minimum follow up after the last patient randomized.

The interim analysis will be conducted after at least 12 months minimum follow-up, and the final analysis will be conducted after at least 24 months minimum follow-up.

With 24 months minimum follow-up at final analysis, it is expected that 466 events will be observed. With an average HR of 0.74 modelled as a 2-piece hazard ratio, a delayed effect with a HR of 1 versus chemotherapy for the first 6 months followed by a constant HR of 0.65 (see Table 8.1.4-3) the power will be approximately 85% with a Type I error of 3% (two-sided) (See Table 8.1.4-4).

For the OS interim and final analyses, all the events reported in the database at time of database lock will be used for the primary analyses.

Table 8.1.4-3: Assumed OS Hazard Rates and Hazard Ratios (Nivolumab plus Chemotherapy vs Chemotherapy)

Periods	Hazard Rates for Chemotherapy	Hazard Ratio
0-3 months	0.036	1
3-6 months	0.06	1
6-24 months	0.08	0.65
>24 months	0.05	0.65

Table 8.1.4-4: Summary of Sample Size Parameters and Schedule of Analyses for OS (Nivolumab plus Chemotherapy vs Chemotherapy)

# with PD-L1 CPS ≥ 5[a]	554
Hypothesized delayed period	6 months
Hypothesized HR after delayed period	0.65
Hypothesized median in control arm	11.1 months
Significance level (2-sided)	0.03
Enrollment Period (from start of 1:1:1)	25.4 months
INTERIM ANALYSIS #1 for OS	
Minimum follow-up/Expected number of events[a,b,c]	12 months/395
Time of analysis[d]	37.4 months

Table 8.1.4-4: Summary of Sample Size Parameters and Schedule of Analyses for OS (Nivolumab plus Chemotherapy vs Chemotherapy)

Significance level[e]	0.0164
Power	64%
FINAL ANALYSIS	
Minimum follow-up/Expected number of events[a,b,c]	24 months/466
Time of analysis[d]	49.4 months
Significance level	0.0252
Power[b]	85%
Average HR	0.74

[a] Based on a 35% prevalence of PD-L1 CPS ≥ 5.

[b] Results based on simulations

[c] Number of events for the nivolumab plus chemotherapy vs. chemotherapy comparison in total.

[d] After first patient randomized to nivolumab + chemotherapy or chemotherapy in 1:1:1 randomization.

[e] Significance levels will be calculated based on the actual number of deaths at each interim analysis

Once the CPS scoring is complete and data is available for all randomized subjects, the target number of OS events at interim and final analyses will be estimated. This will be done using the actual PD-L1 CPS ≥ 5 prevalence and under the following piecewise HR (HR of 1 vs chemotherapy for the first 6 months followed by a constant HR of 0.65). The number of events based on above assumptions at interim and final OS analyses timing will be estimated and the significance levels for OS at interim and final analyses will be determined using the Lan-DeMets α spending function with O'Brien and Fleming type of boundary.[92] At time of these interim and final analyses, significance levels will be adjusted according to actual events observed at OS interim and final analyses. All the details will be documented in the statistical analysis plan.

8.1.5 Power Considerations for Nivolumab Plus Ipilimumab vs Chemotherapy

OS between nivolumab + ipilimumab vs chemotherapy will be tested as a secondary objective. This comparison will be tested if at least one primary endpoint (PFS or OS of nivolumab + chemotherapy vs chemotherapy in subjects with PD-L1 CPS ≥ 5) meets statistical significance. The nivolumab + ipilimumab vs chemotherapy OS comparison will be conducted at the planned final comparison of OS for nivolumab + chemotherapy vs chemotherapy. This corresponds to approximately 36 months of minimum follow-up for the nivolumab + ipilimumab and chemotherapy arm.

Based on the observed data from Keynote 62 study (see Section 1.1.14) where a detriment was observed in the OS KM curves of pembrolizumab vs chemotherapy, a 4-piece HR is assumed for the OS of N+I vs CT with an average HR of 0.7 (see Table 8.1.5-1). With approximately 36 months

minimum follow-up at final analysis it is expected that 240 events will be observed and the power will be range between 63% and 73% for Type I error of 1.5% and 3.5% (two-sided) respectively (see Table 8.1.5-2). See also Section 8.4.2.1 for further details on the type I error control.

Table 8.1.5-1: Assumed OS Hazard Rates and Hazard Ratios (Nivolumab plus Ipilimumab vs Chemotherapy)

Periods	Hazard Rates for Chemotherapy	Hazard Rates for Nivo + Ipilimumab	Hazard Ratio
0-6 months	0.036	0.099	2.75
3-6 months	0.06	0.054	0.9
6-24 months	0.08	0.0328	0.41
>24 months	0.05	0.0205	0.41

Table 8.1.5-2: Summary of Sample Size Parameters and Schedule of Analyses for OS (Nivolumab plus Ipilimumab vs Chemotherapy)

# with PD-L1 CPS ≥ 5[a]	285	285
Hypothesized distribution	See Table 8.1.5-1	See Table 8.1.5-1
Hypothesized median in control arm	11.1 months	11.1 months
Significance level (two-sided)	0.015	0.035
Enrollment Period (from start of 1:1)	18.7 months	18.7 months
Time of analysis /Expected number of events[a,b,c]	54.4/240	54.4/240
Power[c]	63%	73%
Average HR[c]	0.7	0.7

[a] Based on a 35% prevalence of PD-L1 CPS ≥ 5.

[b] After first patient randomized to nivolumab + ipilimumab or chemotherapy in 1:1 randomization.

[c] Results based on simulations.

8.2 Populations for Analyses

Unless indicated otherwise, the populations below apply to both the nivolumab plus ipilimumab vs. chemotherapy and nivolumab plus chemotherapy vs. chemotherapy comparisons.

- 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 concurrently to any treatment arm
- All Measurable Subjects: All randomized subjects who have at least one target/measurable lesion at baseline
- All Subjects with PD-L1 CPS ≥5: All randomized subjects with PD-L1 CPS ≥ 5. Similar population will be defined for other CPS cut off values (eg CPS ≥10, ≥1)

- 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 (PD-L1 expression by TPS and other assays).

8.3 Endpoints

Table 8.3-1 summarizes the most important efficacy endpoints.

Table 8.3-1: Summary of Key Efficacy Endpoints

	Nivolumab plus Chemotherapy vs Chemotherapy	Nivolumab plus Ipilimumab vs Chemotherapy
Primary endpoints	• PFS by BICR in subjects with PD-L1 CPS ≥ 5) • OS in subjects with PD-L1 CPS ≥ 5	
Secondary endpoints	• OS in subjects with PD-L1 CPS ≥ 1, and in all randomized subjects. • OS in subjects PD-L1 CPS ≥ 10 • PFS by BICR in subjects with PD-L1 CPS ≥ 10, 1, or all randomized subjects • ORR by BICR in subjects with PD-L1 CPS ≥ 10, 5, 1 or all randomized subjects	• OS in subjects with PD-L1 CPS ≥ 5, and in all randomized subjects. • OS in subjects PD-L1 CPS ≥ 10 or 1 • ORR, PFS by BICR in subjects with PD-L1 CPS ≥ 10, 5, 1 or all randomized subjects. • TTSD in subjects with PD-L1 CPS ≥ 5 and in all randomized subjects
Exploratory Endpoints	• ORR, PFS by investigator in subjects with PD-L1 CPS ≥10, 5, 1 or all randomized subjects • OS, PFS,[a] ORR[a] in subjects with TPS across cutoffs • OS rates at 18, 24, and 36 months • PFS2 or TSST of next line treatment • DOR[a] • DRR[a] • TTSD in subjects with PD-L1 CPS ≥10, 5, 1, or all randomized subjects • Biomarkers	• ORR, PFS by investigator in subjects with PD-L1 CPS ≥10, 5, 1 or all randomized subjects • OS, PFS,[a] ORR[a] in subjects with TPS across cutoffs • OS rates at 18, 24, and 36 months • PFS 2 or TSST of next line treatment • DOR[a] • DRR[a] • TTSD in subjects with PD-L1 CPS ≥10, or 1 • Biomarkers

[a] By BICR and investigator.

8.3.1 Primary Efficacy Measures

Overall survival (OS). 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 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 subsequent anti-cancer therapy. Subjects who did not have any on-study tumor assessments and did not die (or died after initiation of 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 prior to or on the initiation of the subsequent anti-cancer therapy.

