Observational Study Protocol CA209-6KX

Prospective Evaluation of Nivolumab in Adjuvant Esophageal Cancer/Gastroesophageal Junction Cancer: A Non-interventional Study

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Version 1.1	1 September 2022	Administrative changes Addition of paragraph regarding patient recovery from surgery in section 3.4.1 Addition of biomarkers in section 3.5.2 Addition of subgroup analysis in section 4.1.1.4

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SYNOPSIS

Observational Study Protocol BMS-CA209-6KX

Protocol Title: Prospective Evaluation of Nivolumab in Adjuvant Esophageal Cancer/Gastroesophageal Junction Cancer: A Non-interventional Study

Department: WW Health Economics & Outcomes Research **(**WWHEOR)

Objective(s):

Primary Objective: The primary objective of this study is to estimate real-world disease-free survival (DFS) in adult patients with early-stage esophageal cancer (EC) or gastroesophageal junction cancer (GEJC) initiating adjuvant nivolumab treatment.

Secondary Objectives:

The following secondary objectives will be assessed overall and according to various subgroups of interest, unless otherwise specified:

- To estimate in adult patients with early-stage EC or GEJC initiating adjuvant nivolumab treatment:
  - DFS and DFS rates in subgroups of interest
  - Median overall survival (OS) and OS rates
  - Distant metastasis-free survival (DMFS) and DMFS rates
- To describe disease recurrence patterns in patients with a recurrence, including time to recurrence, type of recurrence (local/regional vs metastatic), and post-recurrence survival (PRS)
- To describe treatment patterns of adjuvant nivolumab (dosing, regimen, indication, treatment rationale, treatment duration, modifications in relation to the management of adverse events [AE], reasons for treatment discontinuation/cessation), subsequent therapy (regimen(s), duration), and time to next treatment (TTNT)
- To estimate from initiation of subsequent treatment, in patients that receive subsequent treatment(s) following adjuvant nivolumab discontinuation:
  - OS and OS rates
  - Progression free survival 2 (PFS2) and PFS2 rates
  - Overall response rate (ORR)
- To describe sociodemographic and clinical characteristics, and treatment history
- To describe incidence and severity of adverse events (AEs) and serious adverse events (SAEs) in relation to nivolumab

Exploratory Objective: The exploratory objective of this study is to evaluate patient satisfaction with adjuvant nivolumab treatment using the Cancer Therapy Satisfaction Questionnaire (CTSQ) and health related quality of life (HR-QoL) by using the Functional Assessment of Cancer Therapy – General 7 item version (FACT-G7) questionnaire.

Study Design: This is a non-interventional, prospective, multinational, multicenter, post-marketing observational study designed to describe the effectiveness and patterns of use of adjuvant nivolumab after resection in patients with early stage (Stage II/III) EC/GEJC. This study will be conducted in the United States (US) and Germany will only collect data available from patients' medical files and other items

routinely collected during disease management in clinical practice. This study is strictly observational, and prescriptions of nivolumab will be at the sole discretion of the treating physician. The overall study duration will be up to 42 months with an enrollment period of 18 months. Data will be collected by sites at Day 0 (baseline) and month 3 (M3), M6, M9, M12, M18, M24, M30, M36, and M42. Follow-up time for the first patient in will be up to 42 months and a minimum of 24 months for the last patient in. Patients will be followed until the end of study period, death, lost to follow-up, or study withdrawal, whichever comes first.

Study Population: Adult subjects diagnosed with early-stage EC/GEJC initiating nivolumab treatment per the clinical care recommendation of their treating physician and meeting the following inclusion criteria and none of the exclusion criteria will be eligible to participate in the study:

Inclusion criteria:

1. Patients aged 18 years or older at the time of informed consent
2. Patients provide voluntary informed consent to participate in the study before inclusion in the study
3. Confirmed diagnosis of resected early stage (Stage II/III) EC or GEJC (histologically or cytologically confirmed stage)
4. Physician decision to treat the patient with adjuvant nivolumab (according to the local label as per country-specific regulations) must be made prior to and independently of participation in the study

Exclusion criteria:

1. Participation in a clinical trial of an investigational drug, concurrently or within the last 30 days (patients who have completed their participation in an interventional trial and who are only followed-up for OS can be enrolled.)
2. Prior treatment with immuno-oncologic agents, including nivolumab, for any indication
3. Patients with a current primary diagnosis of a cancer other than EC or GEJC that requires systemic or other treatment, or has not been treated curatively (as per discretion of the investigator)

Data Collection Methods: Available data from patient's medical records will be entered into the electronic case report form (eCRF) by qualified site staff members. Patient-reported outcomes (PRO) used to assess satisfaction with nivolumab treatment will be completed on paper self-reported questionnaires by patients. Only data obtained according to routine clinical practice and addressing the study objectives will be collected and documented in the study.

Data Analyses: Evaluation of data will be primarily descriptive, and all collected data will be summarized overall and by subgroups of interests. Summary statistics for continuous variables will include the sample size (n), mean, standard deviation, median, minimum, and maximum. For categorical variables, numbers and percentages for each category will be provided and, for qualitative data, frequency and percentage per modality will be presented. The primary outcome will be DFS defined as the time from the date of nivolumab treatment initiation to the first date of disease recurrence or death, whichever occurs first. Time-to-event outcomes (i.e., DFS, OS) will be analyzed using the Kaplan-Meier methods and their corresponding 95% confidence intervals (CI) will be provided.

To address the objectives of the study, the following outcomes, but not limited to, will be assessed:

Primary outcomes

- Median DFS with 95% CI overall from nivolumab treatment initiation

Secondary outcomes

The following secondary outcomes will be assessed overall and by subgroups of interests depending on data availability, unless otherwise specified:

- Effectiveness outcomes in adult patients with early-stage EC or GEJC initiating adjuvant nivolumab treatment:
  - DFS rates and median DFS with 95% CI in subgroup of interest
  - Median OS with 95% CI and OS rates
  - Median DMFS with 95% CI and DMFS rates
- Disease recurrence patterns
  - Median time to recurrence
  - Recurrence rates
  - Type of recurrence (local/regional vs. metastatic)
  - Median PRS with 95% CI and PRS rates
- Patient management and treatment patterns
  - Treatment history for EC/GEJC
  - Nivolumab treatment duration, frequency, and dosing
  - Median with interquartile range (IQR) time between surgical resection and nivolumab initiation
  - Subsequent treatment(s) characteristics
  - Median TTNT with 95% CI
- Effectiveness outcomes in patients that receive subsequent treatment(s) following adjuvant nivolumab discontinuation:
  - Median OS with 95% CI and OS rates
  - Median PFS2 with 95% CI and PFS2 rates
  - ORR
- Patient characteristics
  - Demographics and disease characteristics
  - Concomitant treatments
  - Concurrent medical conditions
- Incidence and severity of AEs and SAEs related to nivolumab

Exploratory outcomes

- Treatment satisfaction prior to and after nivolumab treatment initiation and health related quality of life (HR-QoL) outcomes.

Interim analysis: There will be three interim analyses conducted in accordance with the scientific committee of the study.

Sample Size/Power: The sample size calculation is based on the primary outcome of the study and has been calculated assuming a 40% DFS rate after two years of follow-up and with an absolute precision of

7% for a sample size of 314 patients (accounting for a 10% drop-out rate). These calculations are based on assumptions from the CheckMate577 trial.[1]

Limitations/Strengths: Although all possible measures will be taken to ensure quality and robustness of the data collected, there are some limitations that are inherent to the observational nature of this study including selection bias, attrition bias, and variability in local treatment practices, guidelines, and data quality across sites. Notably, selection bias due to non-consent will be mitigated by providing clear information to patients and physicians on the importance of the study and low burden of participation. Furthermore, the use of a large diverse sample of patients and prescribers from the US and Germany will contribute to the generalizability of the results. The site selection process will ensure that the sites participating are representative of the US and German landscape of EC or GEJC treatment.

Findings from this study will help support results from previous clinical trials and generate real-world effectiveness data in patients initiating nivolumab for the treatment of EC/GEJC. This study will provide a better understanding of the demographics, patterns of care, and clinical outcomes of patients with EC/GEJC treated with nivolumab in routine clinical practice and will be used to inform key stakeholders, patients, healthcare practitioners, guideline committees, and regulatory authorities.

