IQWiG Reports – Commission No. A21-108

Nivolumab (oesophageal or gastrooesophageal junction cancer, adjuvant) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Nivolumab (Karzinome des Ösophagus oder gastroösophagealen Übergangs, adjuvant) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 November 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Table of contents

List of tables[2]

Page

[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AESI	AE of special interest
AJCC	American Joint Committee on Cancer
CRT	chemoradiotherapy
CTCAE	Common Terminology Criteria for Adverse Events
DFS	disease-free survival
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ESMO	European Society for Medical Oncology
FACT-E	Functional Assessment of Cancer Therapy-Esophageal
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
imAE	immune-related AE
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SAP	statistical analysis plan
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug nivolumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 30 August 2021.

Research question

The aim of the present report is the assessment of the added benefit of nivolumab in comparison with watchful waiting as appropriate comparator therapy (ACT) for the adjuvant treatment of adult patients with oesophageal or gastrooesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy (CRT).

The G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2: Research question of the benefit assessment of nivolumab

Therapeutic indication	**ACT**[a]
Adjuvant treatment of carcinoma of the oesophagus or the gastroesophageal junction in adults with pathological residual disease after prior neoadjuvant chemoradiotherapy[b]	Watchful waiting
a. Presented is the respective ACT specified by the G-BA. b. The CA209-577 study included both patients with adenocarcinoma and patients with squamous cell carcinoma in stages II and III (per AJCC 7th edition) after neoadjuvant chemoradiotherapy with R0 resection and residual pathologic disease. Since only patients with complete resection were included, the G-BA assumed that patients with ≥ R1 resection were not comprised by the therapeutic indication. ACT: appropriate comparator therapy; AJCC: American Joint Committee on Cancer; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of added benefit.

Study pool and study design

The CA209-577 study was used for the benefit assessment. The CA209-577 study is an ongoing double-blind RCT on the comparison of nivolumab with placebo. It included adult patients with stage II or stage III (classification per American Joint Committee on Cancer [AJCC] 7th edition) carcinoma of the oesophagus or gastroesophageal junction at the time of initial diagnosis. Patients had to have completed neoadjuvant platinum-based CRT followed by resection prior

to randomization, and have had R0 resection with residual pathologic disease (≥ ypT1 or ≥ ypN1).

Patients with cervical location of the oesophageal cancer were excluded from the study. However, guidelines also do not recommend neoadjuvant CRT for this location, so that the exclusion seems appropriate for the present therapeutic indication. Patients with type III gastrooesophageal junction cancer classified as gastric cancer, or adenocarcinoma with T2N0 status could be included in the study, however. For these, neoadjuvant CRT also does not comply with the treatment recommendations of the guidelines. Based on the available information, it is not possible to precisely estimate for how many patients neoadjuvant CRT was not used in compliance with the guidelines. Overall, it can be assumed that only few patients were concerned, however. This therefore has no consequence for the present benefit assessment.

The CA209-577 study included a total of 794 patients, randomized in a 2:1 ratio either to treatment with nivolumab (N = 532) or to placebo (N = 262).

Treatment with nivolumab in the intervention arm was in compliance with the recommendations of the Summary of Product Characteristics (SPC). The study population was treated until recurrence, unacceptable toxicity, treatment discontinuation following the physician's or patient's decision, or until the regular end of the study treatment after 1 year.

Primary outcome of the CA209-577 study was disease-free survival (DFS). Patient-relevant secondary outcomes were outcomes on mortality, morbidity, health-related quality of life and adverse events (AEs).

Implementation of the appropriate comparator therapy

The G-BA specified watchful waiting as ACT.

The CA209-577 study used placebo as comparator therapy. The study was not designed for a comparison with watchful waiting, but is nonetheless suitable for such a comparison.

Although the examinations carried out in the study do not fully represent guideline recommendations, the examination regimen in the CA209-577 study is overall considered to be a sufficient approximation to the ACT of watchful waiting for the present benefit assessment.

Available data and data cut-offs

Results on 2 data cut-offs are available for the CA209-577 study. The first data cut-off from 3 July 2020 is a planned interim analysis for the primary outcome of DFS. For the first data cut-off, the company presented data on all patient-relevant outcomes, except overall survival, in the dossier. The second data cut-off from 18 February 2021 is an additional exploratory analysis conducted during the approval process at the request of the European Medicines Agency (EMA). In Module 4 P, the company stated that this second data cut-off was conducted only

for the outcome of DFS and, for the second data cut-off, only presented data for DFS and the recurrence rate in the dossier.

The lack of data on overall survival is not appropriate in the present oncological research question. In addition, the reason given by the company that the data were still "immature" only refers to the first data cut-off. However, the company did not provide any data on overall survival for the second data cut-off, either. The resulting uncertainties are considered in the derivation of the added benefit.

The present benefit assessment uses the results of the first data cut-off for the outcomes on health status, health-related quality of life and side effects. For DFS and recurrence rate, the data from the second data cut-off are used.

Risk of bias

The risk of bias across outcomes for the CA209-577 study is rated as low. The outcome-specific risk of bias is also rated as low for the results of the outcomes of recurrence and discontinuation due to AEs, and as high for the results of all other patient-relevant outcomes.

Results

Mortality

Overall survival

There are no data on overall survival. According to the information provided by the company in Module 4 P, at the time point of the first data cut-off on 3 July 2020, the results of the interim analysis on overall survival were still "immature" and were not unblinded. The company did not make a respective statement for the second data cut-off, but also provided no analyses on overall survival. In the present situation, this is not appropriate. In addition, the statement of the company on the non-unblinding of the data on overall survival is not fully comprehensible, as the recurrence rate also includes the event "death without recurrence", for which unblinded data per treatment arm are available.

This results in no hint of added benefit of nivolumab in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

Recurrence

For the outcome of recurrence (operationalized as recurrence rate and DFS), a statistically significant difference in favour of nivolumab in comparison with placebo was shown for both operationalizations. This results in an indication of an added benefit of nivolumab in comparison with watchful waiting.