The same definition will be used for OS and PFS for nivolumab plus ipilimumab, which are secondary endpoints.

8.3.2 Secondary Efficacy Measures

Time to Symptom Deterioration (TTSD) is defined as the time from randomization until a clinically meaningful decline from baseline in GaCS score. A clinically meaningful deterioration is defined as a reduction of 8.2 points in the GaCS score. Subjects who do not deteriorate will be censored at the time of their last GACS assessment. Subjects without baseline GaCS assessment will be censored on the randomization date. Those with baseline GaCS, who do not have any GaCS assessments after randomization will be censored on the day after randomization.

Objective Response Rate (ORR) as assessed by BICR is defined as the number of subjects with a best overall response (BOR) of CR or PR divided by the number of measurable subjects with target lesion at baseline. BOR is defined as the best response designation as determined by the BICR, recorded between the date of randomization and the date of objectively documented progression (per RECIST 1.1 as determined by the BICR) or the date of subsequent anti-cancer therapy, 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 Measures

- PFS by investigator and ORR by investigator are defined the same way as PFS by BICR and ORR by BICR, except that only tumor assessments by investigators 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.

- Durable Response Rate (DRR) (as assessed by BICR and as assessed by investigator) is defined as the number of subjects with objective response whose response lasted for at least 6 months, divided by the number of randomized subjects for each treatment group.
- Overall survival rate at 18, 24, and 36 months is defined as the probability that a subject is alive at 18, 24, and 36 months, respectively, following randomization.
- 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 line 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, including biomarker analysis (Section 5.6), immunogenicity (Section 5.5.1), 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 Characteristic

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

A description of the participant population will be included in a statistical output report, including subgroups of age, gender, and race.

8.4.2 Efficacy Analyses

8.4.2.1 Strong Control Of Type I Error for Primary and Secondary endpoints

For design purposes, the alpha was split using Bonferroni method between the 2 primary endpoints:

1) Comparison of PFS between nivolumab plus chemotherapy and chemotherapy in subjects with PD-L1 CPS ≥ 5, with alpha of 2 %
2) Comparison of OS between nivolumab plus chemotherapy and chemotherapy in subjects with PD-L1 CPS ≥ 5, with alpha of 3 %

For analyses purposes of primary and key secondary endpoints the Bonferroni-based graphical approach[93] will be used and full details will be provided in the statistical analysis plan.

The alpha from the PFS of N+CT vs CT in PD-L1 CPS ≥ 5 testing will be carried to the testing of OS of N+I vs CT in PD-L1 CPS ≥ 5 analysis, should the PFS analysis be statistically significant. If OS of N+CT vs CT is significantly superior in subjects with PD-L1 CPS ≥ 5 then the inherited alpha will be shared equally to secondary endpoints of OS of N+CT vs CT in PD-L1 CPS ≥ 1 subjects and OS of N+I vs CT in PD-L1 CPS ≥ 5. The comparison of OS for N+I vs CT in PD-L1

CPS ≥ 5 may inherit alpha independently from the two primary endpoints and will be tested only once after 36 months of minimum follow-up. The alpha that will be allocated to the comparison of OS for N+I vs CT in PD-L1 CPS ≥ 5 will be 1.5%, 2% or 3.5% depending on the outcome of the primary endpoints for N+CT vs CT. The SAP will document the details of the actual alpha allocation to the secondary endpoints.

8.4.2.2 Analyses for Primary Objectives

Nivolumab plus Chemotherapy vs Chemotherapy

PFS by BICR in subjects expressing PD-L1 with CPS ≥5 will be compared between nivolumab plus chemotherapy vs chemotherapy using a two-sided log rank test, stratified by region (Asia vs US vs rest of world), ECOG status (0 vs 1), chemotherapy regimen (XELOX vs FOLFOX) and TPS PD-L1 (≥ 1% vs < 1% or indeterminate) as recorded in the IRT. A significance level of 2% will be used. The HR with its associated two-sided 98% CI will be estimated via a stratified Cox model with treatment arm as the only covariate in the model. PFS for each treatment arm will be estimated and plotted using the 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.

Overall Survival in subjects with PD-L1 by CPS ≥5 will be compared between nivolumab plus chemotherapy vs chemotherapy using a two-sided log rank test, stratified by region (Asia vs US vs rest of world), ECOG status (0 vs 1), chemotherapy regimen (XELOX vs FOLFOX) and TPS PD-L1 (≥ 1% vs < 1% or indeterminate) as recorded in the IRT. The significance level will be determined using the Bonferroni-based graphical approach. The HR with its associated two-sided CI will be estimated via a stratified Cox model with treatment arm as the only covariate in the model. OS for each treatment arm will be estimated and plotted using the 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.

8.4.2.3 Analyses for Secondary Objectives in Hierarchy

Nivolumab plus Chemotherapy vs Chemotherapy

OS in CPS ≥ 1 and all randomized will be compared using a two-sided log rank test stratified by the same stratification factors as the primary endpoint. The HR with its associated two-sided CI will be estimated via a stratified Cox model with treatment arm as the only covariate in the model. 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.

Nivolumab plus Ipilimumab vs Chemotherapy

Overall survival in subjects with PD-L1 by CPS ≥5 and all randomized will be compared between nivolumab plus ipilimumab vs chemotherapy using a two-sided log rank test stratified by region (Asia vs US vs rest of world), ECOG status (0 vs 1) and TPS PD-L1 (≥ 1% vs < 1% or indeterminate) and as recorded in the IRT.

The HR with its associated two-sided CI will be estimated via a stratified Cox model with treatment arm as the only covariate in the model. 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.

Same methods will be used to analyze OS in subjects with PD-L1 by CPS ≥10 and 1.

Similar methodology will be used for TTSD.

Exploratory Endpoints

Progression-free Survival (PFS) as assessed by BICR/ investigator 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.

Best Overall Response will be summarized by response category for each treatment group.

ORR (as assessed by BICR and as assessed by investigator) and DRR (as assessed by BICR and as assessed by investigator) will be computed in each treatment group along with the exact 95% CI using Clopper-Pearson method.[94] An estimate of the difference in ORRs and DRRs, and corresponding 95% CI will be calculated using Cochran-Mantel-Haenszel 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.

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.

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

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

[redacted] MSI, TMB [redacted] status will be evaluated where possible, as predictive biomarkers, for OS and PFS. Details for these 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-Ga (including FACT-G, FACT-G7 and GaCS) data will be performed in all randomized subjects and in subjects with CPS ≥ 5 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.

The analyses may also be performed for population defined by other CPS cutoff.

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-Ga will be described by treatment group as randomized in the following ways:

- GaCS, FACT-G7, FACT-G, and FACT-Ga 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 GaCS, FACT-G7, FACT-G, FACT-Ga 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 GaCS and FACT-G7 will be described by treatment group as randomized in the following ways:

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

8.4.7 Other Analyses

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

8.5 Interim Analyses

For the nivolumab plus chemotherapy vs chemotherapy comparison, the primary PFS analysis in PD-L1 CPS ≥ 5 is planned to be conducted after 12 months minimum follow-up in all randomized subjects with PD-L1 CPS ≥ 5. An independent statistician external to BMS will perform the analysis; results will be evaluated by the DMC.

The formal interim analyses for OS is also planned at 12 months minimum follow-up after the last patient was randomized. (See Section 8.1.4 for details). 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 each analysis. An independent statistician external to BMS will perform the analysis; results will be evaluated by the DMC. For all analyses, all events reported in the database at the time of the lock will be used.

For the nivolumab plus ipilimumab vs chemotherapy there no interim analysis planned.

The full details of using the graphical approach will be described in the SAP.

In addition to the formal planned PFS and interim analyses for OS, the DMC will have access to periodic unblinded interim reports 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/participants. 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/participants 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/participants 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/biocomparability, 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	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:

If...	Then...
sites stock or commercial supply, or a specialty pharmacy)	• label identification number or batch number • 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/participants 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

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

For each CSR related to this protocol, the following criteria will be used to select the signatory investigator:

- External Principal Investigator designated at protocol development

9.4 Scientific Publications

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 (CTAg) 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 CTAg.

Scientific Publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any principal investigator, sub-investigator or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable subjects with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who make the most significant contributions, as defined above, will be considered by BMS for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

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.