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1 INTRODUCTION

1.1 Study Rationale

Esophageal cancer (EC) is among the top 10 diagnosed malignancies worldwide, accounting for more than half a million new cases every year. It is the sixth leading cause of cancer mortality, with an estimated 500,000 deaths each year globally.[2] The overall five-year survival of EC is less than 20%, with ranges from 5% to 47% depending on whether the cancer is localized, regional, or distant (metastatic).[3] EC affects predominantly the elderly population, with the incidence of new cases peaking between 65 and 70 years of age.[4] Men are disproportionally affected by EC, with a male to female ratio ranging from 3:1 to 4:1.[5]

In the United States (US), it is estimated that in 2022, approximately 20,640 new cases (16,510 men and 4,130 women) of EC will be diagnosed, and 16,410 (13,250 men and 3,160 women) people will die from the disease, representing 3.4% of all cancer deaths in the country.[4] In Germany, cancer registry data reported that in 2020, an estimated 7,900 new cases (6,100 men and 1,800 women) of EC were diagnosed and 6,500 people died from the disease, accounting for 2.6% of cancer-related mortality.[6,7]

EC can be classified into two main histological subtypes: squamous cell carcinomas (SCC), which develop in epithelial mucosal cells located in the inner layer of the esophagus, most frequently in the cervical and upper and middle thoracic areas, and adenocarcinomas, which occur in glandular cells mainly located in the lower part of the esophagus.[8] In the West, adenocarcinoma that arises from the gastroesophageal junction, which includes approximately the first two inches (5 cm) of the stomach (according to Siewert classification), is a rare type of cancer with epidemiological characteristics more similar to those of esophageal adenocarcinoma than gastric adenocarcinoma. Hence, in the US and European Union, gastroesophageal junction cancer (GEJC) is generally treated as other esophageal adenocarcinomas.[9,10]

Worldwide esophageal SCC remains the most prevalent subtype, representing more than 85% of all incident cases of EC, especially in South America, Africa, and Asia.[11] However, in Western countries, the incidences of esophageal adenocarcinoma and GEJC have been increasing dramatically over the past three decades and are predicted to surpass those of SCC in the upcoming years.[11] Lifestyle risk factors for the development of esophageal SCC include low socioeconomic status, excess alcohol consumption, tobacco use, and micronutrient deficiencies. Esophageal adenocarcinoma and GEJC have been linked to obesity, tobacco use, gastroesophageal reflux disease, and Barrett's esophagus.[8,12,13] A similar trend has been observed in Asia, possibly due to the current availability of Helicobacter pylori eradication therapy, a high prevalence of gastroesophageal reflux disease and obesity, and dietary factors.[14]

Approximately 50% of ECs are locally or locoregionally advanced at presentation and thus amenable to potentially curative locoregional therapy.[15] Neoadjuvant chemoradiotherapy followed by surgery is a widely used standard of care for patients with resectable, locally advanced esophageal adenocarcinoma or GEJC.[16-19] However, only approximately 25% to 30% of patients treated according to the standard of care achieve a pathological complete response (pCR), resulting in a five-year survival rate of 50%. The remaining 70% to 75% of patients whose tumors do not achieve pCR (non-pCR) have a significantly lower five-year survival rate of 37%, and this is even lower in lymph node-positive patients, where the five-year survival is

17%.[20] This highlighted the need for adjuvant treatments to improve survival and health outcomes in these patients.

In recent years, immune checkpoint inhibitors, especially those that target the programmed cell death protein-1 (PD-1) / programmed cell death ligand-1 (PD-L1) axis have been the subject of increased interest as clinical data have demonstrated their efficacy against various malignancies, including EC. PD-1 and PD-L1 inhibitors have also presented a broad anti-cancer therapeutic use, including as diagnostic tool and neoadjuvant and adjuvant therapies.[21,22]

Nivolumab (Opdivo®; Bristol Myers Squibb [BMS]) is a fully human immunoglobulin G4 monoclonal antibody that binds to the PD-1 receptor, and which is used in patients with EC/GEJC as adjuvant therapy. PD-1 is an inhibitory receptor expressed on activated T cells that can negatively regulate T cell-mediated immune responses and promotes tumor development; by interacting with PD-1, nivolumab blocks PD-1 interaction with the ligands PD-L1 and PD-L2. This enables the release of PD-1 pathway-mediated inhibition of T cell immune response, including the anti-tumor immune response, thereby reducing tumor growth, and promoting tumor rejection.[23,24]

The efficacy and safety of nivolumab in patients with resectable, locally advanced EC or GEJC has been demonstrated in CheckMate 577 (NCT02743494), a global, randomized, double-blind, placebo-controlled phase III trial that evaluated nivolumab as adjuvant treatment after neoadjuvant chemoradiotherapy and surgery.[1] The trial population consisted of adult patients with resected (R0) stage II or III EC or GEJC who had received neoadjuvant chemoradiotherapy and had residual pathological disease. A total of 794 patients were randomly assigned at a ratio of 2:1 to receive nivolumab (532 patients) or placebo (262 patients, including two patients who did not receive the placebo). Patients were administered nivolumab at a dose of 240 mg every two weeks for 16 weeks, followed by nivolumab at a dose of 480 mg every four weeks or matching placebo. The trial intervention lasted for a maximum duration of a year. The primary efficacy endpoint was disease-free survival (DFS), defined as the time between randomization and the first recurrence (local, regional, or distant from the primary resected site) or death, from any causes, as assessed by the investigator prior to subsequent anti-cancer therapy. The median follow-up duration was 24.4 months at primary completion interim analysis.[1]

Among patients who received nivolumab, the median DFS was doubled as compared with patients who received placebo: 22.4 months (95% confidence interval [CI] 16.6 to 34.0) vs. 11.0 months (95% CI 8.3 to 14.3). The hazard ratio for disease recurrence or death was 0.69 (96.4% CI 0.56 to 0.86; $p<0.001$). The efficacy of nivolumab compared with placebo was observed across multiple prespecified subgroups based on demographic and baseline disease characteristics, including age group (≥65 and <65), sex, race, region, disease stage at diagnosis (II and III), histologic type (SCC and adenocarcinoma), and tumor cell PD-L1 expression. More than half of the trial patients had lymph node-positive disease at baseline and, despite the poor prognosis in these patients, nivolumab was associated with improvement in DFS, with a 31% reduction in the risk of recurrence or death.[1]

The safety profile of nivolumab was consistent with those observed in previous trials in patients with gastroesophageal and other solid tumors. Grade 3 or 4 adverse events (AE) that were considered by the investigators to be related to the trial regimen were more common in the nivolumab group (in 71 of 532 patients [13%]) compared with the placebo group (in 15 of 260

patients [6%]). The most common grades 3 or 4 select treatment-related AEs (TRAEs) in the nivolumab group were pneumonitis (in four patients [<1%]) and rash (in four patients [<1%]). In the placebo group, each of these AEs was observed in one patient each (<1%). The most common AEs of any grades that were classified as related to the trial regimen by the investigators were fatigue, diarrhea, pruritus, and rash in the nivolumab group and diarrhea and fatigue in the placebo group.[1]

Based on the results of CheckMate 577 trial, in May 2021 and July 2021, the Food and Drug Administration (FDA) and European Commission, respectively, approved nivolumab for patients with resected EC or GEJC with residual pathologic disease who have received neoadjuvant chemoradiotherapy.[25,26]

To improve the understanding of the effectiveness and health benefits of nivolumab treatment beyond the randomized controlled trials (RCT) setting, the present prospective, multicountry, multicenter, observational study has been designed to collect real-world data during the post-market authorization approval period. This study aims to describe the real-world effectiveness, patient characteristics, treatment patterns, AEs, and patient satisfaction with nivolumab in patients with early stage (II or III) EC or GEJC initiating treatment in routine clinical practice in the US and Germany.

1.2 Research Questions

This study aims to address the following research questions:

- What is the real-world effectiveness of adjuvant nivolumab overall and according to various subgroups of interest?
- What is the profile of patients initiating adjuvant nivolumab?
- What is the pattern of use of adjuvant nivolumab, including dosing, regimen, indication, treatment rationale, treatment duration, modifications in relation to the management of AEs, and reasons for treatment discontinuation?
- What are the subsequent treatments and the outcomes in patients that receive these treatment(s) following adjuvant nivolumab?
- What is the patient HR-QoL and satisfaction with adjuvant nivolumab treatment?

2 OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to estimate real-world disease-free survival (DFS) in adult patients with early-stage esophageal cancer (EC) or gastroesophageal junction cancer (GEJC) initiating adjuvant nivolumab treatment.