Health status (EQ-5D VAS)

The time to definitive deterioration by 15 points (scale range 0 – 100) is considered for the outcome of health status (EQ-5D visual analogue scale [VAS]). There was no statistically significant difference between the treatment arms. This results in no hint of added benefit of nivolumab in comparison with watchful waiting; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life was recorded with the disease-specific instrument of Functional Assessment of Cancer Therapy-Esophageal (FACT-E). The time to definitive deterioration of the FACT-E total score by 15% of the scale range (scale range 0 – 176) is considered. There was no statistically significant difference between the treatment arms. This results in no hint of added benefit of nivolumab in comparison with watchful waiting; an added benefit is therefore not proven.

Side effects

SAEs and severe AEs

There was no statistically significant difference between the treatment arms for the outcomes of serious AEs (SAEs) and severe AEs. In each case, this results in no hint of greater or lesser harm from nivolumab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference to the disadvantage of nivolumab compared with placebo was shown for the outcome of discontinuation due to AEs. This results in a hint of greater harm from nivolumab in comparison with watchful waiting.

Specific AEs

Immune-related SAEs and immune-related severe AEs

There was no statistically significant difference between the treatment arms for the outcomes of immune-related SAEs and immune-related severe AEs. In each case, this results in no hint of greater or lesser harm from nivolumab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Infections and infestations (severe AES) and blood and lymphatic system disorders (severe AEs)

A statistically significant difference to the disadvantage of nivolumab in comparison with placebo was shown for each of the outcomes of infections and infestations (severe AEs) and blood and lymphatic system disorders (severe AEs). In each case, this results in a hint of greater harm from nivolumab versus watchful waiting.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of the added benefit of the drug nivolumab in comparison with the ACT is assessed as follows:

Overall, there are positive and negative effects of different extent, with the probability of an indication for the positive effect, and a hint for each of the negative effects.

A positive effect of nivolumab in comparison with watchful waiting with the extent "considerable" was shown for the outcome of recurrence. In contrast, there are negative effects from nivolumab in comparison with watchful waiting in the category of serious/severe side effects. Here, greater harm of major extent was shown for the outcome of discontinuation due to AEs. There is greater harm of minor extent for one of the 2 specific AEs, and of considerable extent for the other. No data are available for overall survival. However, overall survival of the patients is of particular importance in the present oncological indication. The lack of these data is not appropriate in the present situation and is not sufficiently justified by the company. However, it can be assumed that the results on overall survival would only have an influence on the overall conclusion on added benefit if a disadvantage of nivolumab was shown. Based on the available information (e.g. results on SAEs, data on subsequent therapies), there are no hints that such a disadvantage in comparison with watchful waiting is to be expected. The resulting uncertainties are considered in the balancing regarding the added benefit and, together with the negative effects, result in a downgrading of the extent.

In summary, there is an indication of a minor added benefit of nivolumab versus the ACT of watchful waiting for adult patients with oesophageal or gastrooesophageal junction cancer who have residual pathologic disease following prior neoadjuvant CRT.

Table 3 shows a summary of the probability and extent of added benefit of nivolumab.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Nivolumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adjuvant treatment of carcinoma of the oesophagus or the gastroesophageal junction in adults with pathological residual disease after prior neoadjuvant chemoradiotherapy[b]	Watchful waiting	Indication of minor added benefit[c]

a. Presented is the respective ACT specified by the GBA.
b. The CA209-577 study included both patients with adenocarcinoma and patients with squamous cell carcinoma in stages II and III (per AJCC 7th edition) after neoadjuvant chemoradiotherapy with R0 resection and residual pathologic disease. Since only patients with complete resection were included, the G-BA assumed that patients with ≥ R1 resection were not comprised by the therapeutic indication.
c. Only patients with an ECOG PS of 0 or 1 were included in the CA209-577 study. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.

ACT: appropriate comparator therapy; AJCC: American Joint Committee on Cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of nivolumab in comparison with watchful waiting as ACT for the adjuvant treatment of adult patients with oesophageal or gastrooesophageal junction cancer who have residual pathologic disease following prior neoadjuvant CRT.

The G-BA's specification of the ACT results in the research question presented in Table 4.

Table 4: Research question of the benefit assessment of nivolumab

Therapeutic indication	**ACT**[a]
Adjuvant treatment of carcinoma of the oesophagus or the gastroesophageal junction in adults with pathological residual disease after prior neoadjuvant chemoradiotherapy[b]	Watchful waiting
a. Presented is the respective ACT specified by the GBA. b. The CA209-577 study included both patients with adenocarcinoma and patients with squamous cell carcinoma in stages II and III (per AJCC 7th edition) after neoadjuvant chemoradiotherapy with R0 resection and residual pathologic disease. Since only patients with complete resection were included, the G-BA assumed that patients with ≥ R1 resection were not comprised by the therapeutic indication. ACT: appropriate comparator therapy; AJCC: American Joint Committee on Cancer; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on nivolumab (status: 2 July 2021)
- bibliographical literature search on nivolumab (last search on 2 July 2021)
- search in trial registries/trial results databases for studies on nivolumab (last search on 1 July 2021)
- search on the G-BA website for nivolumab (last search on 1 July 2021)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab (last search on 10 September 2021); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

2.3.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: nivolumab vs. placebo

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
CA209-577	Yes	Yes	No	Yes [3]	Yes [4-7]	Yes [8,9]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The CA209-577 study was used for the benefit assessment. The study pool concurs with that of the company.