11 LIST OF ABBREVIATIONS

Term	Definition
ADA	anti-drug antibody
AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APC	antigen presenting cell
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AT	aminotransferase
BA/BE	bioavailability/bioequivalence
BMS	Bristol-Myers Squibb
BICR	Blinded Independent Review Committee
BOR	best overall response
BP	blood pressure
BSA	body surface area
BSC	best supportive care
BUN	blood urea nitrogen
Ca	calcium
Cavgss	average concentration at steady state
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
Cmax	maximum observed concentration
CMV	cytomegalovirus
CNS	Central Nervous System
CPS	combined positive score
CR	complete response
CrCl	creatinine clearance

Term	Definition
CRF	case report form, paper or electronic
CT	computed tomography
CT	chemotherapy
CTAg	clinical trial agreement
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-cell lymphoma 4
CV	coefficient of variation
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DOR	duration of response
[redacted]	[redacted]
[redacted]	[redacted]
EC50	concentration of a drug producing half-maximal response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
eg	exempli gratia (for example)
EHR/EMR	electronic health record/electronic medical record
EOT	end of treatment
EQ-5D-3L	EuroQol questionnaire comprising 5 dimensions, with each dimension having 3 levels
EQ-VAS	EuroQol Visual Analog Scale
EWB	emotional well-being
FACT-Ga	Functional Assessment of Cancer Therapy-Gastric
FACT-G7	7-item version of FACT-General
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FLP	5-fluorouracil plus leucovorin and cisplatin
FOLFOX	oxaliplatin + leucovorin + 5-fluorouracil

Term	Definition
FPFV	First patient first visit
FSH	follicle stimulating hormone
FU or F/U	follow-up
FWB	functional well-being
g	gram
GaCS	Gastric Cancer Subscale
GC	gastric cancer
GCP	Good Clinical Practice
GEJ	gastroesophageal junction
GFR	glomerular filtration rate
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
Her2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HNPCC	hereditary nonpolyposis colorectal cancer
HR	hazard ratio
HRT	hormone replacement therapy
IB	Investigator Brochure
IC50	concentration of an inhibitor where binding is reduced by half
ICF	informed consent form
ICH	International Council on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
IHC	immunohistochemistry
IMAE	immune-mediated adverse event

Term	Definition
IMG	immunogenicity
IMP/IP	investigational (medicinal) products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IRC	Independent Review Committee
irPFS	immune-related progression-free survival
IRT	Interactive (voice/web) Response Technology
IU	International Unit
IV	intravenous
K	potassium
kg	kilogram
KM	Kaplan-Meier
1L/2L	first-line/second-line
L	liter
[redacted]	[redacted]
LDH	lactate dehydrogenase
LFT	liver function test
LLN	lower limit of normal
mg	milligram
[redacted]	[redacted]
min	minute
mL	milliliter
mOS	median overall survival
MRI	magnetic resonance imaging
MSI	microsomal instability
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
N/A	not applicable
NaCl	sodium chloride

Term	Definition
NCI	National Cancer Institute
nM	nano-molar
NSCLC	non-small cell lung cancer
N+CT	nivolumab plus chemotherapy
N+I	nivolumab plus ipilimumab
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PEM + CT	pembrolizumab + chemotherapy
PD	progressive disease
PD-1/PD-L1/PD-L2	programmed cell death protein 1/programmed cell death ligand 1 or 2
PFS	progression-free survival
PFS2	progression after the next line of therapy
PK	pharmacokinetics
PO	per os (oral route of administration)
PPK	population PK
PR	partial response
PT	Preferred Term
PWB	physical well-being
Q2W/Q3W	every 2 weeks/every 3 weeks
QD	quaque die, once daily
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
ROW	Rest of the World
RT-PCR	reverse transcription-polymerase chain reaction
S1	tegafur/gimeracil/oteracil potassium
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation

Term	Definition
SNP	single nucleotide polymorphism
SOC	System Organ Class
SUSAR	Suspected, Unexpected Serious Adverse Reaction
SWB	social/family well-being
t1/2	half-life; time of clearance of 1/2 of drug concentration
Tmax	time of maximum observed concentration
[redacted]	[redacted]
TSH	thyroid stimulating hormone
TTSD	time to symptom deterioration
TSST	Time to second subsequent therapy
ULN	upper limit of normal
Vc	volume of central compartment
Vz	Volume of distribution at terminal phases
WBC	white blood cell
WOCBP	women of childbearing potential
XELOX	Oxaliplatin + Capecitabine

12 REFERENCES

REFERENCES FOR THE USE OF CONDOMS WITH SPERMICIDE

Kestelman P. et. al., Efficacy of the Simultaneous Use of Condoms and Spermicides Family Planning Perspectives. Vol 23 (5); October 1991.

Gabbay MB, Thomas J, Gibbs A, Hold P. A Randomized Crossover Trial of the Impact of Additional Spermicide on Condom Failure Rates. Sex Transm Dis 2008; 35: 862-8.

[1] GLOBOCAB 2012: Estimated Cancer Incidence, Mortality and prevalence Worldwide in 2012 http://globocan.iarc.fr.

[2] Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014.CA Cancer J Clin. 2014 Jan-Feb;64(1):9-29.

[3] Bertuccio P, Chatenoud L, Levi F, et al. Recent patterns in gastric cancer: a global overview. Int J Cancer 2009;125:666.

[4] Lichtenstein P, Holm NV, Verkasalo PK, et al: Environmental and heritable factors in the causation of cancer. N Engl J Med 2000;343:78-85.

[5] Lauren P. The two histological main types of gastric carcinoma: Diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand. 1965;64:31.

[6] Power DG and Reynolds JV. Localized adenocarcinoma of the esophagogastric junction-is there a standard of care? Cancer Treatment Review 2010;36:400-409.

[7] Hasegawa S and Yoshikawa T. Review article: Adenocarcinoma of the esophagogastric junction: incidence, characteristics and treatment strategies. Gastric Cancer 2010;13:63-73. Doi10.1007/s10120-010-0555-2.

[8] Integrated genomic characterization of oesophageal carcinoma. The Cancer Genome Atlas Research Network. Nature Vol 541, 12 January 2017

[9] NCCN guideline Esophageal Cancer (version 4.2017. https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. Accessed:06-Dec-2017

[10] F. Lordick, C. Mariette, K. Haustermans, R. et al. Oesophageal Cancer: ESMO Clinical Practice Guidelines. Ann Oncol (2016) 27 (suppl 5): v50-v57

[11] NCCN guideline Gastric cancer (Ver 3.0, 2015). http://www.nccn.org/professionals/physician_gls/f_guidelines_nojava.asp. Accessed: 18-Mar-2016.

[12] Waddell T, Verheij M, Allum W, et al. Gastric cancer†: ESMO–ESSO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol (2013) 24 (suppl 6): vi57-vi63.

[13] Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3).Gastric Cancer 2011;14:113-123.

[14] Ohtsu A, Shah MA, Cutsem EV, et al. Bevacizumab in Combination With Chemotherapy As First-Line Therapy in Advanced Gastric Cancer: A Randomized, Double-Blind, Placebo-Controlled Phase III Study. J Clin Oncol 2011;29:3968-3976.

[15] Cunningham D, Starling N, Rao S, et al. Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer. N Engl J Med 2008;358:36-46.

[16] Yamada Y, Higuchi K, Nishikawa K, et al. Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naïve patients with advanced gastric cancer. Annals of Oncology 2015;26:141-148.

[17] Cutsem EV, Moiseyenko VM, Tjulandin S, et al. Phase III Study of Docetaxel and Cisplatin Plus Fluorouracil Compared With Cisplatin and Fluorouracil as First-Line Therapy for Advanced Gastric Cancer: A Report of the V325 Study Group. J Clin Oncol 2006;24:4991-4997.

[18] Lordick F, Kang YK, Chung HC, et al. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. Lancet Oncol 2013;14:490.

[19] Bang YJ, Cutsem EV, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376:687-97.

[20] Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous Cell Non-Small-Cell Lung Cancer. N Engl J Med. 2015 Jul 9;373(2):123-35.

[21] Larkin J, Chiarion‐Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 2015;373:23-34.

[22] Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015 Nov 5;373(19):1803-13.

[23] YK Kang, N Boku, T Satoh et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017; 390: 2461–71

[24] Opdivo (nivolumab) US Prescribing Information. Bristol-Myers Squibb, 2016. http://packageinserts.bms.com/pi/pi_opdivo.pdf. Accessed 18-Mar-2016.