2.2 Secondary Objectives

The following secondary objectives will be assessed overall and according to various subgroups of interest, unless otherwise specified:

- To estimate in adult patients with early-stage EC or GEJC initiating adjuvant nivolumab treatment:
  - DFS and DFS rates in subgroups of interest only
  - Median overall survival (OS) and OS rates
  - Distant metastasis-free survival (DMFS) and DMFS rates
- To describe treatment patterns of adjuvant nivolumab (dosing, regimen, indication, treatment rationale, treatment duration, modifications in relation to the management of AE, reasons for treatment discontinuation/cessation) and subsequent therapy (regimen, duration) and time to next treatment (TTNT)
- To estimate from initiation of subsequent treatment, in patients that receive subsequent treatment(s) following adjuvant nivolumab discontinuation:
  - OS and OS rates
  - Progression free survival 2 (PFS2) and PFS2 rates
  - Overall response rate (ORR)
- To describe disease recurrence patterns in patients with a recurrence, including time to recurrence, type of recurrence (local/regional vs metastatic), and PRS
- To describe sociodemographic and clinical characteristics, and treatment history
- To describe incidence and severity of AEs and SAEs in relation to nivolumab

2.3 Exploratory Objective

The exploratory objective of this study is to evaluate patient satisfaction with adjuvant nivolumab treatment using the Cancer Therapy Satisfaction Questionnaire (CTSQ) and HR-QoL by using the Functional Assessment of Cancer Therapy – General 7 (FACT-G7) questionnaire.

3 STUDY DESIGN

3.1 Overview of Study Design

This is a non-interventional, prospective, multinational, multicenter, post-marketing observational study designed to describe the real-world effectiveness and patterns of use of adjuvant nivolumab in patients with early stage (Stage II/III) EC or GEJC. This study will be conducted in the US and Germany will collect data available from patients' medical files and other items routinely collected during disease management in clinical practice and patient-reported outcomes (PRO) related to treatment satisfaction and quality of life.

This study is strictly observational and does not result in interference with standard medical care; thus, it will not impact the treatment of study participants. Prescriptions of nivolumab will be at

the sole discretion of the treating physician. Patients are to be enrolled into this non-interventional, primary data collection study no earlier than the decision to initiate treatment with nivolumab and no later than the first dose of nivolumab treatment. It is mandatory that the treating physician's decision to start treatment with nivolumab for early-stage EC or GECJ is taken independently and before the decision to invite the patient to participate in the study. Day 0 corresponds to the day of nivolumab initiation (administration of the first dose of treatment). The local investigator is responsible for the exact procedures of administration of nivolumab, and concomitant medications and therapies deemed necessary for the supportive care and safety of the patients.

Once the decision to prescribe nivolumab is taken by the medical team/physicians according to usual practice, patients will be screened for selection criteria. If the patient meets all inclusion criteria and none of the exclusion criteria, the investigator should then invite the patient to participate in the study and collect their consent to participate. Enrollment in the study is then clearly distinguished from the therapeutic decision to initiate nivolumab.

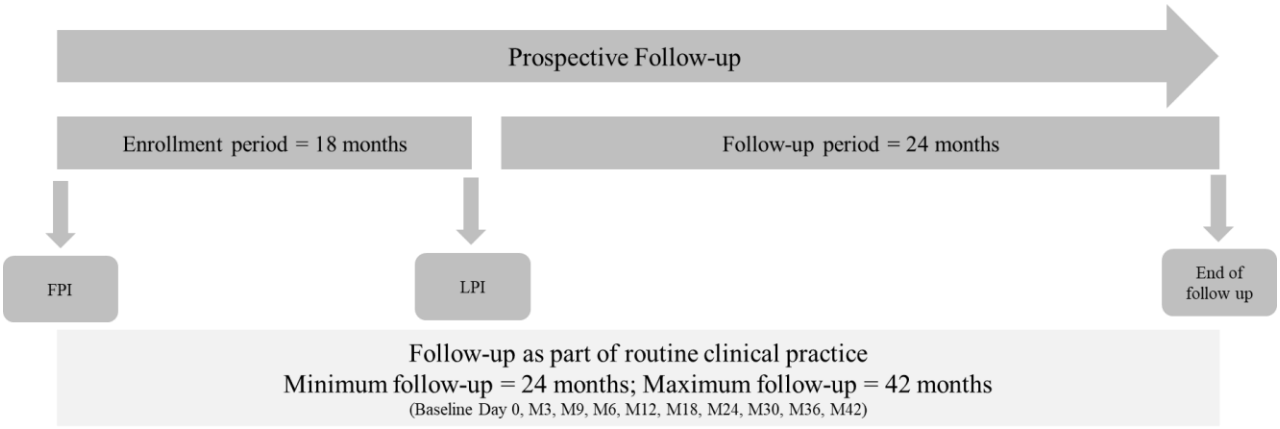
Physicians will be asked to enroll eligible patients consecutively until the total expected study sample size is reached or the end of the enrollment period (whichever occurs first). The enrollment period is anticipated to last approximately 18 months. The follow-up time will vary between patients due to the nature of the study with ongoing enrollment; patients will be followed for up to 42 months for the first patient in and up to 24 months for the last patient in. Patients will be followed until the end of study period, death, lost to follow-up, or withdrawal, whichever comes first. Patients will be censored at last record or assessment for those lost to follow-up.

Assessment schedules will be performed according to routine local clinical practice. Data collection and data entry by sites will start at Day 0 (baseline, i.e., the day of nivolumab initiation), and at the following months with a time window of +/- 15 days: months 3, 6, 9, 12, 18, 24, 30, 36, and 42 counted relative to treatment initiation (two and 3.5 years after nivolumab initiation for the first and last patient in, respectively). As this is a non-interventional study, no visits or measurements will be made mandatory by the protocol, and data collection at these pre-specified timepoints will only take place if the patient visits the site as per standard of care. Investigators or qualified research staff should collect data from the visit nearest to the time point.

Sites will receive fees to compensate for the time spent for data collection and entry into eCRFs. Since the study is intended to reflect usual clinical practice, physicians will not be required to perform any mandatory patient assessments or laboratory tests that they would not ordinarily do in treating their patients. This protocol requires that sites submit all relevant documentation to their respective institutional review board (IRB) or Ethics Committee (EC) and obtain approval or acknowledgment of notification, depending on the local requirements. Participating patients must provide written informed consent prior to study commencement, and they have the right to withdraw from the study at any time. This study will be conducted with support of a clinical research organization (CRO).

An overview of study design and data collection is shown in Figure 1.

Figure 1. Study Design.



Abbreviations: FPI = first patient in; LPI = last patient in

3.2 Study Sites

Eligible patients will be selected from over 12 sites in Germany and approximately 28 sites in the US. A feasibility study will be conducted as part of the site activation process to ensure optimal nivolumab prescribing patterns and large volumes of patients given the relatively low prevalence of these diseases. After the feasibility assessment, sites with representative medical practices, geographical diversity, and epidemiological data describing the variety of real-life aspects of EC or GEJC treatment will be included in this study. Patient selection will be based on systematic sampling technique, i.e., all consecutive eligible patients are expected to be included in the study.

3.3 Study Population

3.3.1 Inclusion Criteria

To be enrolled in the study patients must meet the following criteria:

1. Patients aged 18 years or older at the time of informed consent
2. Patients provide voluntary informed consent to participate in the study before inclusion in the study
3. Confirmed diagnosis of resected early-stage (Stage II/III) EC or GEJC (histologically or cytologically confirmed stage)
4. Physician decision to treat the patient with adjuvant nivolumab (according to the local label as per country-specific regulations) must be made prior to and independently of participation in the study

3.3.2 Exclusion Criteria

Patients that meet one or more of the following criteria will not be enrolled in any component of the study:

1. Participation in a clinical trial of an investigational drug, concurrently or within the last 30 days (patients who have completed their participation in an interventional trial and who are only followed-up for OS can be enrolled)
2. Prior treatment with immuno-oncologic agents including nivolumab for any indication
3. Patients with a current primary diagnosis of a cancer other than EC or GJEC that requires systemic or other treatment, or has not been treated curatively (as per discretion of the investigator)

3.4 Data Collection Process

3.4.1 PRO Instruments

PROs will be collected in the context of this study. Specifically, the validated Cancer Therapy Satisfaction Questionnaire (CTSQ) will be self-administered in a paper format in the primary languages spoken at study sites. The CTSQ is a self-administered questionnaire that assesses patient satisfaction with and preference for chemotherapy, hormonal therapy, and biological therapies orally (pill) and/or via intravenous administration within the past four weeks.

Patients will be asked to complete the self-administered CTSQ once per visit and at the time points defined in the protocol until nivolumab discontinuation, the end of study period, death, lost to follow-up, or withdrawal, whichever comes first.

Additionally, the validated Functional Assessment of Cancer Therapy – General 7 (FACT-G7) will be evaluated in this study. The seven-items included in this questionnaire are GP1 “I have lack of energy”, GP2 “I have pain”, GP3 “I have nausea”, GP4 “I worry that my condition will get worse”, GP5 “I am sleeping well”, GP6 “I am able to enjoy my life”, and GP7 “I am content with the quality of my life right now”. Patients will be asked to complete the self-administered FACT-G7 once per visit and at the time points defined in the protocol until nivolumab discontinuation, the end of study period, death, lost to follow-up, or withdrawal, whichever comes first.