2.3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: nivolumab vs. placebo

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CA209-577	RCT, double-blind, parallel	Adult patients (≥ 18 years) ▪ with histologically confirmed stage II or stage III carcinoma of the oesophagus or gastroesophageal junction[b] ▪ after prior neoadjuvant chemoradiotherapy and R0 resection[c] ▪ with residual pathologic disease (≥ ypT1 or ≥ ypN1) ▪ with ECOG PS 0 or 1	Nivolumab (N = 532) Placebo (N = 262)	Screening: 49 days[d] Treatment: until recurrence, unacceptable toxicity, treatment discontinuation following the investigator's or patient's decision, maximum of 1 year Observation[e]: outcome-specific, at most until 5 years after end of treatment of the last patient	170 study centres in Argentina, Australia, Belgium, Brazil, Canada, China, Czech Republic, Denmark, France, Germany, Hong Kong, Hungary, Ireland, Israel, Italy, Japan, Mexico, Netherlands, Poland, Romania, Russia, Singapore, South Korea, Spain, Switzerland, Taiwan, Turkey, United Kingdom, USA 7/2016–ongoing First data cut-off[f]: 3 July 2020 Second data cut-off[g]: 18 February 2021	Primary: disease-free survival Secondary: overall survival, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Per AJCC 7th edition; disease stage at the time of initial diagnosis; patients could have squamous cell carcinoma or adenocarcinoma.
c. Resection had to be performed in a window of 4 to 16 weeks prior to randomization (before protocol amendment 06 [4 May 2017], this was 4 to 14 weeks).
d. The screening phase was increased to 49 days only per protocol amendment 06 (4 May 2017). Before, it was 28 days.
e. Outcome-specific information is described in Table 9.
f. The first interim analysis for the outcome of disease-free survival (DFS) was planned after occurrence of 374 DFS events; the final analysis for the outcome was planned after 440 DFS events. At the time of the first data cut-off (3 July 2020), 396 DFS events had occurred. Due to the positive result on DFS, the interim analysis was subsequently considered as the final analysis. The first interim analysis for the outcome of overall survival was planned for the same time point as the first interim analysis for the outcome of DFS. However, the company stated that the results on overall survival were still "immature" at the time of the first data cut-off and were thus not unblinded. The final analysis on overall survival is planned after 460 deaths.
g. In the approval process, an additional exploratory analysis (second data cut-off on 18 February 2021) on DFS was conducted at the request of the EMA. In Module 4 P, the company stated that this second data cut-off was only conducted for the outcome of DFS.

AE: adverse event; AJCC: American Joint Committee on Cancer; DFS: disease-free survival; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EMA: European Medicines Agency; N: number of randomized patients; RCT: randomized controlled trial

Table 7: Characteristics of the interventions – RCT, direct comparison: nivolumab vs. placebo

Study	Intervention	Comparison
CA209-577	Nivolumab 240 mg IV every 2 weeks, for 16 weeks from week 17: nivolumab 480 mg IV every 4 weeks	Placebo IV every 2 weeks, for 16 weeks from week 17: placebo IV every 4 weeks
	Dose adjustment: No dose adjustment allowed; treatment interruption due to toxicity possible[a]	
	Required pretreatment ▪ neoadjuvant platinum-based chemoradiotherapy with subsequent resection[b] **Prohibited prior and concomitant treatment** ▪ any antineoplastic therapy for treatment of resected oesophageal or gastrooesophageal junction carcinoma ▪ systemic corticosteroids (> 10 mg/day prednisolone or equivalent)[c] or immunosuppressants ≤ 14 days before start of the study medication ▪ anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibodies, or other antibodies or drugs specifically targeting T-cell co-stimulation or checkpoint pathways **Permitted concomitant treatment** ▪ corticosteroids in forms of administration with minimal systemic absorption and < 3 weeks of corticosteroids for prophylaxis or for treatment of non-autoimmune conditions	

a. Therapy may be interrupted, delayed or discontinued. During the first 16 weeks, delays are possible for up to 42 days, then for up to 70 days. Longer delays have to be approved by the medical monitor.
b. Resection had to be performed in a window of 4 to 16 weeks prior to randomization (before protocol amendment 06 [4 May 2017], this was 4 to 14 weeks).
c. During the study, higher dosages are only allowed for adrenal replacement therapy.

CD137: cluster of differentiation 137; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; IV: intravenous; PD-L1/L2: programmed cell death ligand 1/2; RCT: randomized controlled trial

The CA209-577 study is an ongoing, double-blind RCT on the comparison of nivolumab against placebo. It included adult patients with stage II or stage III (classification per AJCC 7th edition) carcinoma of the oesophagus or gastroesophageal junction at the time of initial diagnosis [10]. Patients had to have completed neoadjuvant platinum-based CRT followed by resection prior to randomization, and have had R0 resection with residual pathologic disease (≥ ypT1 or ≥ ypN1). Patients had to be in good general condition at enrolment, corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. Patients additionally had to have disease-free status documented by a complete physical examination and imaging studies within 4 weeks prior to randomization.

Patients with cervical location of the oesophageal cancer were excluded from the study. However, guidelines also do not recommend neoadjuvant CRT for this location, so that the exclusion seems appropriate for the present therapeutic indication. Patients with type III gastrooesophageal junction cancer classified as gastric cancer, or adenocarcinoma with T2N0 status could be included in the study, however. For these, neoadjuvant CRT also does not comply with the treatment recommendations of the guidelines [11-13]. Based on the available information, it is not possible to precisely estimate for how many patients neoadjuvant CRT

was not used in compliance with the guidelines. Overall, it can be assumed that only few patients were concerned, however, as, on the one hand, only 5% of the patients with type III gastrooesophageal junction carcinoma were included. On the other hand, patients with adenocarcinoma with T2N0 status are in stage II, and thus comply with the inclusion criteria of the study, only if the tumour also has a grade of differentiation of G3. Patients with a lower grade of differentiation are to be allocated to stage I. The dossier does not provide information on how many patients with adenocarcinoma with T2N0 status and a differentiation grade of G3 were included in the study. Based on the patient characteristics (see Table 9), it cannot be assumed, however, that this was the case in a relevant proportion of patients. This therefore has no consequence for the present benefit assessment.

The determination of programmed cell death ligand 1 (PD-L1) expression of the tumour tissue was required for study inclusion. PD-L1 status had to be assessed by a central laboratory; and the resected tumour tissue had to be obtained within 16 weeks prior to randomization, but after completed CRT. Patients were included in the study regardless of PD-L1 expression, however. PD-L1 expression was determined using a DAKO immunohistochemistry assay.

The CA209-577 study included a total of 794 patients, randomized in a 2:1 ratio either to treatment with nivolumab (N = 532) or to placebo (N = 262). Randomization was stratified by the factors of PD-L1 status (≥ 1% versus < 1% or indeterminate/non-evaluable), pathologic lymph node status (≥ ypN1 versus ypN0), and histology (squamous versus adenocarcinoma).