[25] Summary of Product Characteristics (SmPC), Nivolumab. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003985/WC500189765.pdf. Accessed: 18-Mar-2016.

[26] Yervoy (Ipilimumab) US Prescribing Information. Bristol-Myers Squibb, 2016. http://packageinserts.bms.com/pi/pi_yervoy.pdf. Accessed: 18-Mar-2016.

[27] Summary of Product Characteristics (SmPC), Ipilimumab. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002213/WC500109299.pdf. Accessed: 18-Mar-2016.

[28] Curran MA, Montalvo W, Yagita H, et al. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. PNAS 2010;107: 4275-80.

[29] CA209067: A Phase 3, Randomized, Double-Blind Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab Versus Ipilimumab Monotherapy in Subjects with Previously Untreated Unresectable or Metastatic Melanoma. Document Control Number: [redacted].

[30] Wu C, Zhu Y, Jiang J et al. Immunohistochemical localization of programmed death-1 ligand-1 (PD-L1) in gastric carcinoma and its clinical significance. Acta Histochem. 2006;108(1):19-24.

[31] Ohigashi Y, Sho M, Yamada Y et al. Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer. Clin Cancer Res. 2005;11(8):2947-53.

[32] Böger C, Behrens HM, Mathiak. M et al. PD-L1 is an independent prognostic predictor in gastric cancer of Western patients. Oncotarget. 2016 Apr 26; 7(17): 24269–24283.5.

[33] Saito H, Kono Y, Murakami Y et al. Highly Activated PD-1/PD-L1 Pathway in Gastric Cancer with PD-L1 Expression. Anticancer Research 38: 107-112 (2018)

[34] Schl€oßer, HA, Drebber U, Kloth M, et al. Immune checkpoints programmed death 1 ligand 1 and cytotoxic T lymphocyte associated molecule 4 in gastric adenocarcinoma. Oncoimmunology 2016, VOL. 5, NO. 5, e1100789

[35] Tamura T, Ohira M, Tanaka H, et al. Programmed Death-1 Ligand-1 (PDL1) Expression Is Associated with the Prognosis of Patients with Stage II/III Gastric Cancer. Anticancer Research, 35: 5369-5376 (2015)

[36] Kim JW, Nam KH, Ahn SH, et al. Prognostic implications of immunosuppressive protein expression in tumors as well as immune cell infiltration within the tumor microenvironment in gastric cancer. Gastric Cancer. 2016 Jan;19(1):42-52.

[37] Le DT, Bendell J, Calvo E, et al. Safety and Activity of Nivolumab Monotherapy in Advanced and Metastatic Gastric or Gastroesophageal Junction Cancer (GC/GEC): Results From the CheckMate-032 Study. ASCO GI 2016, abstract 6.

[38] Bang YJ, et al. Relationship between PD-L1 expression and clinical outcomes in patients with advanced gastric cancer treated with the anti-PD-1 monoclonal antibody pembrolizumab (MK 3475) in KEYNOTE-012.ASCO 2015, abstract 4001.

[39] Chung HC, Arkenau HT, Wyrwicz L, et al. Avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with advanced gastric or gastroesophageal junction cancer: a phase Ib trial. ESMO 2015, Abstract No. 2364.

[40] Moehler M, Cho JY, KimA YH, et al. Randomized, Open-Label, Two-Arm Phase 2 Trial Comparing the Efficacy of Sequential Ipilimumab Versus Best Supportive Care Following First-Line Chemotherapy in Patients with Unresectable, Locally Advanced/Metastatic Gastric or Gastro-Esophageal Junction Cancer. 2016 ASCO in progress

[41] Opdivo (nivolumab) US Prescribing Information. Bristol-Myers Squibb, Revised: March 2019. http://packageinserts.bms.com/pi/pi_opdivo.pdf. Accessed 24-Jun-2019.

[42] Lebb C; Meyer N; Mortier L, et all. Evaluation of Two Dosing Regimens for Nivolumab in Combination With Ipilimumab in Patients With Advanced Melanoma: Results From the Phase IIIb/IV CheckMate 511 Trial. ;J Clin Oncol 37:867-875.

[43] Pfirschke C; Engblom C; Immunogenic Chemotherapy Sensitizes Tumors to Checkpoint Blockade Therapy, Immunity 44, 343–354, February 16, 2016

[44] Rizvi N, Hellmann M, Brahmer J, et al. Nivolumab in Combination With Platinum-Based Doublet Chemotherapy for First-Line Treatment of Advanced Non–Small-Cell Lung Cancer. Clin Oncol 2016, 34:2969-2979.

[45] Kelly K, Crowley J, Bunn PA Jr, et al: Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non–small-cell lung cancer: A Southwest Oncology Group trial. J Clin Oncol 19: 3210-3218, 2001

[46] Sandler A, Gray R, Perry MC, et al: Paclitaxelcarboplatin alone or with bevacizumab for non-smallcell lung cancer. N Engl J Med 355:2542-2550, 2006

[47] Scagliotti GV, De Marinis F, Rinaldi M, et al: Phase III randomized trial comparing three platinumbased doublets in advanced non-small-cell lung cancer. J Clin Oncol 20:4285-4291, 2002

[48] Scagliotti GV, Parikh P, von Pawel J, et al: Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapynaive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 26:3543-3551, 2008

[49] Schiller JH, Harrington D, Belani CP, et al: Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346:92-98, 2002

[50] Kang YK, Kato K, Chung HC et al. Interim Safety and Clinical Activity of Nivolumab in Combination With S-1/Capecitabine Plus Oxaliplatin in Patients With Previously Untreated Unresectable Advanced or Recurrent Gastr. ESMO 2017, abstract 671P.

[51] Fuchs CS, Ohtsu A, Tabernero J et al. Preliminary safety data from KEYNOTE-059: pembrolizumab plus 5-fluorouracil (5-FU) and cisplatin for first-line treatment of advanced gastric cance. ASCO 2016. Abstract. 4037.

[52] Schadendorf D et al Efficacy and quality of life outcomes in patients with advanced melanoma (MEL) who discontinued treatment with nivolumab (NIVO) plus ipilimumab (IPI) due to toxicity in a phase III trial (CheckMate 067). 2016 Annual Meeting of the European Association of Dermato-Oncology; August 31-September 3, 2016; Vienna, Austria.

[53] Schadendorf D, et al. Pooled Analysis of Long-Term Survival Data from Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. J Clin Oncol 2015; 33: 1889-94.

[54] Brahmer J, et al. Five-year follow-up from the CA209-003 study of nivolumab in previously treated advanced non-small cell lung cancer: clinical characteristics of long-term survivors. Oral presentation presented at: American Association for Cancer Research (AACR) Annual Meeting; April 1-5, 2017; Washington, DC, USA.

[55] Felip E et al., Three-year follow-up from Checkmate 017/057: Nivolumab versus docetaxel in patients with previously treated advanced non-small lung cancer (NSCLC). Poster discussion presentation at the European Society of Medical Oncology Annual Meeting. 2017 Sep 8-12; Madrid, Spain. Poster 1301PD

[56] Herbst RS et al. KEYNOTE-010: Durable clinical benefit in patients with previously treated, PD-L1-expressing NSCLC who completed pembrolizumab. Poster presentation at the World Conference on Lung Cancer 2016 Dec 4-7; Vienna, Austria.

[57] Robert, C et al. Long-term outcomes in patients with ipilimumab-naive advanced melanoma in the phase 3 KEYNOTE-006 study who completed pembrolizumab treatment; Journal of Clinical Oncology 2017 35:15_suppl, 9504-9504

[58] Spigel DR, et al. Randomized results of continuous vs 1-year fixed-duration in patients with advanced non-small cell lung cancer. Oral presentation at the European Society of Medical Oncology Annual Meeting. 2017 Sep 8-12; Madrid, Spain

[59] Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015 Oct 22;373(17):1627-39.

[60] M Reck, D Rodríguez-Abreu, A G. Robinson et al. Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. N Engl J Med 2016; 375:1823-1833

[61] H Chung et al. Avelumab (MSB0010718C; anti-PD-L1) in patients with advanced gastric or gastroesophageal junction cancer from the JAVELIN Solid Tumor phase 1b trial: analysis of safety, clinical activity. ASCO 2016, abstract 4009.