Since HR-QoL of patients in the real-world setting is likely to be adversely affected by recovery from surgery, specific questions around recovery from surgery will be included in the eCRF to minimize confounding of HR-QoL data.

3.4.2 Patient Data

eCRF will be used by study investigators or qualified research staff members to enter data into the electronic database capture (EDC) system. As part of the routine care, study investigators will evaluate or ask patients about their disease history, treatment history, and any AEs experienced since the previous clinical visit and the related information. AEs will be collected according to guidelines and timelines in Section 7.1.1.

As this is a non-interventional study, mandatory assessments will not be required from the study sites or patients. However, data collection/reporting will be conducted in a consistent way among different sites/countries whenever possible to avoid bias in the data collection process. Data will

be entered by all sites into eCRFs, with monitoring for source data verification. Data will be collected from eCRFs, which are to be completed by site staff. Patients will report treatment satisfaction via paper-based or electronic-based, validated questionnaires.

3.5 Definitions of Study Variables

3.5.1 Outcome Variables

3.5.1.1 Clinical Outcomes

Table 1 presents the definitions of the clinical outcome variables and **Table 2** presents definitions of clinical primary and secondary effectiveness outcomes that will be continuously evaluated as part of the study in all nivolumab patients and in patients that receive subsequent treatment(s) following nivolumab treatment.

Table 1. Clinical Outcomes Definition

Outcomes	Type of variables	Definition
Disease progression	Categorical	Disease progression will be evaluated at each available tumor assessment, which is collected either at first assessment after initial treatment' or during follow-up: • Investigator assessed: o Disease progression = Yes, if best therapy tumor response = disease progression o Disease progression = No, if best therapy tumor response = complete/ near complete response, tumor shrinkage or mixed response • Per RECIST[27]: o Disease progression = Yes, if best therapy tumor response = PD o Disease progression = No, if best therapy tumor response=CR, PR, or SD
Recurrence	Categorical	Recurrence is defined as the detection of relapse of neoplastic disease during follow-up after nivolumab treatment initiation as assessed by the investigator
Type of recurrence (local/regional, metastatic)	Categorical	• Local recurrence is defined as a cancer that after treatment reappears at the primary site, i.e., at the site where it originated. • Regional recurrence is defined as cancer that reappears after treatment in the lymph nodes or tissues near the primary site. • Metastatic (distant) recurrence is defined as cancer that spreads (metastasizes) after treatment to distant organs or tissues such as the brain, kidneys, lungs, liver, or bone marrow.

Abbreviations: CR=Complete Response; PD=Progressive Disease; PR=Partial Response; SD=Stable Disease

Table 2: Primary and Secondary Effectiveness Outcomes Definition

Outcomes	Type of variables	Definition

Effectiveness outcomes in patients initiating adjuvant nivolumab treatment		
DFS	Time-to-event	Time between initiation of nivolumab treatment and the first date of recurrence (local, regional, or distant from the primary resected site) or death from any causes, whichever occurs first, as assessed by the investigator prior to subsequent anti-cancer therapy.
DFS rates	Continuous	DFS rates are defined as the probability that a patient is alive and presents no signs of recurrence at specific time points, following adjuvant nivolumab initiation.
OS	Time-to-event	Time between initiation of nivolumab treatment until date of death due to any cause. Patients who are alive at last visit will be censored on date last known to be alive.
OS rates	Continuous	OS rates are defined as the probability that a patient is alive at specific time points, following adjuvant nivolumab initiation.
DMFS	Time-to-event	Time between initiation of nivolumab treatment and date of appearance of distant metastasis or death from any causes, whichever occurs first, as assessed by the investigator prior to subsequent anti-cancer therapy.
DMFS rates	Continuous	DFS rates are defined as the probability that a patient is alive and presents no signs of metastasis at specific time points, following adjuvant nivolumab initiation.
Time to recurrence	Continuous	Time between initiation of nivolumab treatment and the first date of recurrence.
Recurrence rates	Categorical	Recurrence rates are defined as disease recurrence (i.e., local/regional, metastatic) at specific time points, following adjuvant nivolumab initiation.
PRS	Time-to-event	PRS is defined as the interval from the date of any recurrence to the date of death from any cause. Patients who are alive at last visit will be censored on date last known to be alive.
Effectiveness outcomes in patients that receive subsequent treatment(s) following adjuvant nivolumab discontinuation:		
OS of subsequent treatment	Time-to-event	Time between initiation of subsequent treatment until date of death due to any cause. Patients who are alive at last visit will be censored on date last known to be alive.
OS rates of subsequent treatment	Continuous	OS rates are defined as the probability that a patient is alive at specific time points, following subsequent treatment initiation.
PFS2	Time-to-event	Time between initiation of subsequent treatment and date of disease progression or death if occurred before progression. In case of censored event, the duration of response is censored on the date of last tumor assessment or enrollment (whichever occurs last)
PFS2 rates	Continuous	PFS2 rates are defined as the probability that a patient is alive and presents no signs of disease progression at specific time points, following subsequent treatment initiation.
ORR of subsequent treatment	Continuous	Total number of patients with CR or PR to subsequent treatment divided by the total number of patients.

Abbreviations: CR = Complete Response; DFS = Disease-Free Survival; DMFS = Distant Metastasis-Free Survival; OS = Overall Survival; ORR = Overall Response Rate; PFS2 = Progression-Free Survival 2; PR = Partial Response; PRS = Post-Recurrence Survival

3.5.1.2 Treatment Pattern Outcomes

The variables used to evaluate treatment patterns, changes in treatment, and outcomes throughout the follow-up period are described in **Table 3.** Data necessary to derive these outcomes will be collected if available. In this study, Day 0 is defined as the date of initiation of nivolumab treatment.

All baseline characteristics such as treatment or disease history will be collected retrospectively. As this data will be assessed before the date and time of the first dose of adjuvant nivolumab treatment, if the time (onset time of event or evaluation time) is missing or not collected, the following definitions will apply:

- Pre-treatment diseases/conditions will be defined as diseases/conditions with an onset date prior to but not including the day of the first dose of adjuvant nivolumab.
- Baseline measurements are defined as measurements at nivolumab initiation (i.e., Day 0) or prior to the day of the first dose of nivolumab. If there are multiple valid assessments, the assessment closest to the day (and time, if collected) of the first dose of nivolumab treatment will be used as the baseline measurements. If multiple assessments are collected on the same date (and time, if collected), the assessment with the latest database entry date (and time, if collected) will be considered as baseline.

Table 3. Treatment Pattern Outcomes Definition and Timing

Variables	Definition	Timing
Cancer treatment history		
Type of prior therapy	Type of therapies received prior to initiation of nivolumab treatment (e.g., radiotherapy, chemotherapy, targeted therapy, systemic treatment, platinum-based therapy) and details (if applicable, e.g., regimens, dosing)	Baseline
Start and end dates for each prior therapy	Date of initiation and discontinuation of each prior therapy	
EC/GEJC stage when treated with prior therapy	EC/GEJC Stage (i.e., I, II or III) and staging using Tumor (T), node (N), and metastasis (M) (TNM) system during prior therapy	
Indication for prior therapy	Treatment indication	
Prior therapy setting	Neoadjuvant/adjuvant/palliative	
Surgery for cancer	Information on cancer surgery including, date, type, resection status (e.g., R0, R1), results, and setting	
Concomitant medications during prior therapy	Other medications received during prior cancer treatment	
Nivolumab treatment		

Variables	Definition	Timing
EC/GEJC stage at initiation	EC/GEJC Stage (i.e., II or III) and staging using TNM system at nivolumab treatment initiation	Day 0
Indication for nivolumab	Treatment indication	
Start date of nivolumab treatment	Date of nivolumab initiation	
Time from surgery to nivolumab initiation	Time from date of surgery to treatment nivolumab initiation	
Dosing	Dosing (i.e., frequency, dose, and number of administered doses), dose modifications (reasons for dose/frequency changes, interruption, and discontinuation)	All visits[1]
Other treatment(s)		
Concomitant type of treatment or therapies and details	Type of treatment or therapies receive in parallel of nivolumab treatment and details (e.g., medications, radiotherapy, chemotherapy, systemic therapy, or surgical treatment)	All visits[1]
Systemic treatment details, if applicable	• Type (Immunotherapy, targeted therapy, other) • Drug names • Dosage • Number of received administrations • Start date, end date	
At completion/discontinuation of nivolumab treatment		
End date of nivolumab treatment	Date of nivolumab treatment completion/discontinuation	All visits[1]
Permanent discontinuation of nivolumab	Permanent discontinuation is defined as 3 missed infusions. If nivolumab is restarted after 3 missed infusions, it should be considered as a new line of therapy (LOT).	
Temporary discontinuation	Temporary discontinuation is defined as 1 or 2 skipped infusions.	
Reason(s) for discontinuation	Reasons: death, disease progression, study drug related toxicity, non-study drug related toxicity, patient request, pregnancy, lost to follow-up, other	
Time-to-treatment discontinuation	Time from date of nivolumab treatment initiation to date of last infusion + 2 or 4 (if administered every 4 weeks) weeks (first 'missed' infusion), or the date of failure from a competing risk (e.g., death)	
Subsequent treatment after nivolumab discontinuation	• Yes/No • Type of treatment and details • Start date, end date	
TTNT	• Start date, end date of nivolumab treatment • Start date, end date of subsequent treatment(s)	
Modifications in relation to the management of AEs	Any changes in nivolumab treatment related to the management of AEs	
Treatment outcomes		
Disease stage after nivolumab treatment	EC/GEJC stage (i.e., II or III) and stage using TNM system	