Treatment with nivolumab in the intervention arm was in compliance with the recommendations of the SPC [14]. Correspondingly, dose adjustment was not allowed; treatment interruptions due to toxicity were possible and were largely in compliance with the SPC [14].

The study population was treated until recurrence, unacceptable toxicity, treatment discontinuation following the physician's or patient's decision, or until the regular end of the study treatment after 1 year. Switching to the treatment of the other study arm was not planned.

Primary outcome of the CA209-577 study was DFS. Patient-relevant secondary outcomes were outcomes on mortality, morbidity, health-related quality of life and AEs.

Implementation of the appropriate comparator therapy

The G-BA specified watchful waiting as ACT.

The CA209-577 study used placebo as comparator therapy. The study was not designed for a comparison with watchful waiting, but is nonetheless suitable for such a comparison. This is explained below.

The following examinations were performed for the assessment of the health status or the detection of recurrences in the CA209-577 study:

- Targeted physical examination, determination of weight and ECOG PS, as well as laboratory tests, during the treatment phase and at the start of each treatment cycle (see Table 7) and at follow-up visit 1 (30 days [± 7 days] after the last dose of the study medication) and at follow-up visit 2 (84 days [± 7 days] after follow-up visit 1).
- Imaging (computed tomography or magnetic resonance imaging) every 12 weeks during the first 2 years, then every 6 to 12 months until recurrence or at most until 5 years after randomization.

According to the S3 guideline and the European Society for Medical Oncology (ESMO) guideline, after-care should focus on symptoms, nutrition and psychosocial support. The goal is to detect impairment of functions affecting quality of life in connection with a recurrence or as benign complications of treatment. Symptom-oriented anamnesis and physical examination are described as a basic component of after-care. In the first 6 months, the nutritional status should also be monitored regularly, including dietary counselling [11-13]. Beyond this, the guidelines do not provide any specific information on the frequency or duration of specific examinations in the context of after-care.

The examinations performed in the CA209-577 study do not fully represent the guideline recommendations. In particular, no mention is made of dietary counselling or rehabilitative measures. In contrast, cross-sectional imaging was performed regularly even though this is not explicitly provided for in the S3 and ESMO guidelines. Despite the deviations from the guideline recommendations, patients in the CA209-577 study overall received close and targeted examinations to detect their health status as well as local, regional and distant recurrences, so that the examination regimen is overall considered to be a sufficient approximation to the ACT of watchful waiting.

Available data and data cut-offs

Results on 2 data cut-offs are available for the CA209-577 study:

- First data cut-off on 3 July 2020: interim analysis planned per study protocol for the primary outcome of DFS after occurrence of 374 DFS events. The final analysis for the outcome of DFS was planned after at least 440 events. At the time of the first data cut-off, 396 DFS events had occurred. Due to the superiority, the result of the interim analysis was considered the final analysis. For the first data cut-off, the company presented data on all patient-relevant outcomes, except overall survival, in the dossier. According to the company, the data for overall survival were still “immature” at the first data cut-off, so that the data were not unblinded, and there are therefore no results yet for overall survival. The final analysis of overall survival is planned after 460 deaths. According to the EMA assessment report, 228 deaths had occurred at the time of the first data cut-off. The analyses for the outcome of overall survival are expected for the end of the third quarter of 2024.

The lack of data on overall survival is not appropriate in the present oncological research question. In addition, the reason given by the company that the data were still "immature" only refers to the first data cut-off, but not to the second data cut-off conducted at the request of the EMA (see next bullet point). However, the company did not provide any data on overall survival for this second data cut-off, either. According to the study protocol, the first interim analysis on overall survival was planned after 299 deaths. It is not comprehensible why no information was provided by the company in this regard. The resulting uncertainties are considered in the derivation of the added benefit (see Sections 2.4.3 and 2.5.2 for more information).

- Second data cut-off on 18 February 2021: additional exploratory analysis conducted during the approval process at the request of the EMA. In Module 4 P, the company stated that this second data cut-off was conducted only for the outcome of DFS and, for the second data cut-off, only presented data for DFS and the recurrence rate in the dossier.

In deviation from the specification in the dossier template [15] the company did not present any analyses for the second data cut-off for further patient-relevant outcomes. This was not sufficiently justified by the company. The available analyses of the first data cut-off are nevertheless used for the assessment of the outcomes on health status, health-related quality of life and side effects for the following reasons: The time interval between the 2 data cut-offs is relatively short (about 7 months). At the time of the first data cut-off, only few patients were still under treatment (31 [5.8%] versus 19 [7.3%] patients) and about 75% of the patients had achieved follow-up visit 2 (corresponding, for example, to the maximum documentation period for health-related quality of life). Overall, it is therefore not assumed that there would be a relevant change between the first and the second data cut-off in the effects for the mentioned outcomes. Deviating from the company's approach, due to the longer observation period, only data of the second data cut-off are used for DFS and recurrence rate.

Follow-up observation

Table 8 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 8: Planned duration of follow-up – RCT, direct comparison: nivolumab vs. placebo

Study **Outcome category** **Outcome**	**Planned follow-up observation**
CA209-577	
Mortality	
Overall survival	At most until 5 years after end of treatment of the last patient
Morbidity	
Recurrence[a]	Until recurrence, at most until 5 years after end of treatment of the last patient
Health status (EQ-5D VAS)	Until 2 years after the last dose of the study medication
Health-related quality of life (FACT-E)[c]	▪ Until 128 days after the last dose of the study medication
Side effects	
All outcomes in the side effects category	100 days after the last dose of the study medication

a. Presented based on the recurrence rate and disease-free survival, includes the events of local recurrence, regional recurrence, distant metastases, and death without recurrence.
b. Regular imaging to record recurrences was only performed until 5 years after the first dose.
c. The oesophageal cancer subscale (ECS) is recorded until 2 years after the last dose of the study medication. This alone is unsuitable to represent health-related quality of life (see Section 2.4.1).