[62] Charles S. Fuchs, et al. Pembrolizumab (pembro) vs paclitaxel (PTX) for previously treated advanced gastric or gastroesophageal junction (G/GEJ) cancer: Phase 3 KEYNOTE-061 trial. ASCO 2018 abstract. 4062

[63] Kang H, Kauh J. Chemotherapy in the Treatment of Gastric Cancer: Is there a global standard? Current Treatment Options in Oncology 2011;12:96-106.

[64] Al-Batran SE, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 2008;26:1435.

[65] van Meerten E, Eskens FA, van Gameren EC, et al. First-line treatment with oxaliplatin and capecitabine in patients with advanced or metastatic oesophageal cancer: a phase II study. Br J Cancer 2007;96:1348.

[66] Jatoi A, Murphy BR, Foster NR, et al. Oxaliplatin and capecitabine in patients with metastatic adenocarcinoma of the esophagus, gastroesophageal junction and gastric cardia: a phase II study from the North Central Cancer Treatment Group. Ann Oncol 2006;17:29.

[67] Montagnani F, Turrisi G, Marinozzi C Effectiveness and safety of oxaliplatin compared to cisplatin for advanced, unresectable gastric cancer: a systematic review and meta-analysis. Gastric Cancer. 2011;14(1):50.

[68] Park YH, Lee JL, Ryoo BY, et al. Capecitabine in combination with Oxaliplatin (XELOX) as a first-line therapy for advanced gastric cancer. Cancer Chemother Pharmacol 2008;61:623-629.

[69] I Chau, AR Norman, D Cunningham, et al. Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer--pooled analysis from three multicenter, randomized, controlled trials using individual patient data. J Clin Oncol, 22 (12) (2004), pp. 2395–2403

[70] Chen G, Emens LA. Chemoimmunotherapy: reengineering tumor immunity.Cancer Immunol Immunother. 2013 Feb;62(2):203-16.

[71] Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15:7412-20.

[72] https://www.agilent.com/cs/library/usermanuals/public/29219_pd-l1-ihc-22C3-pharmdx-gastric-interpretation-manual_us.pdf

[73] K Kulangara, L Guerrero, A Posch et al. Investigation of PD-L1 expression and response to pembrolizumab (pembro) in gastric cancer (GC) and cervical cancer (CC) using combined positive score (CPS) and tumor proportion score (TPS). ASCO 2018 abstract 4065.

[74] K Shitara, M Özgüroğlu, Y Bang et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial.Lancet,June 4, 2018 http://dx.doi.org/10.1016/S0140-6736(18)31257-1

[75] Yung-Jue Bang, K Muro, CS. Fuchs et al. KEYNOTE-059 cohort 2: Safety and efficacy of pembrolizumab (pembro) plus 5-fluorouracil (5-FU) and cisplatin for first-line (1L) treatment of advanced gastric cancer. ASCO 2017 abstract 4012

[76] Tabernero J, Bang Y-J, Fuchs CS et al. KEYNOTE-062: Phase III study of pembrolizumab (MK-3475) alone or in combination with chemotherapy versus chemotherapy alone as first-line therapy for advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma. ASCO 2019 abstract LBA4007.

[77] Pardoll D. Does the immune system see tumors as foreign or self? Annu Rev Immunol. 2003;21:807-39.

[78] Zitvogel L, Tesniere A, Kroemer G. Cancer despite immunosurveillance: immunoselection and immunosubversion. Nat Rev Immunol. 2006;6:715-27.

[79] Dunn GP, Bruce AT, Ikeda H, et al. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol. 2002;3:991-8.

[80] Greenwald RJ, Freeman GH, Sharpe AH. The B7 family revisited. Annu Rev Immunol. 2004;23:515-48.

[81] Zhang Y, Huang S, Gong D, et al. Programmed death-1 upregulation is correlated with dysfunction of tumor-infiltrating CD8+ T lymphocytes in human non-small cell lung cancer. Cell and Mol Immunol 2010;7:389-95.

[82] Sharpe AH, Wherry EJ, Ahmed R, et al. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. Nature Immunol. 2007;8:237-45.

[83] Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Eng J Med 2012; 366: 2443-54.)

[84] Alegre ML, Noel PJ, Eisfelder BJ, et al. Regulation of surface and intracellular expression of CTLA4 on mouse T cells. J Immunol 1996; 157:4762-70.

[85] Postow MA, Harding J, Wolchok JD. Targeting immune checkpoints: Releasing the restraints on anti-tumor immunity for patients with melanoma. Cancer J 2012; 18:153-159.

[86] Nivolumab Investigator Brochure Version 15; 24-Jun-2016.

[87] Ipilimumab population pharmacokinetics and exposure-response analyses in subjects with advanced melanoma (CA184004, CA184007, CA184008, and CA184022). Bristol-Myers Squibb; 2010. Document Control No. [redacted].

[88] Ipilimumab Investigator Brochure Version 19; 02-Mar-2016.

[89] Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009;15:7412-20.

[90] Umar A, Boland Cr, Terdiman JP, et al. Revised Bethesda Guidelines for Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome) and Microsatellite Instability. J Nat Cancer Inst 2004;96:261-68.

[91] Fuchs C , Shitara K, Di Bartolomeo M et al RAINFALL: A randomized, double-blind, placebo-controlled phase III study of cisplatin (Cis) plus capecitabine (Cape) or 5FU with or without ramucirumab (RAM) as first-line therapy in patients with metastatic gastric or

gastroesophageal junction (G-GEJ) adenocarcinoma.ASCO GI Cancers Symposium 2018, abstract # 5.

[92] Lan KKG, Lachin JM, Implementation of Group Sequential Logrank Tests in a Maximum Duration Trial, Biomatrics 46, 759-770, September 1990.

[93] Bretz, F., Maurer, W., Brannath, W., and Posch, M. (2009). A graphical approach to sequentially rejective multiple test procedures. Statistics in Medicine, 28(4):586–604.

[94] Clopper, CJ and Pearson, ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 26: 404-413, 1934

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.

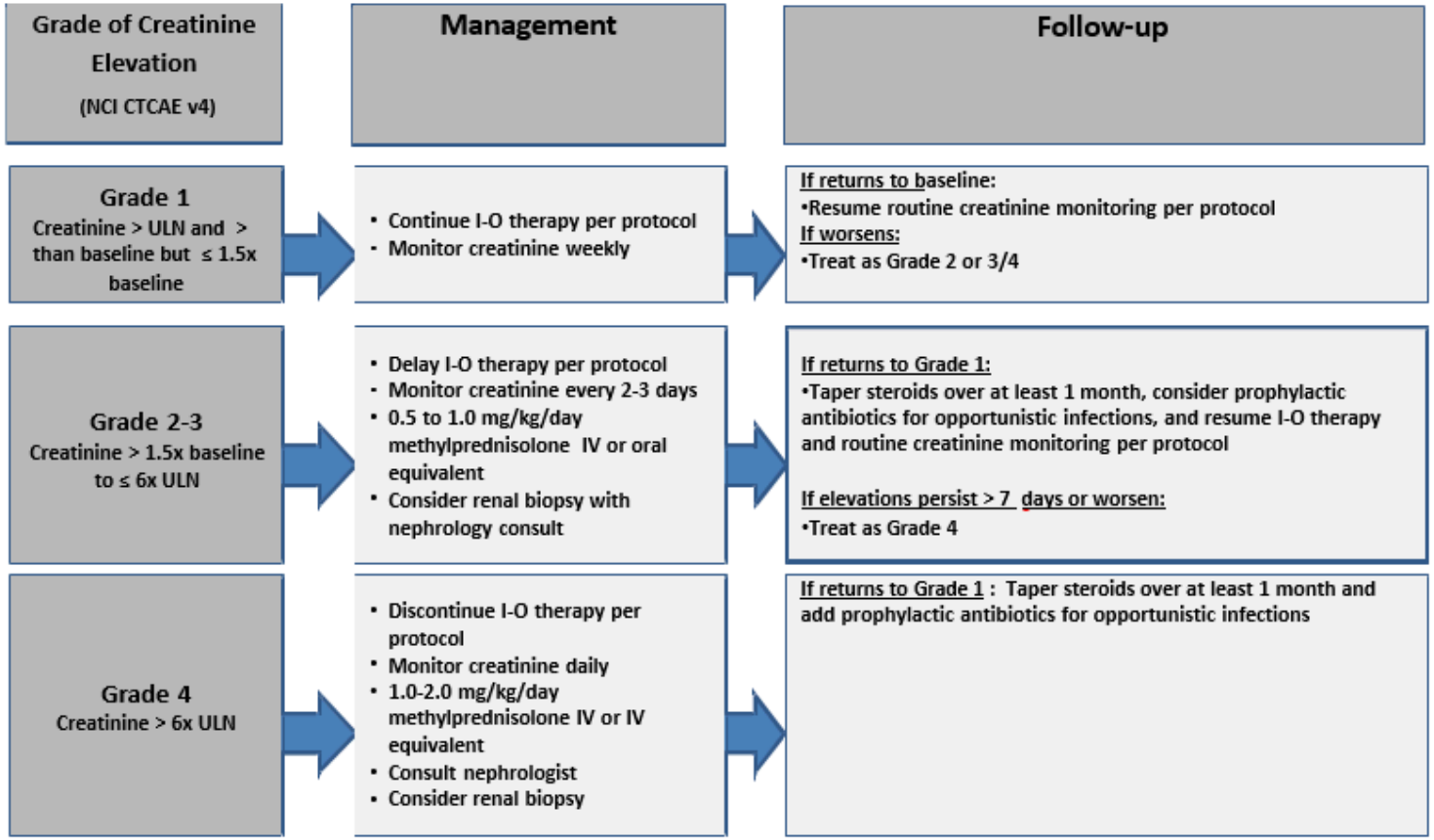
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: 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-2019