Variables	Definition	Timing
Recurrence	• Yes/No • Date of recurrence • Type of recurrence (i.e., local, regional, distant)	All visits[1]
Disease progression	• Yes/No (as assessed by investigator or RECIST criteria) • Date of disease progression	
Medical imaging test to assess treatment outcomes	Medical imaging test used to assess recurrence or disease progression (e.g., computed tomography (CT) / magnetic resonance imaging (MRI), Conventional X-ray, PET) and details including method of assessment (i.e., by RECIST or as assessed by the treating physician) and date of assessment	
Death	• Yes/No • Date of death • Cause of death	

[1] Data will be collected at visits Day 0, and Months 3, 6, 9, 12, 18, 24, 30, 36, and 42.

Abbreviations: AEs = adverse events; CT = computed tomography; EC = esophageal cancer; GEJC = gastroesophageal junction cancer; MRI = magnetic resonance imaging; PET = positron emission tomography; RECIST= Response evaluation criteria in solid tumors; TNM=Tumor Node Metastasis

3.5.1.3 Sociodemographic and Clinical Characteristics

Table 4 4 summarizes the definition and timing of the sociodemographic and clinical outcomes that will be collected, if available, from routine clinical practice visits. Completeness of all variables (e.g., race) may be dependent on country-specific data privacy regulations.

Table 4. Sociodemographic and Clinical Characteristics Definitions and Timing

Variables	Definition	Timing
Patient demographics and vital signs		
Sex	Male/Female	Baseline
Race (if allowed)	White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Not collected at site	
Ethnicity (if allowed)	Hispanic or Latino, Not Hispanic or Latino, Japanese, Not Japanese, Not collected at site	
Country	US, Germany	
Age	Calculated from year of birth to Day 0	
Height	Units	
Weight	Units	All visits[1]
BMI	Derived from weight and height	
Medical history		
History of other primary malignancies and details	Yes/No, details information including, primary site, date of diagnosis and stage	Baseline

Variables	Definition	Timing
Smoking	Current, Past, Never	
Alcohol use	Yes/No, duration, volume per week	
Previous enrollment in an interventional study (RCTs) and details	Yes/No, date of enrollment; treatment, start and end date	
Comorbidities and details	Diagnosis date and name of diagnosis, grouped using the National Cancer Institute (NCI) Comorbidity Index.	Baseline and all visits[1]
Disease characteristics		
Initial diagnosis	Date of initial diagnosis	Baseline
Disease stage at initial diagnosis	EC/GEJC stage (i.e., I, II or III) and stage using TNM system	
Tumor location at initial diagnosis	EC (upper, middle, lower area of the esophagus) or GEJC (Siewert type I, II or III, if available)	
Tumor histology at initial diagnosis	SCC or adenocarcinoma	
Margins	Negative (clear), positive (involved), close margins	
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 on a light or sedentary nature • 2: Ambulatory and capable of all self-care but unable to carry out work activities. Up and about more than 50% of waking hours • 3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours • 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair • 5: Dead	Baseline and all visits[1]
Pathological lymph-node status	ypN0, ypN1, ypN2, ypN3, unknown	
Pathological tumor status	ypT0, ypT1, ypT2, ypT3, ypT4, unknown	
Biomarkers (if available)		
Tumor cell PD-L1 expression	Tumor cell PD-L1 expression levels and cells assessed. This will be used to group PD-L1 expression into ≥1%, <1%, or Indeterminate/non-evaluable and to derive the combined positive score (CPS) score which is defined as PD-L1 positive tumor cells + PD-L1 positive mononuclear inflammatory cells)/Total tumor cells) × 100.	Baseline and all visits[1]
HER2 status	Positive, negative, not reported	
Tumor Mutational Burden (TMB)	Number of non-inherited mutations per million bases (Mb)	Baseline
Epstein-Barr virus positivity	Yes/No	
Microsatellite Instability (MSI)	Stable/Low/High	
Circulating tumor (ct) DNA	Absent/Detectable	

Variables	Definition	Timing
Metastasis	Yes/No	All visits[1]
Sites of metastases	Lung, brain, liver, peritoneum, bone, lymph nodes, other	

[1] Data will be collected at visits Day 0, and Months 3, 6, 9, 12, 18, 24, 30, 36, and 42.

Abbreviations: BMI body mass index; CPS= Combined Positive Score; ct=circulating tumor; DNA= Deoxyribonucleic Acid; EC = esophageal cancer; ECOG = Eastern Cooperative Oncology Group; GEJC = gastroesophageal junction cancer; HER=Herceptin; Mb=Million base; MSI=Microsatellite Instability; NCI = National Cancer Institute; OS = overall survival; PD-L1 = programmed cell death ligand-1; RCT = randomized controlled trial; TMB=Tumor Mutational Burden; US = United States

3.5.1.4 Incidence, Severity, and Management of AEs

This section describes the outcomes that will be used to evaluate the frequency, severity, and management of treatment-related AEs, select AEs, and other immune-related AEs. Data necessary to derive these outcomes will be collected if available. AE collection and reporting will follow the guidelines outlined in Section 7.1.

Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Treatment-related Adverse Events

Treatment-related AEs are those events with a relationship to the study drug recorded as "Related" on the eCRF.

Immune-related Select Adverse Events

Among the immune-related AEs, a category of "select AEs" will be created to group the most common and impactful AEs, providing a better estimate of the frequency of similar types of organ-related AEs. These select AEs are further defined as follows:

- May differ from or be more severe than AEs caused by non-immunotherapies
- May require unique (non-standard) intervention such as immuno-suppressants (or hormone replacement therapy)
- Early recognition and management may mitigate severe toxicity

"Select AEs" category:

- Pneumonitis
- Diarrhea/Colitis
- Hepatitis
- Nephritis and renal dysfunction
- Endocrinopathies

- Pruritus
- Rash
- Severe infusion reactions

Other Immune-Related AEs

In this study, immune-related AEs are defined as nivolumab treatment-related AEs that are consistent with the immune-based mechanisms of action of nivolumab, per investigator-assessed causality, and can occur during or after nivolumab treatment. Select AEs are special group of AEs, which follow the criteria listed above. Immune-related AEs that are not categorized as select AEs are considered as other immune-related AEs. Other immune-related AEs may include:

- Myocarditis
- Arthralgias
- Uveitis
- Pancreatitis
- Demyelination
- Guillain-Barre Syndrome
- Myasthenic syndrome
- Encephalitis

3.5.1.5 Patient-reported Outcome

In this study, patient satisfaction with nivolumab treatment will be assessed using the CTSQ at baseline and at the visits indicated in **Table 5**. In addition, three items form the FACT-G questionnaire will be assessed at baseline and at visits indicated in **Table 5.** Patient-reported outcomes will only be collected for 12 months, which is the treatment duration for nivolumab.

Table 5. Cancer Therapy Satisfaction Questionnaire

PRO	Definition	Timing
CTSQ	The revised CTSQ is 16-item instrument measuring three domains: Expectations of Therapy (5 items), Feelings about Side Effects (4 items), and Satisfaction with Therapy (7 items).	Day 0, and Months 3, 6, 9, and 12
FACT-G7	GP1 “I have lack of energy” GP2 “I have pain” GP3 “I have nausea” GP4 “I worry that my condition will get worse” GP5 “I am sleeping well” GP6 “I am able to enjoy my life” GP7 “I am content with the quality of my life right now”	Day 0, and Months 3, 6, 9, and 12

Abbreviations: CTSQ=Cancer Therapy Satisfaction Questionnaire; FACT-G7=Functional Assessment of Cancer Therapy – General 7

3.5.2 Other Covariates/Control Variables

Table 6 list the variables that will be used to assess the representativeness of the study population.