ECS: oesophageal cancer subscale; FACT-E: Functional Assessment of Cancer Therapy-Esophageal; RCT: randomized controlled trial; VAS: visual analogue scale

Health status was not observed over the entire study period, but over a relevant period of up to 2 years after completion of the treatment.

The observation periods for the outcomes in the categories of health-related quality of life and side effects were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus up to 128 days or 100 days after the last dose). However, to be able to draw a reliable conclusion on the total study period or the time to patient death, it would be necessary to record these outcomes as well for the total period, as was done for survival.

Characteristics of the study population

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population – RCT, direct comparison: nivolumab vs. placebo (multipage table)

Study Characteristic Category	Nivolumab N[a] = 532	Placebo N[a] = 262
Study CA209-577		
Age [years], mean (SD)	61 (9)	60 (10)
Sex [F/M], %	16/84	15/85
Family origin, n (%)		
Caucasian	432 (81)	216 (82)
Black	7 (1)	2 (1)
Asian	83 (16)	34 (13)
Other	10 (2)	10 (4)
Smoking status, n (%)		
Current/former[b]	378 (71)	183 (70)
Never	148 (28)	76 (29)
Unknown	6 (1)	3 (1)
ECOG PS, n (%)		
0	308 (58)	156 (60)
1	224 (42)	106 (41)
Disease stage (UICC)[c] at initial diagnosis, n (%)		
II	179 (34)	99 (38)
III	351 (66)	163 (62)
Unknown	2 (< 1)	0 (0)
Location of disease at study entry, n (%)		
Oesophageal cancer	311 (59)	151 (58)
Lower third	202 (38)	96 (37)
Middle third	82 (15)	46 (18)
Upper third	27 (5)	9 (3)
Gastrooesophageal junction cancer[d]	221 (42)	111 (42)
Type I	91 (17)	49 (19)
Type II	99 (19)	46 (18)
Type III	26 (5)	14 (5)
Unknown	5 (1)	2 (1)
Histology, n (%)		
Adenocarcinoma	376 (71)	187 (71)
Squamous cell carcinoma	155 (29)	75 (29)
Other	1 (< 1)	0 (0)
Pathologic tumour status at study entry, n (%)		
ypT0	31 (6)	16 (6)
ypT1/ypT2	202 (38)	106 (41)
ypT3/ypT4	296 (56)	140 (54)
Unknown	3 (1)	0 (0)

Table 9: Characteristics of the study population – RCT, direct comparison: nivolumab vs. placebo (multipage table)

Study Characteristic Category	Nivolumab N[a] = 532	Placebo N[a] = 262
Pathologic lymph node status at study entry, n (%)		
ypN0	227 (43)	109 (42)
≥ ypN1	305 (57)	152 (58)
Unknown	0 (0)	1 (< 1)
PD-L1 tumour expression status at baseline		
≥ 1%	89 (17)	40 (15)
< 1%	374 (70)	196 (75)
Indeterminate/non-evaluable	69 (13)	26 (10)
Treatment discontinuation[e, f], n (%)[g]	272 (51)	142 (54)
Treatment phase completed[e], n (%[g])	229 (43)	99 (38)
Study discontinuation, n (%)	ND	ND

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding column if the deviation is relevant.
b. Including e-cigarettes.
c. Concurs with the criteria of the AJCC classification used for study inclusion (see Table 6).
d. According to Siewert-Stein.
e. Information refers to the first data cut-off on 3 July 2020. At the second data cut-off, no patients were under treatment anymore. 259 (48.7%) patients in the nivolumab arm und 115 (43.9%) patients in the control arm fully completed the treatment phase.
f. The most common reasons for discontinuation were recurrent disease (nivolumab: 149 [28%], placebo: 113 [43%]), followed by toxicity (nivolumab: 57 [11%], placebo: 8 [3%]). Percentages calculated by the Institute.
g. Institute's calculation.

AJCC: American Joint Committee on Cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation; UICC: Union for International Cancer Control

The patient characteristics between both treatment arms of the CA209-577 study were balanced. The clear majority of patients were men and of Caucasian family origin. The mean age of the patients was about 60 years. About 59% of the patients had an ECOG PS of 0. At about 65%, the larger proportion of patients were in disease stage III at the time of initial diagnosis. Most patients had adenocarcinoma (71%); 29% had squamous cell carcinoma; the carcinoma was located in the oesophagus in about 58%, and in the gastrooesophageal junction in about 42%. In both treatment arms, the most common reasons for treatment discontinuation were recurrent disease (nivolumab arm: 28%; control arm: 43%), followed by toxicity (nivolumab arm: 11%; control arm: 3%), with different frequencies in the 2 arms.

Information on the course of the study

Table 10 shows the mean/median treatment duration of patients and the median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: nivolumab vs. placebo

Study **Duration of the study phase** **Outcome category**	**Nivolumab** **N = 532**	**Placebo** **N = 262**
CA209-577		
Treatment duration[a] [months]		
Median [min; max]	10.14 [< 0.1; 14.2]	8.99 [< 0.1; 15.0]
Mean (SD)	7.58 (ND)	7.64 (ND)
Observation period [months]		
Median [min; max][b]	24.41 [6.2; 44.9]	24.51 [7.8; 42.8]
Overall survival	No data available[c]	
Morbidity	ND	
Health-related quality of life	ND	
Side effects	ND	

a. In relation to patients who received at least one dose of the study medication (nivolumab arm N = 532; control arm N = 260).
b. Time between randomization and first data cut-off (3 July 2020).
c. There are no data on overall survival. According to the information provided by the company in Module 4 P, at the time point of the first data cut-off on 3 July 2020, the results of the interim analysis on overall survival were still "immature" and were not unblinded.

max: maximum; min: minimum; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The median treatment duration in the nivolumab arm of the CA209-577 study was 10.14 months, only slightly longer than in the control arm at 8.99 months. Information on the median observation period is only available for the time between randomization and the first data cut-off. This is very similar between the treatment arms. However, the company provided no data on the outcome-specific observation period in Module 4 P of its dossier.