Renal Adverse Event Management Algorithm

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

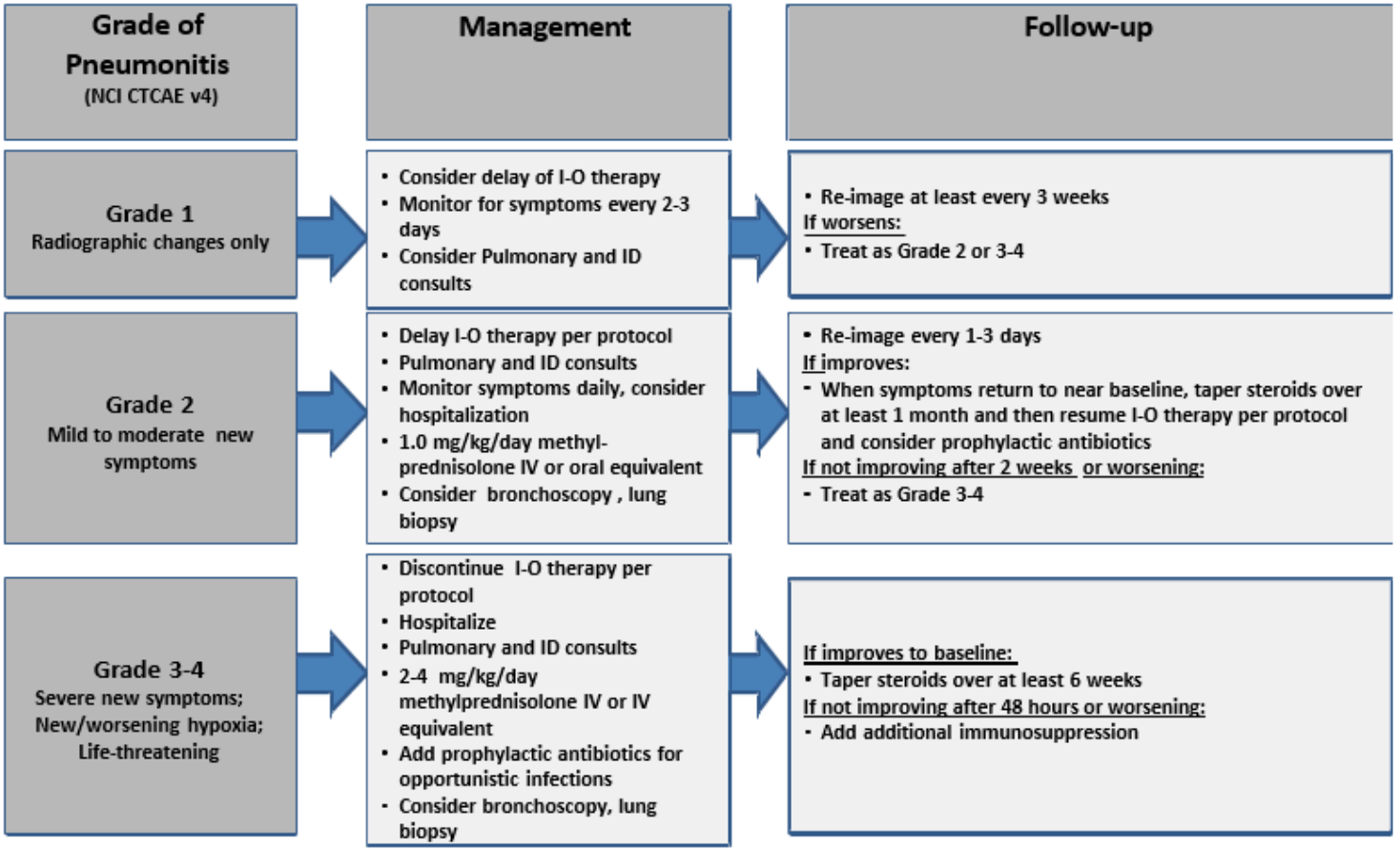


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

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.

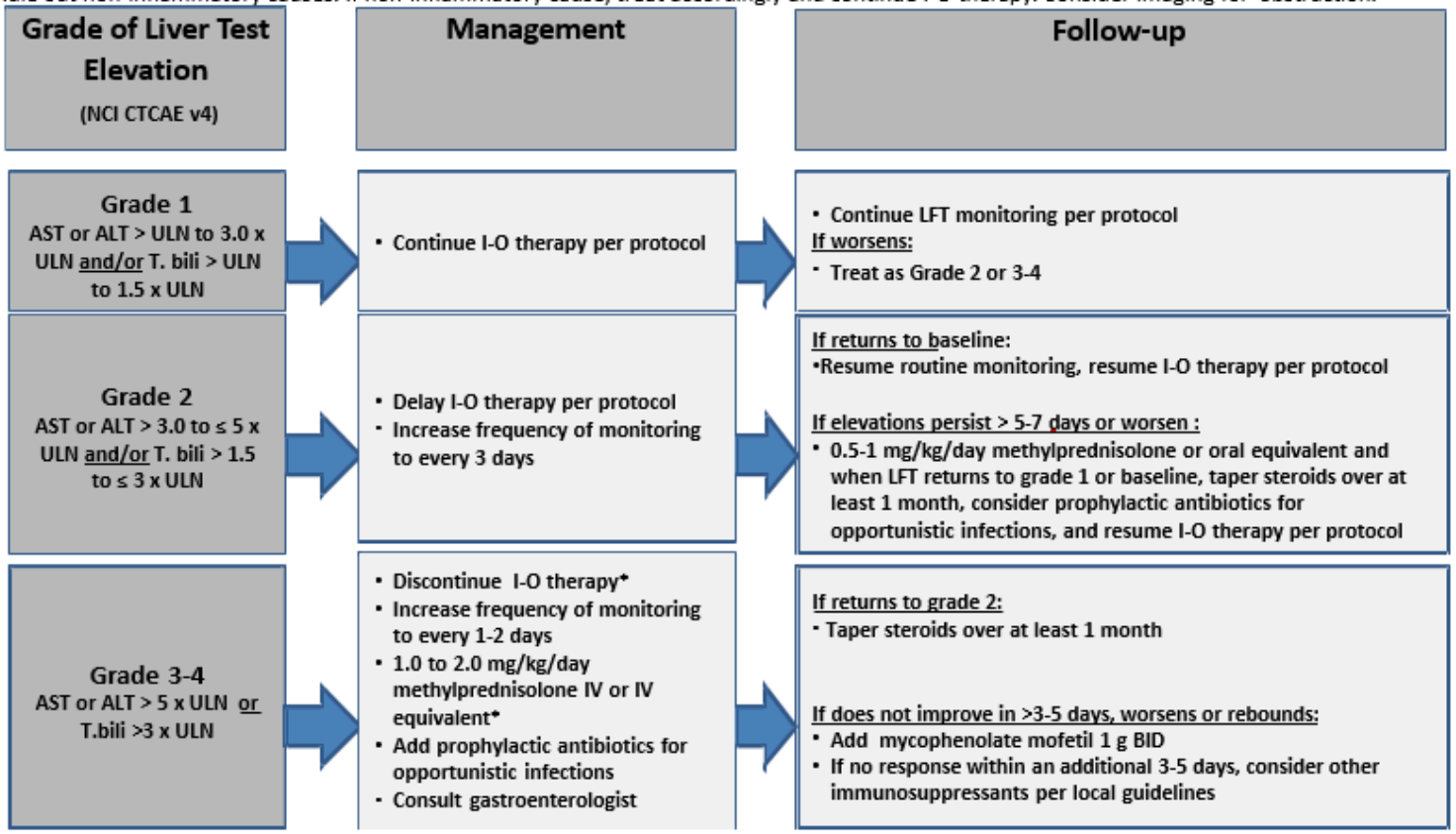


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

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.