Table 6. Variables Used to Assess Sample Representativeness

Variables	Definition
Country	Country site (i.e., US, Germany)
Type of institution	Office-based/community hospital-based/university hospital-based
Specialization of the treating physician	Oncologist and/or treating physician
Hospital activity	Number of patients with EC/GEJC, as evaluated during feasibility assessment
Hospital location	Geographical region within each country

Abbreviations: EC=Esophageal Cancer; GEJC=Gastroesophageal Junction Cancer; US=United States

4 STATISTICAL ANALYSIS

4.1 Statistical Analysis Methods

4.1.1 General Aspects

This study is purely descriptive, and no formal hypotheses will be tested. An overview of planned statistical analyses is provided in Sections 4.1.1 to 4.1.4. A standalone statistical analysis plan (SAP) will describe in detail all planned statistical analyses to be performed for this study.

The SAP will include tables, listings, figure shells to be populated during the interim and final data analyses, and details of changes in the planned analysis post-protocol finalization if applicable. It will also provide a description of the methods to deal with missing data, censoring, and procedures to control for potential sources of bias and their influence on the results.

All analyses will be conducted in accordance with the study objectives, SAP, and applicable guidelines. Statistical methods will be driven, in part, by the final sample size and the number of events. Results will be rounded to one decimal place; therefore, percentages may not always add up to 100. Standard deviation and 95% CIs will be calculated when relevant. The statistical analyses will be performed using SAS enterprise 7.1 or above, or SAS 9.4 or above. All patients who meet eligibility criteria will be included in the analysis data set.

4.1.1.1 Descriptive statistics

All collected data and outcomes will be analyzed using descriptive statistics and summarized in tables, listings, and figures as appropriate. Continuous variables will be described with summary statistics such as number of subjects, mean, standard deviation, median, first quartile, third quartile, and minimum and maximum values. For each categorical variable, the frequency and percentage in each category will be reported. Percentages will be calculated using the specified denominator in the table. The frequency and percentage of patients with missing data for each data point will be presented. For continuous and categorical variables, CIs of 95% will be calculated when relevant.

4.1.1.2 Time-to-Event Analyses

Time-to-event analysis will be used for outcomes that assess the length of time until the occurrence of a predefined outcome. The following time-to-event outcomes defined in Section 3.5.1 will be analyzed for all nivolumab patients, for patients that receive subsequent(s) treatments following nivolumab, and by subgroup of interests if sample size allows:

- DFS
- OS
- PFS2
- DMFS
- PRS

The time-to-event for each outcome during the study period will be reported in months, and summarized descriptively (minimum, median, quartiles, and maximum). Kaplan-Meier (KM) curves will be used to illustrate the survival probability estimates and the number of patients at risk over time for the overall population and by subgroup of interests when relevant. Median survival time estimates and survival probabilities (with two-sided 95% CIs) at each study period timepoint will be provided.

4.1.1.3 Missing Data

All efforts will be made to prevent missing data to the extent possible through various strategies set forth in the design and the conduct of the study. Should missing data occur, they will be analyzed as they are recorded in the study eCRFs and the level of missing data for all variables will be reported and the patterns of missing described. The impact of missing data on interpretation of findings will be acknowledged and discussed in the final study report. Further details on handling of missing data will be described in the SAP.

4.1.1.4 Subgroup Analyses

To meet the secondary and exploratory objectives, study outcomes will be summarized by subgroups of interest, depending on relevance, data availability and sample size including but not limited to:

- Patient and clinical characteristics:
  - Country (US, Germany)
  - Sex (Male vs. female)
  - Age group (≤65 vs. >65)
  - Race
  - Resection status (R0 vs R1)
  - Disease stage
  - ECOG
  - Tumor location

- Histology
- Pathologic lymph node status (ypN0 vs. ≥ ypN1)
- Pathologic tumor status (ypT0 vs. ≥ ypT1)
- Tumor cell PD-L1 expression
- Type of recurrence (local/regional vs. distant)

Furthermore, subgroup analyses (if sample size allows) will be performed according to Checkmate 577-like patient population vs. non-Checkmate 577 like patient population, using the key inclusion/exclusion criteria from the Checkmate-577 trial to determine the subgroups. This subgroup analysis will be performed to establish nivolumab safety and effectiveness in these two patient populations. If outcomes are similar between the two patient populations, this would support the use of nivolumab in almost all patients with EC and or GEJC.

4.1.1.5 Sensitivity Analyses

Sensitivity analyses to assess the impact of missing data on the study's estimates will be performed. In addition, sensitivity analyses may also be conducted to examine the extent to which changes in certain methods or assumptions affect the results, for example excluding from the analysis patients with history of another primary malignancy. All sensitivity analyses will be fully outlined in the SAP.

4.1.2 Analysis Plan for Primary Objective

The primary outcome of this study, DFS, will be estimated and plotted using the KM estimator for up to 42 months follow-up.

- Median DFS and the corresponding two-sided 95% CIs will be estimated.

4.1.3 Analysis Plan for Secondary Objectives

4.1.3.1 Secondary Effectiveness Outcomes

The analysis of OS and DMFS for all nivolumab patients and OS and PFS2 for patients that receive subsequent treatment following nivolumab treatment discontinuation will be performed following a similar procedure as for DFS (see Section 4.1.2) and will be estimated and plotted using the KM estimator overall and by subgroup of interests.

- Median DFS in subgroup of interest (overall DFS is assessed a primary outcome) and DFS rates will be estimated and reported along with the corresponding two-sided 95% Cis
- Median OS with the corresponding two-sided 95% CIs will be reported. OS rates will be estimated and reported along with the corresponding two-sided 95% CIs.

- Median DMFS and the corresponding two-sided 95% CIs will be estimated. DMFS rates will be estimated and the corresponding two-sided 95% CIs will be reported.
- Median PFS2 and the corresponding two-sided 95% CIs will be estimated. PFS2 rates will be estimated and the corresponding two-sided 95% CIs will be reported.
- Median ORR the corresponding two-sided 95% CIs
- Where adequate follow-up data is available median DFS, OS, PFS2, DMFS and ORR with their corresponding two-sided 95% CIs will be estimated in subgroup of interests (see section 4.1.1.4) as described for the overall population.

4.1.3.2 Disease Recurrence Patterns

Descriptive statistics will be used to summarize the characteristics of patients with a recurrence, notably the type of recurrence (local/regional vs. metastatic) and the subsequent treatments after recurrence. PRS will be estimated as described in Section 4.1.2 for patients with recurrent EC of GEJC and the corresponding two-sided 95% CIs will be reported.

Where adequate follow-up data is available, the above outcomes will be estimated for the subgroups detailed in the SAP.

4.1.3.3 Patient Management and Treatment Patterns

Descriptive statistics will be used to summarize patient management and treatment patterns.

- Cancer treatment history for EC or GEJC prior initiation of nivolumab will be summarized descriptively.
- Nivolumab treatment characteristics including duration, frequency, dosing, interruptions, permanent discontinuations of nivolumab, factors associated with the initiation and/or discontinuation of nivolumab, reasons for discontinuations, modifications in relation to the management of AEs and time-to-treatment discontinuation will be summarized using descriptive statistics
- Subsequent treatment characteristics including type of treatment, duration, frequency, dosing, TTNT, will also be summarized descriptively.

4.1.3.4 Sociodemographic and Clinical Characteristics

All baseline data (i.e., sociodemographic, disease characteristics, comorbidities, concomitant treatments, disease history, concurrent medical conditions, prior treatments for EC/GEJC, cancer diagnosis, and laboratory data) will be summarized overall and by subgroup of interests, using standard descriptive analyses as described in Section 4.1.1.

4.1.3.5 Nivolumab Related Adverse Events

All treatment-related AEs will be coded by severity grade. Descriptive statistics will be used to describe the frequency and severity of select AEs, other immune-related AEs, and other

treatment-related AEs and toxicities. The incidence will be calculated as the number of patients with AEs divided by total patients. AEs by subgroup of interests will be described; however, it is anticipated that the analysis will be limited by sample size.

4.1.4 Analysis Plan for Exploratory Objectives

PRO analysis of patient satisfaction with nivolumab treatment will be assessed using CTSQ and FACT-G7 instrument. CTSQ scores results overall and for each of the three domains: Expectations of Therapy (five items), Feelings about Side Effects (four items), and Satisfaction with Therapy (seven items) will be summarized using standard descriptive statistics (see Section 4.1.2). The FACT-G7 will include items GP1 “I have lack of energy”, GP2 “I have pain”, GP3 “I have nausea”, GP4 “I worry that my condition will get worse”, GP5 “I am sleeping well”, GP6 “I am able to enjoy my life”, and GP7 “I am content with the quality of my life right now”, and will be summarized using standard descriptive statistics (see Section 4.1.2).