Information on subsequent therapies

Table 11 shows the subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent antineoplastic therapies (≥ 1% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: nivolumab vs. placebo

Study Regimen Drug class Drug	Patients with subsequent therapy n (%) Nivolumab N = 532	 Placebo N = 262
CA209-577		
Total[a]	157 (29.5)	111 (42.4)
Radiotherapy	43 (8.1)	41 (15.6)
Surgical intervention	28 (5.3)	20 (7.6)
Systemic therapy	125 (23.5)	89 (34.0)
Immunotherapy	4 (0.8)	19 (7.3)
Anti-PD-1	4 (0.8)	17 (6.5)
Investigational antineoplastic drugs[b]	0 (0)	3 (1.1)
Nivolumab	3 (0.6)	8 (3.1)
Pembrolizumab	1 (0.2)	7 (2.7)
Targeted therapy	13 (2.4)	11 (4.2)
Ramucirumab	13 (2.4)	9 (3.4)
Chemotherapy	123 (23.1)	85 (32.4)
Capecitabine	20 (3.8)	20 (7.6)
Carboplatin	7 (1.3)	9 (3.4)
Cisplatin	27 (5.1)	13 (5.0)
Docetaxel	13 (2.4)	7 (2.7)
Fluorouracil	80 (15.0)	50 (19.1)
Fluorouracil/leucovorin/oxaliplatin	7 (1.3)	8 (3.1)
Gimeracil/oteracil/tegafur	7 (1.3)	3 (1.1)
Irinotecan	20 (3.8)	11 (4.2)
Oxaliplatin	71 (13.3)	50 (19.1)
Paclitaxel	32 (6.0)	23 (8.8)
Trastuzumab	10 (1.9)	12 (4.6)
Not allocated	52 (9.8)	38 (14.5)
Folinic acid	6 (1.1)	1 (0.4)
Leucovirin	30 (5.6)	24 (9.2)

a. It was possible for a patient to have more than one type of subsequent therapy. Subsequent therapy was defined as initiated therapy.
b. According to the information provided by the company, this includes pembrolizumab vs. placebo as well as sintilimab. It is assumed that pembrolizumab in comparison with placebo was administered in the context of an RCT, and it cannot be determined to which treatment arm the patients were randomized.

n: number of patients with subsequent therapy; N: number of analysed patients; PD-1: programmed cell death 1; RCT: randomized controlled trial

Subsequent therapies after recurrence of the disease were allowed without restrictions for patients in both study arms. Overall, 29.5% of the patients in the nivolumab arm and 42.4% of the patients in the control arm were receiving subsequent antineoplastic therapy at the first data

cut-off. Systemic therapy was the most common subsequent therapy in both study arms (nivolumab arm: 23.5%; control arm: 34.0%). Of these, 23.1% of patients in the nivolumab arm and 32.4% in the control arm received chemotherapy, with fluorouracil and oxaliplatin being the most frequently used drugs. Radiotherapy as subsequent therapy was administered to 8.1% of the patients in the nivolumab arm and 15.6% of the patients in the control arm. Guidelines recommend systemic therapy for palliative treatment. Radiotherapy (e.g. external radiotherapy or brachytherapy) is also an option [11-13]. Overall, the subsequent therapies used in the CA209-577 study are in line with guideline recommendations.

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: nivolumab vs. placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
CA209-577	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes for the CA209-577 study is rated as low.

Transferability of the study results to the German health care context

In the opinion of the company, the results of the CA209-577 study are transferable to the German health care context. It justified this assessment primarily with the good comparability of the age at disease onset and the sex ratio (higher proportion of men), as well as with a high proportion of patients of Caucasian family origin, the smoking status and the recommendations of German guidelines regarding neoadjuvant CRT in stage II and III.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - overall survival
- Morbidity
  - recurrence
  - health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - measured using the FACT-E total score
- Side effects
  - SAEs
  - severe AEs, operationalized as Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3
  - discontinuation due to AEs
  - immune-related AEs (SAEs and severe AEs)
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from the selection by the company, which used further outcomes in the dossier (Module 4 P).

Table 13 shows for which outcomes data were available in the included study.

Table 13: Matrix of outcomes – RCT, direct comparison: nivolumab vs. placebo

Study	Outcomes										
	Overall survival	Recurrence[a]	Health status (EQ-5D VAS)	Health-related quality of life (FACT-E)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Immune-related SAEs[c]	Immune-related severe AEs[b, c]	Infections and infestations (SOC, severe AEs[b])	Blood and lymphatic system disorders (SOC, severe AEs[b])
CA209-577	No[d]	Yes[e]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Presented based on the recurrence rate and disease-free survival, includes the events of local recurrence, regional recurrence, distant metastases, and death without recurrence.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of select AEs is used.
d. There are no data on overall survival. According to the information provided by the company in Module 4 P, at the time point of the first data cut-off on 3 July 2020, the results of the interim analysis on overall survival were still "immature" and were not unblinded.
e. Data from the second data cut-off (18 February 2021) are used.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACT-E: Functional Assessment of Cancer Therapy-Esophageal; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on the outcomes of health status (EQ-5D VAS) and health-related quality of life (FACT-E)

- For health-related quality of life, the FACT-E was recorded in the study during the treatment phase up to and including follow-up visit 2 (at most 128 days after the last dose of the study medication). The FACT-E comprises the FACT-General (FACT-G) and the oesophageal cancer subscale (ECS). In the subsequent survival follow-up, only the FACT-G7 (a shortened version of the FACT-G) and the ECS were recorded, but not the complete FACT-E. However, FACT-G7 and ECS are unsuitable for representing the complex construct of health-related quality of life. Only the data on the FACT-E total score are therefore considered for the outcome of health-related quality of life.
- For the EQ-5D VAS and the FACT-E, the company presented responder analyses on the time to definitive deterioration in Module 4 P. The company defined the definitive deterioration for both outcomes as a deterioration by at least the response threshold starting from the baseline value and without subsequent improvement back to a value above the response threshold. The company's dossier states that the definition likewise applies to all subsequent follow-up values. Patients for whom no data were available after the initial deterioration were rated as definitely deteriorated. However, the company did not state for either outcome how many patients per treatment arm with initial deterioration and without further data were rated as definitely deteriorated.