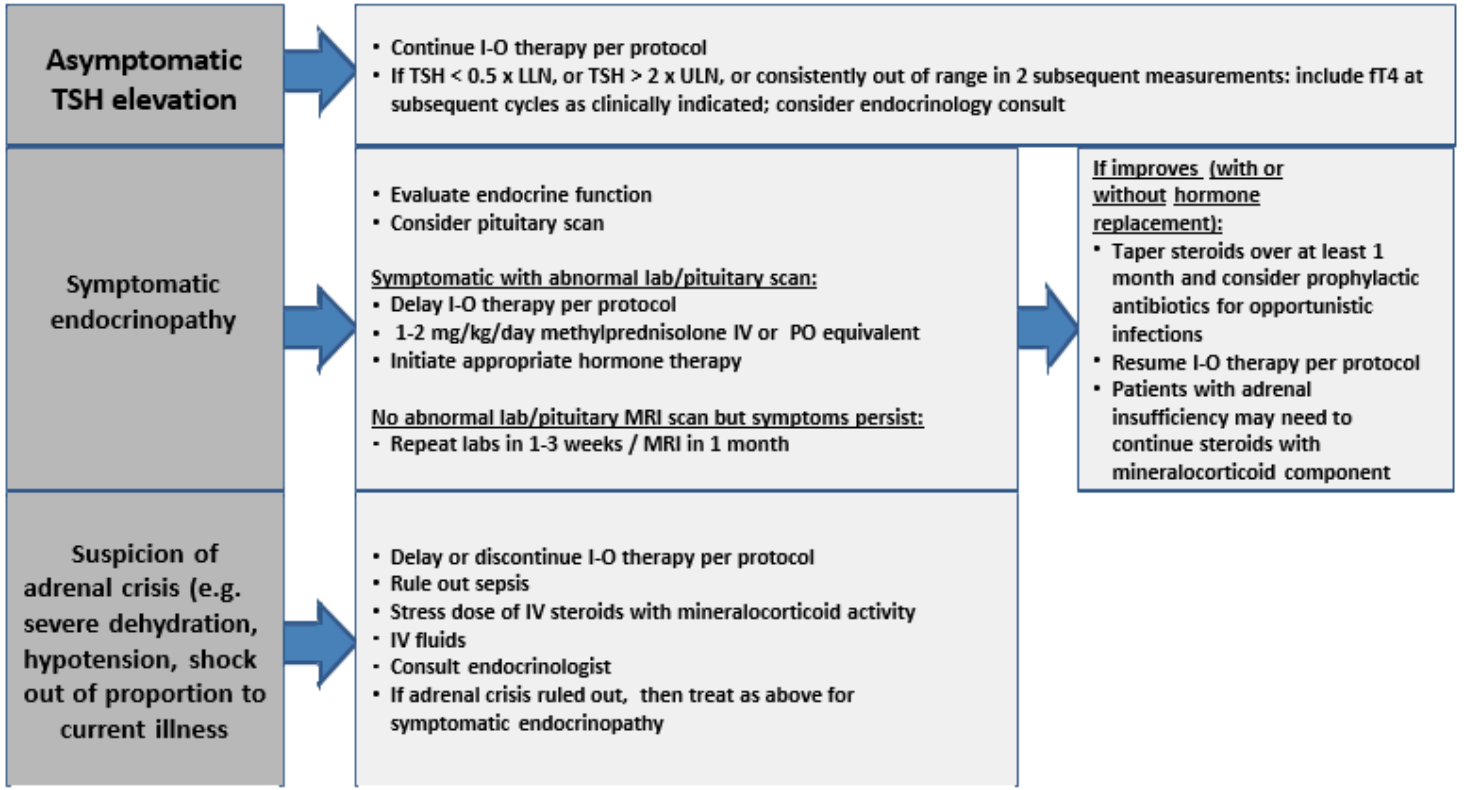
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

27-Jun-2019

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.

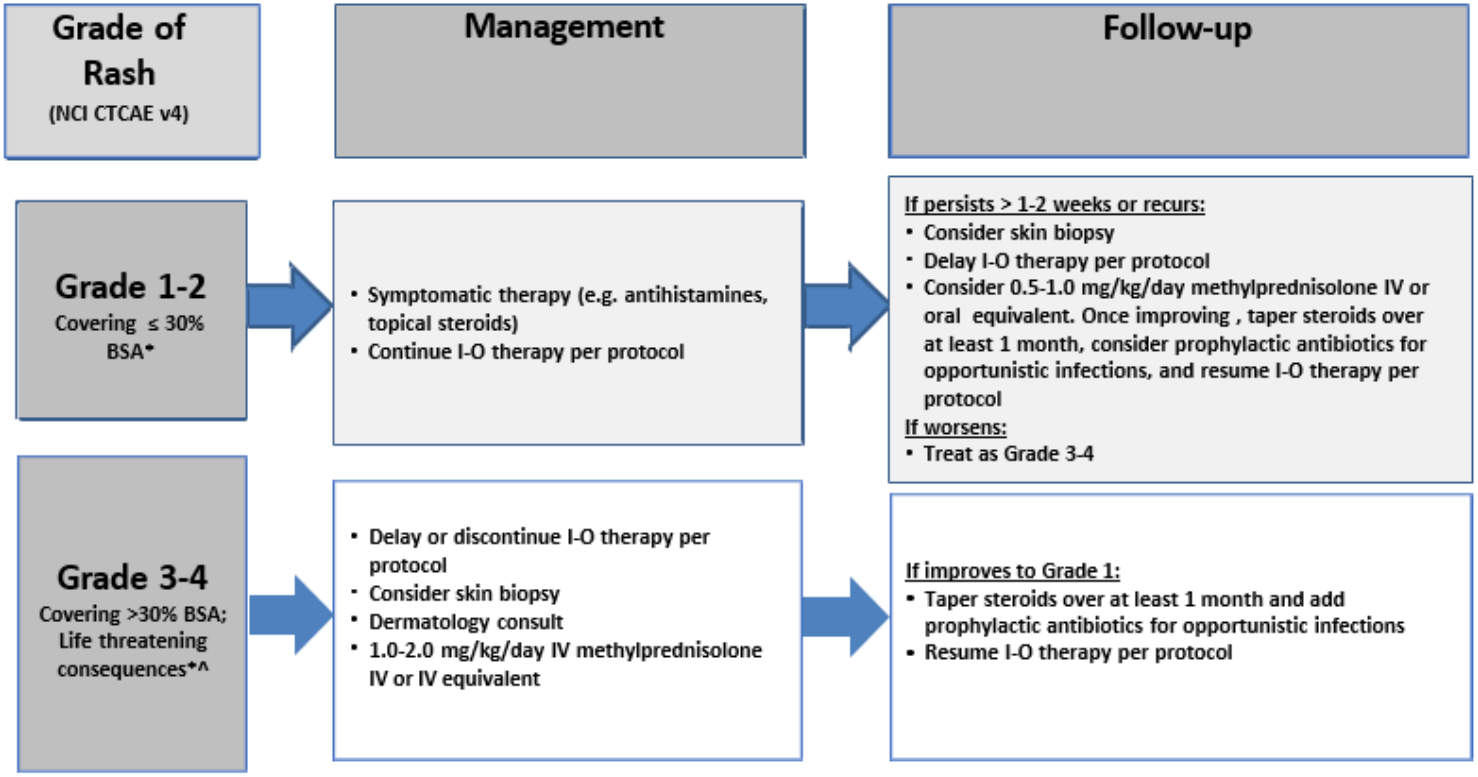


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

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.