Data will be recorded at Day 0, and Months 3, 6, 9, and 12 (counted relative to treatment initiation). Mean change from Day 0 to assessment points throughout the study will be evaluated. At each timepoint for analysis, the number of patients who completed the patient satisfaction questionnaire and the FACT-G7 will be reported as a percentage of eligible patients.

4.2 Sample Size

The sample size calculation is based on the primary outcome of the study and has been calculated assuming a 40% DFS rate after two years of follow-up and with an absolute precision of 7% for a sample size of 314 patients (to account for 10% drop-out). These calculations are based on assumptions from the CheckMate577 trial.[1]

Table 7: Sample Sizes and Absolute Rates (%)

DFS rate (%)	Absolute precision (%)	N	N (Considering 10% drop-out rate)
20%	6%	685	754
	7%	504	555
	8%	385	424
30%	6%	526	579
	7%	387	426
	8%	296	326
40%	6%	386	425
	7%	**285**	**314**
	8%	217	239
50%	6%	268	295
	7%	197	217
	8%	151	167

5 STUDY LIMITATIONS/STRENGTHS

5.1 Study Limitations

Although all possible measures will be undertaken to ensure quality and robustness of the data collected, some limitations are inherent to the observational nature of this study that should be acknowledged. Potential limitations and proposed strategies to address them are described in the following sections.

Selection bias

The target population, i.e., the entire group of individuals from which this study will conduct research in and draw conclusions from is the population of patients with early-stage EC or GEJC initiating adjuvant nivolumab treatment in real-world settings in the US or Germany. The following selection biases may compromise the representativeness of the target sample population.

Selection bias due to non-consent will be mitigated by providing clear information to physicians and patients on the importance of the study and the absence of burden for them. Physicians may also be inclined to select their "best" patients for the study, which could affect the representativeness of the study sample. To prevent this, clear instructions and methodological patient sampling will be provided to physicians who will be asked notably to include proposed enrollment in the study to all eligible patients and include all consecutive patients in the study.

The extent of the selection bias will be monitored via the maintenance of an enrollment log at the site, which will anonymously list all eligible patients, consenting status and characteristics, and inform the implementation of mitigation strategies if threats to representativeness are observed.

Attrition bias

In a prospective observational study, patients who are lost to follow-up or withdrawn from the study are the main source of attrition bias This bias may compromise sample representativeness and impact the interpretation of the results if there are significant differences in baseline characteristics or outcomes between patients that remain in the study and those who are lost to follow-up. If the proportion of patients lost to follow-up is non-negligible, the target precision for the primary outcome may not be reached and impact the interpretation of the findings.

To prevent this risk and minimize its potential impact, all efforts will be made to collect data from the closest previous visit and physicians will be encouraged to contact the patient to receive survival information and the vital status of patients lost to follow-up or who withdrawn from the study. A discontinuation case report form will be provided to physicians to document the reasons for discontinuation in the study.

Hawthorne effect

Participation in an observational study may influence physicians' behaviors and adjust their practice regarding nivolumab treatment and EC/GEJC patient management. The potential for this bias has been acknowledged and, in this study, only incident (new) users of nivolumab will be included and no comparison will be made with prevalent nivolumab users.

Measurement error and misclassification

Clear information and definitions of the variables measured will be provided to limit the risks of measurement errors and misclassification of study outcomes. However, as this study is observational, non-interventional and aims at describing routine clinical practice, it is anticipated that some measurement errors may occur as tools used to assess patients may vary across treating physicians, sites, and countries. Notably, disease progression and recurrence measurements may particularly be prone to measurement errors as various methods may be used to assess these outcomes for example not all physicians may use Response Evaluation Criteria in Solid Tumors1.1 criteria to assess disease progression.[27]

Missing data

As is the nature of non-interventional studies, reporting of outcomes is voluntary and data are collected according to routine clinical practice; therefore, not all patients may complete PRO assessment that missing data may occur. However, every effort will be implemented to minimize the impact of missing data in the study design and the conduct of the study. For these purposes the following strategies will be implemented:

- Collecting only variables that addressed the study objectives to minimize site/patient reporting burden
- Including "not applicable" or "not done" on eCRFs to differentiate these from truly unknown values
- Standardizing the data abstraction form across sites
- Ensuring that sites and data abstractors are properly trained on data collection
- Setting reporting windows around pre-specified target time point
- Checking for patterns of missingness and addressing any issues through targeted operational strategies
- Implementing direct-to-patient strategies to facilitate capture of patient-reported information

Sensitivity analysis will be performed to evaluate the impact of missing data on the study outcomes and any impact of missing data on the interpretation of the results will be discussed in the final study report.

Risk of under-recruitment

The precision of the estimates and interpretation of the results might be compromised in case of under-recruitment. This risk may occur as patient enrollment will start a limited amount of time after approval of nivolumab in patients with EC or GEJC. This risk will be mitigated by close monitoring of patients' enrollment and if necessary, by increasing the enrollment period or the maximum number of patients by site.

Overall, the impact that potential biases will have on the study results is currently unknown. Still, each potential source of bias will be evaluated descriptively, assessed by sensitivity analyses, and discussed in the reports.

5.2 Study Strengths

Real-world data

This is the first study collecting real-world data conducted in the US or Germany among patients with EC or GEJC who start nivolumab adjuvant therapy for the first time. The results of this study will help support findings from previous clinical trials and provide a better understanding of the demographics, patterns of care, and clinical outcomes of patients with EC/GEJC treated with nivolumab in routine clinical practice. This study will be critical to inform key stakeholders, patients, healthcare practitioners, guideline committees, and regulatory authorities.

Generalizability of study results

Patients will be treated as per local regulations and standards of care in real-world settings. The site selection process will ensure that the sites participating are representative with regard to the US or German landscape of EC or GEJC treatment. This study has been designed with minimal selection criteria to broaden the segment of patients with EC or GEJC and reach a high level of external validity.

6 STUDY CONDUCT

This study will be conducted in accordance with International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices and applicable regulatory requirements.

Real-world data are needed to generate real-world evidence to complement those obtained from RCTs and to demonstrate effectiveness in the studied population and in patient subgroups (e.g., specific histology, by country). Additionally, real-world evidence has been used to characterize levels and patterns of use (e.g., dosing, regimen, indication, treatment rationales, modification in relation to management of AEs, alone, sequentially, or in combination with other drugs). Real-world data tend to be more inclusive than RCT data due to less restrictive patient inclusion criteria (e.g., age, prior treatment, comorbidities, frailty) and, if follow-up is sufficient, can be a longer-term approach to understanding the impact of a drug in each target population. Therefore, data collected through prospective observational studies can be used to meet the requirements of prescribers, regulators, or payers for ongoing access to novel therapeutics.

The central aims of the study are descriptive, and are designed to capture to describe the outcomes, patient characteristics, safety profile, and treatment patterns in adult patients with EC or GEJC who start a new systemic treatment with nivolumab for the first time, and among other subgroups of interest (e.g., line of therapy, histology, country-specific) or treatment patterns (e.g., prior adjuvant therapies). Remote or on-site data monitoring will be conducted during the study to examine compliance with the protocol and adherence to the data collection procedures. There will be regular communication with all sites to assess recruitment progress and address any issues as they arise. Edit checks, described in the

Data Management Plan, and tested prior to starting data entry process, will be defined to ensure validity of the database with a focus on missing, implausible, or inconsistent data. The SAP will be prepared and approved prior to database lock. Data monitoring will close at each site after the completion of the follow-up assessment of the last patient, entry of all data, and resolution of all

outstanding monitoring issues and data queries. The database will then be locked and transferred to statisticians for analysis.

6.1 Ethics Committee Review and Informed Consent

6.1.1 Ethics Committee Review

The investigator must ensure that the required approvals from ethics committees, independent review committees, regulatory authorities, and/or other local governance bodies are obtained before study initiation at the site.

6.1.2 Informed Consent

In accordance with local regulations, subjects should provide written consent (e-consent) before enrollment into the study. Investigators must ensure that patients, or, in those situations where consent cannot be given by patients, their legally acceptable representatives, are clearly and fully informed about the purpose of the study, potential risks, the patient's rights and responsibilities when participating in this study. If local regulations do not require an informed consent document to be signed by the patient, the site staff should document key elements of the informed consent process in the patient's chart.

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document patient outcome, if applicable. The investigator would inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved adverse events.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

6.2 Responsibilities within the Study

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with and be prepared by BMS.

6.2.1 Sponsor Roles and Responsibilities

The study shall be conducted based on the roles and responsibilities outlined in Table 8.