The company provided no data on the outcome-specific observation period in Module 4 P of its dossier. Since, on the basis of the available information on the treatment and observation period (Table 10), the planned follow-up observation (Table 8) and the comparable return rates of the questionnaires between the arms, it is assumed that the median observation periods for the EQ-5D VAS and the FACT-E are sufficiently comparable between the treatment arms, the results of the responder analyses on the time to definitive deterioration are nevertheless used for the benefit assessment. The existing uncertainty regarding the proportion of patients who had initial deterioration and subsequent lack of recordings and were rated as definitely deteriorated is taken into account in the assessment of the risk of bias (see Section 2.4.2).

- The company presented analyses on different response thresholds for both outcomes. For the EQ-5D VAS, these were analyses on the response thresholds of ≥ 7 points, ≥ 10 points, and on 15% of the scale range (15 points, scale range 0–100). For the FACT-E total score, it presented analyses on the response thresholds of ≥ 9.5 points, ≥ 13.1 points, and 15% of the scale range (26.4 points, scale range 0–176). In each case, the response threshold of 15% was analysed post hoc. The response criterion of 15% of the respective scale range, which was used in the analyses presented by the company, fulfils the requirements for response criteria of reflecting with sufficient certainty a change that is perceivable for patients, as defined by the *General Methods* of the Institute [1]. The analyses of this response threshold are therefore used for the benefit assessment. The further responder analyses on the EQ-5D VAS with a response threshold of ≥ 7 and ≥ 10 points provided by the company are presented as supplementary information in Appendix E of the full dossier assessment.

Notes on side effect outcomes

- The company presented event time analyses for all side effect outcomes. Considering event time analyses is of particular relevance in group comparisons with different mean observation periods [1]. However, due to the comparable treatment durations (see Table 10), it is assumed in the present situation that the observation periods between the study arms are also comparable. In the assessment of side effects, it is primarily relevant in how many patients an event occurred. In addition, when considering the time until occurrence of the event, effects can also result solely from an earlier or later occurrence of the event and not on the basis of the proportions. For this reason, the relative risk is used in the present assessment.
- Immune-related AEs: In Appendix 4 G of the dossier, the company provided supplementary analyses on AEs of special interest predefined in the statistical analysis plan (SAP) (immune-related AEs [“imAEs”], specific AEs (“select AEs”) and further AEs of special interest [“AESIs”]). In addition, analyses of severe events (operationalized as CTCAE grade ≥ 3) and serious events are available for these outcomes. In the dossier, the company stated that the AEs of special interest it referred to as “imAEs”, with the exception of endocrine imAEs, were events requiring immunomodulatory therapy. This

operationalization is unsuitable for fully representing immune-related AEs. The outcome of AEs of special interest referred to as "select AEs" by the company, however, is a selection of System Organ Classes (SOCs) and Preferred Terms (PTs) that belong to the typical immune-related AEs and for which treatment of the AEs with immunosuppression (e.g. with corticosteroids) could, but did not have to, be necessary. In addition, it presented the list of PTs that were included as events in the analysis of the "select AEs". This operationalization is considered a sufficient approximation for immune-related AEs. Both severe AEs (CTCAE grade ≥ 3) and SAEs were considered. A list of the categories of immune-related AEs, severe immune-related AEs (CTCAE grade ≥ 3) and immune-related SAEs that occurred in the CA209-577 study can be found as supplementary information in Appendix D of the full dossier assessment.

2.4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: nivolumab vs. placebo

Study	Study level	Outcomes										
		Overall survival	Recurrence[a]	Health status (EQ-5D VAS)	Health-related quality of life (FACT-E)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Immune-related SAEs[c]	Immune-related severe AEs[b, c]	Infections and infestations (SOC, severe AEs[b])	Blood and lymphatic system disorders (SOC, severe AEs[b])
CA209-577	L	–[d]	L[e]	H[f]	H[f]	H[g]	H[g]	L[h]	H[g]	H[g]	H[g]	H[g]

a. Presented based on the recurrence rate and disease-free survival, includes the events of local recurrence, regional recurrence, distant metastases, and death without recurrence.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of select AEs is used.
d. There are no data on overall survival. According to the information provided by the company in Module 4 P, at the time point of the first data cut-off on 3 July 2020, the results of the interim analysis on overall survival were still "immature" and were not unblinded.
e. Data from the second data cut-off (18 February 2021) are used.
f. For the operationalization "definitive deterioration", it cannot be estimated how many patients with initial deterioration without further data were rated as definitely deteriorated; in addition, decreasing return of questionnaires over the course of the study.
g. Incomplete observations for potentially informative reasons.
h. Despite low risk of bias, the certainty of results for the outcome of discontinuation due to AEs was assumed to be limited (see running text below).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACT-E: Functional Assessment of Cancer Therapy-Esophageal; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias for the result on the outcome of recurrence is rated as low. The risk of bias of the results of the outcomes of health status (EQ-5D VAS) and health-related quality of life (FACT-E) is rated as high. For the patients included in the analysis, the return of questionnaires decreased. There is also no information on the proportion of patients with initial deterioration and subsequent lack of recordings who were rated as definitely deteriorated. It cannot be assessed whether this was balanced between the treatment arms (see also See Section 2.4.1).

The risk of bias of the results of the outcomes of SAEs, severe AEs (overall rate and specific AEs), as well as immune-related SAEs/severe AEs is rated as high. For the mentioned outcomes of the category of side effects, there are incomplete observations for potentially informative reasons due to the follow-up observation linked to the treatment duration and a possible association between outcome and reason for treatment discontinuation.

The risk of bias for the results of the outcome of discontinuation due to AEs is rated as low. Despite a low risk of bias, the certainty of results is limited for the outcome of discontinuation due to AEs. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome of discontinuation due to AEs to be recorded. This means that, after discontinuation for other reasons, AEs that would have led to discontinuation may have occurred, but that the criterion of discontinuation can no longer be applied to them. It cannot be estimated how many AEs this concerns.