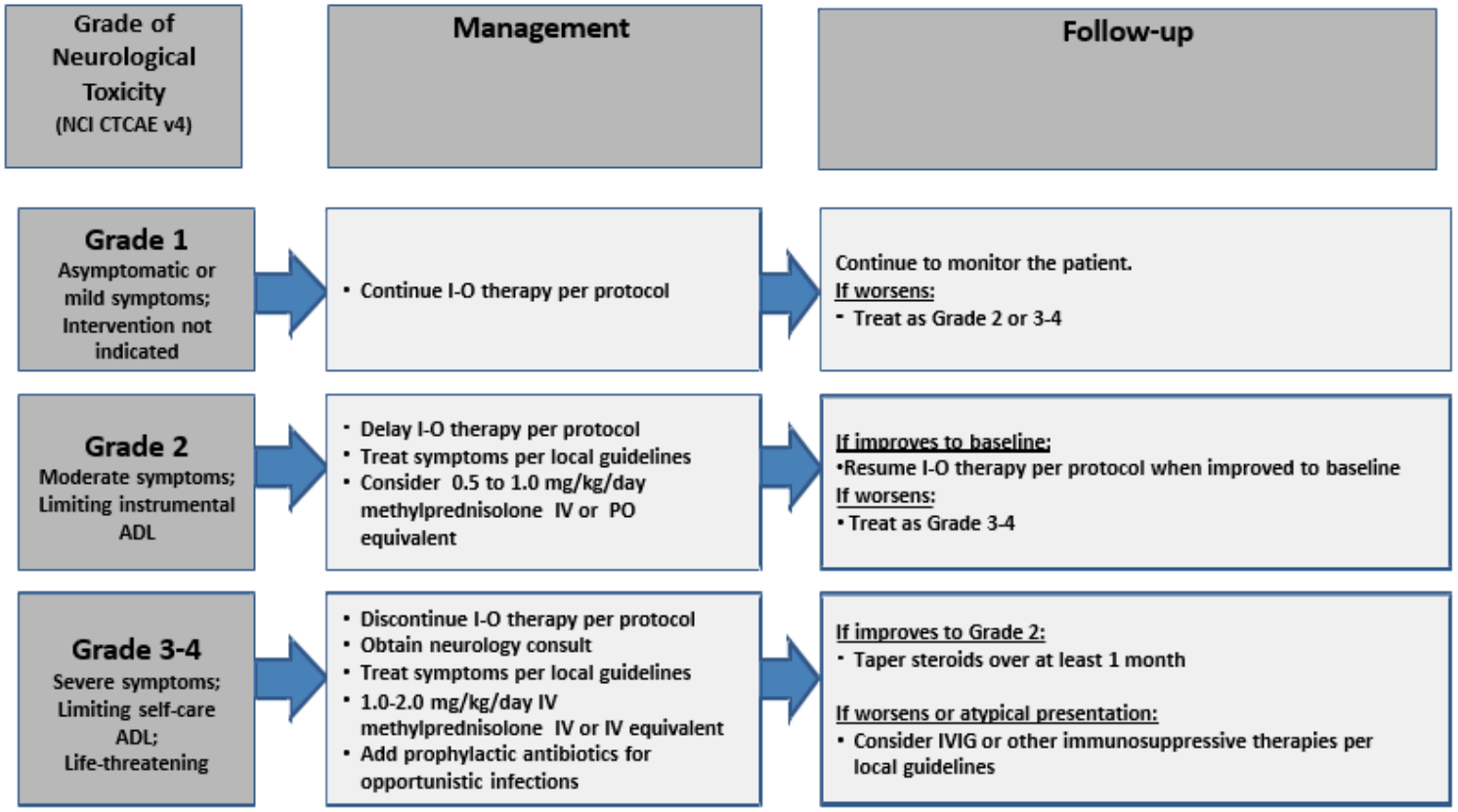
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^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-2019

Neurological Adverse Event Management Algorithm

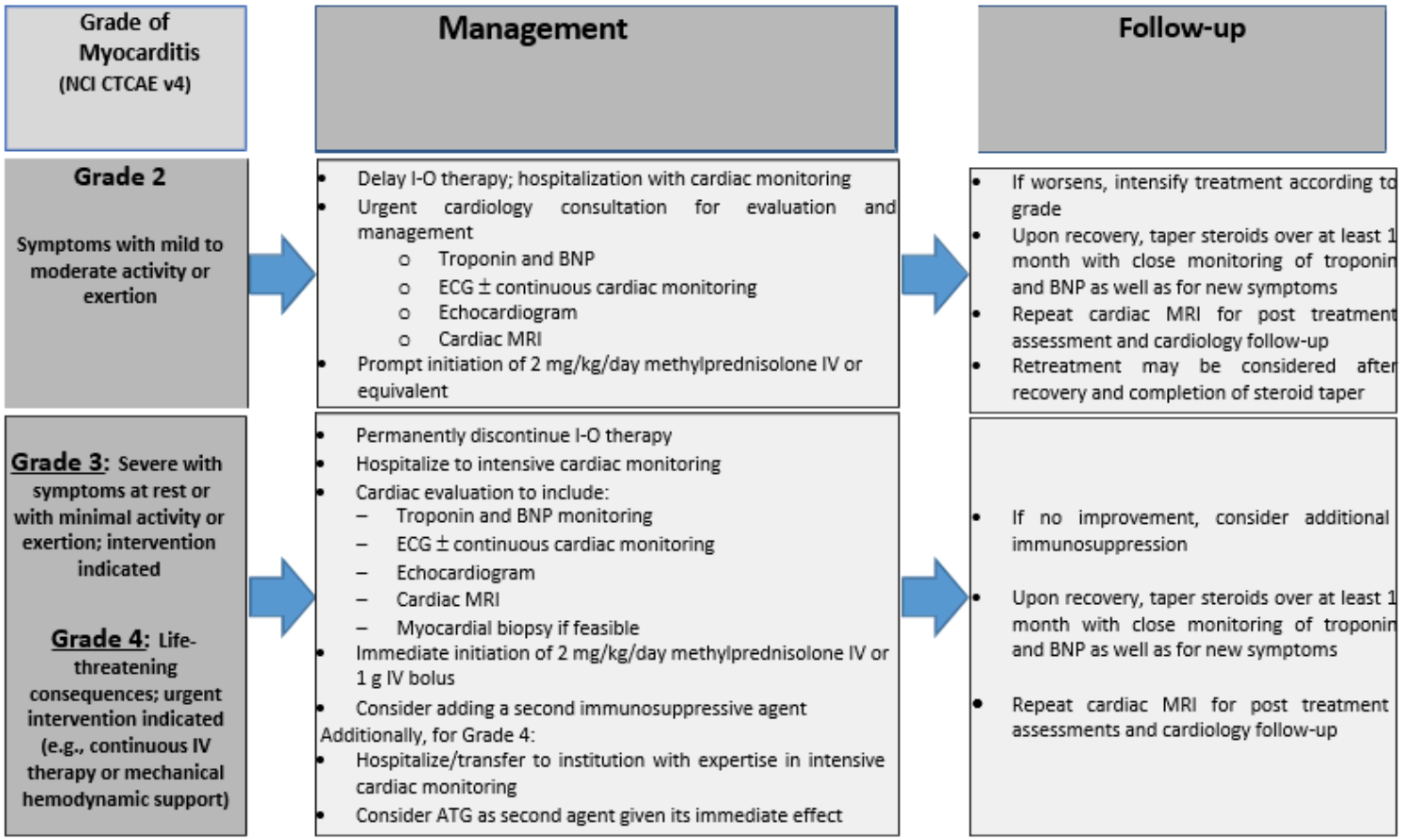
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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-2019

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, 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.

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

27-Jun-2019

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.

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 device (IUD)[c] • Intrauterine hormone-releasing system (IUS)[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 5. • 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

Unacceptable Methods of Contraception
• 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 the end of relevant systemic exposure defined as 7 months after the end of treatment in the male participant.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of treatment.
- Refrain from donating sperm for the duration of the study treatment and for 7 months after the end of treatment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 6.4.

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 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

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

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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 within 4 weeks 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) that is defined in the study protocol.

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]

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	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.