Table 8. Study Roles and Responsibilities

Responsibilities	**Roles**
Study synopsis and study protocol	CRO/BMS
CRF development	CRO
Study management	
Site identification	CRO/BMS
Site initiation/management	CRO
Data collection	CRO

Responsibilities	Roles
Statistical analysis	
Statistical analysis plan	CRO/BMS
Database development	CRO
Data monitoring/management	CRO
Statistical analyses (interim and final)	CRO
Study reports (interim and final)	CRO

Abbreviations: BMS = Bristol Myers Squibb; CRO = clinical research organization

6.2.2 CRO Roles and Responsibilities

See Table 8.

6.3 Confidentiality of Study Data

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

For the purposes of protecting a patient's identity, a unique code will be assigned to each patient, such as a series of numbers and/or letters (for example, CA180330-0001-00001). The data that is recorded with the patient's assigned code is called “key-coded data.” Key-coded study data will be managed by the sponsor and/or its delegates in a study-specific electronic database (the “study database”). Only the investigator and the site staff have access to the link between patient’s assigned code and the patient’s identity. However, in case of an audit or inspection, subject to local laws and regulations, government officials, IRB/ethics committee representatives and sponsor representatives may access this information at the study site. If the study requires on-site monitoring, subject to local laws and regulations, sponsor representatives will also access the primary data source at the study site. Data that could directly identify the patient will not be collected in the “study database.”

6.4 Quality Control

Representatives of BMS and/or its delegates must be allowed to visit all study site locations to assess the data quality and study integrity. On site or remotely, they will review study files and, if allowed by local laws and regulations, patient medical charts to compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to case report forms, 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.

For quality assurance, throughout the development of the study synopsis and protocol, the Strengthening the Reporting of Observational studies in Epidemiology guidelines (http://www.strobe-statement.org/) will be followed for the design and reporting of observational studies.

6.5 Database Retention and Archiving of Study Documents

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study. Location of database and supporting documentation will be outlined in the final observational study report.

6.6 Registration of Study on Public Website

This study will be registered on clinicaltrials.gov.

7 ADVERSE EVENT REPORTING

Adverse Event Definitions

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Events Collected for this Study

Serious and non-serious AEs:

- Related AEs (adverse drug reactions) should be reported without time limitation
- Non-related AEs should be reported until 100 days after the last administration of nivolumab.

Although not always AEs by regulatory definition, the following events associated with a BMS product must be reported:

- Any occurrence of a possible exposure of a pregnant woman to a product (this could involve a patient or the partner of a male patient or a pregnant female who came in contact with the medication while dispensing) or exposure (to infant) during lactation.
- All reports of elevated/ questionable or indeterminate beta human chorionic gonadotropin or positive urine pregnancy tests after administration of a product
- Exposure (to fetus) during pregnancy, exposure (to infant) during lactation, and paternal exposure
- Overdose
- Lack of efficacy
- Abuse
- Misuse
- Off-label use

- Occupational exposure
- Medication error and potential medication error
- Suspected transmission of an infectious agent, e.g., any organism, virus or infectious particle pathogenic or non-pathogenic, via the medicinal product
- Unintended benefit.

The AEs under study require a causal assessment.

The causal relationship to the BMS product under study is determined by a physician and should be used to assess all AEs under study. The causal relationship should be one of the following:

- Related: There is a reasonable causal relationship between the BMS product under study and the AE.
- Not related: There is not a reasonable causal relationship between the BMS product under study and the AE.

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

A ***non-serious AE*** is an AE not classified as serious.

An ***SAE*** is any untoward medical occurrence that at any dose:

1. Results in death
2. Is life-threatening (defined as an event in which the patient 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)
3. Requires inpatient hospitalization or causes prolongation of existing hospitalization. The following hospitalizations are not considered SAEs in BMS 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
    - Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy).
    - Medical/surgical admission other than to remedy ill health and planned prior to entry into the study.
    - Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reasons).
    - Admission for administration of subsequent anti-cancer therapy in the absence of any other SAEs (applies to oncology protocols).

4. Results in persistent or significant disability/incapacity
5. Is a congenital anomaly/birth defect
6. 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 patient or may require intervention [e.g., 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

The following should also be classified as SAE:

- Suspected transmission of an infectious agent, pathogenic or nonpathogenic, via the BMS product under study
- Overdose of BMS product under study
- Cancer after exposure to a BMS product under study
- Pregnancy of female patient or female partner of male patient exposed to a BMS product under study.

7.1 Adverse Event Collection and Reporting

7.1.1 Adverse Event Collection

Following the patient's consent to participate in the study, all AEs under study, as well as those meeting the definition of an AE, whether or not related to the product(s) under study, must be reported individually in the time frames noted below.

All AEs collected will also be reported in aggregate in the final study report. Where primary data collection practices allow, data tables should be clearly labeled to distinguish between related and non-related AE data.

7.1.2 Adverse Event Reporting

All AEs (serious and non-serious) must be recorded on the Solicited and Non-interventional Research AE/SAE Form and reported to BMS (or designee). SAEs must be reported promptly but not to exceed the lesser of one business day or three calendar days (or a timeline otherwise agreed to with WWPS.PVPELS@bms.com) to comply with regulatory requirements. A form should be completed for any event where doubt exists regarding its status of seriousness. Non-serious AEs must be reported to BMS (or designee) within seven business days. Non-serious AEs should be reported as SAEs if they become serious.

All AEs must be reported by confirmed facsimile (fax) transmission or reported via electronic mail to:

Email Address: Worldwide.Safety@BMS.com

Facsimile Number: 609-818-3804

If only limited information is initially available, follow up reports may be required.

For studies capturing AEs through EDC, electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

7.1.2.1 Pregnancy

If it is discovered a patient is pregnant or may have been pregnant at the time of exposure to the BMS product under study, the pregnancy, AEs associated with maternal exposure and pregnancy outcomes must be recorded on a Pregnancy Surveillance Form and reported to BMS (or designee) within 24 hours/one business day of becoming aware of the pregnancy by confirmed fax or reported via electronic mail to Worldwide.Safety@BMS.com. If only limited information is initially available, follow-up reports may be required. The original BMS forms are to remain on site. Follow-up information should be obtained on pregnancy outcomes for one year following the birth of the offspring.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

7.1.2.2 Other Adverse Event Reporting

All AEs not under study that occurred while taking any BMS product should be reported to BMS or to the concerned competent authorities via the national spontaneous reporting system. Investigators/healthcare professionals should follow local requirements for product safety reporting.

7.2 Product Quality Complaints

Product Quality Complaints (PQC) (as defined under 7. ADVERSE EVENT & PRODUCT QUALITY COMPLAINT REPORTING, or to be found at http://www.globalbmsmedinfo.com) associated with a BMS product, shall be reported to BMS no later than one business day or three calendar days, whichever is earlier after becoming aware of the event.

PQC information shall be reported to the BMS contact for the receipt of safety information for the country where the reporter is located. BMS contact information can be found at http://www.globalbmsmedinfo.com. Service Provider shall comply with BMS's reasonable follow-up requests.

8 GLOSSARY OF TERMS AND LIST OF ABBREVIATIONS

8.1 Glossary of Terms

Not applicable.

8.2 List of Abbreviations

Term	Definition
AE	Adverse Event
BMI	Body Mass Index
BMS	Bristol Myers Squibb
CI	Confidence Interval
CR	Complete Response
CRO	Clinical Research Organization
ct	Circulating tumor
CTSQ	Cancer Therapy Satisfaction Questionnaire
DFS	Disease-Free Survival
DMFS	Distant Metastasis-Free Survival
EC	Esophageal Cancer
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
FACT-G	Functional Assessment of Cancer Therapy - General
FDA	Food and Drug Administration
FPI	First Patient In
GEJC	Gastroesophageal Junction Cancer
HER	Herceptin
HR-QoL	Health Related Quality of Life
ICMJE	International Committee of Medical Journal Editors
IQR	Interquartile Range
IRB	Institutional Review Board
KM	Kaplan-Meier
LPI	Last Patient In
MSI	Microsatellite Instability
ORR	Overall Response Rate
OS	Overall Survival
pCR	pathological Complete Response
PD	Progressive Disease
PD-1	Programmed cell Death protein-1
PD-L1	Programmed cell Death ligand-1
PFS	Progression Free Survival
PR	Partial Response

Term	Definition
PRO	Patient Reported Outcome
PRS	Post-Recurrence Survival
RCT	Randomized Controlled Trial
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCC	Squamous Cell Carcinoma
TMB	Tumor Mutational Burden
TTNT	Time To Next Treatment
US	United States

9 SCIENTIFIC PUBLICATIONS

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 (i.e., 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 (e.g., evaluable subjects with quality data or data generation), analysis, or interpretation of data for the work (e.g., problem solving, advice, evaluation, insights and conclusion)
2. Drafting the work or revising it critically for important intellectual content
3. Final approval of the version to be published
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 for authorship of the publication.

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