2.4.3 Results

Table 15 and Table 16 summarize the results of the comparison of nivolumab with placebo in adult patients with oesophageal or gastrooesophageal junction cancer who have residual pathologic disease following prior neoadjuvant CRT. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Event time analyses for the outcome of EQ-5D VAS with the response criteria of ≥ 7 and ≥ 10 points are presented in Appendix E of the full dossier assessment.

The available Kaplan-Meier curves on the presented event time analyses can be found in Appendix B of the full dossier assessment. The company did not present Kaplan-Meier curves on the event time analyses for the EQ-5D VAS and the FACT-E with the response threshold of 15% of the respective scale range. Tables on common AEs, SAEs, severe AEs and discontinuations due to AEs are presented in Appendix C of the full dossier assessment. A list of the occurred categories of immune-related AEs, severe immune-related AEs (CTCAE grade ≥ 3) and immune-related SAEs is presented as supplementary information in Appendix D of the full dossier assessment.

Table 15: Results (mortality, morbidity; health-related quality of life) – RCT, direct comparison: nivolumab vs. placebo (multipage table)

Study	Nivolumab		Placebo		Nivolumab vs. placebo
Outcome category **Outcome**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[a]**
CA209-577					
Mortality					
Overall survival			No data available[b]		
Morbidity					
Recurrence					
Recurrence rate[c, d]	532	– 268 (50.4)	262	– 171 (65.3)	RR: 0.77 [0.69; 0.87][e]; < 0.001[f]
Local recurrence	532	– 36 (6.8)	262	– 23 (8.8)	–
Regional recurrence	532	– 34 (6.4)	262	– 25 (9.5)	–
Distant metastases	532	– 169 (31.8)	262	– 113 (43.1)	–
Death without recurrence	532	– 29 (5.5)	262	– 10 (3.8)	–
Disease-free survival[c]	532	22.41 [16.95; 33.64] 268 (50.4)	262	10.35 [8.31; 13.93] 171 (65.3)	0.67 [0.55; 0.81]; < 0.001
Health status (EQ-5D VAS)[g]	532	39.10 [36.47; NC] 85 (16.0)	262	NR [35.61; NC] 37 (14.1)	1.11 [0.75; 1.64]; 0.607[h]
Health-related quality of life					
FACT-E[g]	532	NA [NC; NC] 38 (7.1)	262	NA [NC; NC] 20 (7.6)	0.98 [0.57; 1.68]; 0.933[h]
EWB (supplementary information)	532	16.95 [16.13; NC] 84 (15.8)	262	NR [15.74; NC] 36 (13.7)	1.22 [0.82; 1.81]
SWB (supplementary information)	532	NA [NC; NC] 64 (12.0)	262	NR [15.70; NC] 32 (12.2)	0.98 [0.64; 1.52]
PWB (supplementary information)	532	NR [15.90; NC] 80 (15.0)	262	NR [15.74; NC] 39 (14.9)	1.07 [0.73; 1.57]
FWB (supplementary information)	532	16.43 [16.13; NC] 81 (15.2)	262	NR [16.13; NC] 36 (13.7)	1.09 [0.73; 1.62]
ECS (supplementary information)				ND[i]	

Table 15: Results (mortality, morbidity; health-related quality of life) – RCT, direct comparison: nivolumab vs. placebo (multipage table)

Study	Nivolumab		Placebo		Nivolumab vs. placebo
Outcome category Outcome	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]

a. HR and CI from stratified Cox model, p-value from log-rank test, stratified by PD-L1 status (≥ 1%, < 1% or indeterminate/non-evaluable), pathologic lymph node status (positive [≥ ypN1], negative [ypN0]), and histology (squamous cell carcinoma, adenocarcinoma) according to IRT.
b. According to the information provided by the company in Module 4 P, at the time point of the first data cut-off on 3 July 2020, the results of the interim analysis on overall survival were still "immature" and were not unblinded.
c. Data from the second data cut-off (18 February 2021) are used.
d. Proportion of patients, individual components are presented in the lines below.
e. Based on Cochran-Mantel-Haenszel method, stratified by PD-L1 status (≥ 1%, < 1% or indeterminate/non-evaluable), pathologic lymph node status (positive [≥ ypN1], negative [ypN0]), and histology (squamous cell carcinoma, adenocarcinoma) according to IRT.
f. Institute's calculation (unconditional exact test [CSZ method according to [16]].
g. Analyses of the time to definitive deterioration, defined as a decrease in score by 15% of the scale range (EQ-5D VAS: 0 to 100; FACT-E: 0 to 176).
h. p-value from Cox model, stratified by PD-L1 status (≥ 1%, < 1% or indeterminate/non-evaluable), pathologic lymph node status (positive [≥ ypN1], negative [ypN0]), and histology (squamous cell carcinoma, adenocarcinoma) with baseline value as covariate.
i. The company presented no analyses on follow-up visit 2 for this subscale.

CI: confidence interval; ECS: oesophageal cancer subscale; EWB: emotional wellbeing; FACT-E: Functional Assessment of Cancer Therapy-Esophageal; FWB: functional wellbeing; IRT: interactive response technology; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PWB: physical wellbeing; RCT: randomized controlled trial; RR: relative risk; SWB: social wellbeing

Table 16: Results (side effects) – RCT, direct comparison: nivolumab vs. placebo

Study Outcome category Outcome	Nivolumab N	Nivolumab Patients with event n (%)	Placebo N	Placebo Patients with event n (%)	Nivolumab vs. placebo RR [95% CI]; p-value[a]
CA209-577					
Side effects					
AEs (supplementary information)[b]	532	511 (96.1)	260	241 (92.7)	–
SAEs[b]	532	173 (32.5)	260	81 (31.2)	0.99 [0.82; 1.21]; 0.961
Severe AEs[b, c]	532	214 (40.2)	260	94 (36.2)	1.04 [0.87; 1.23]; 0.736
Discontinuation due to AEs[b]	532	73 (13.7)	260	15 (5.8)	2.38 [1.39; 4.06]; < 0.001
Immune-related AEs (supplementary information)	532	375 (70.5)	260	142 (54.6)	–
Immune-related SAEs	532	34 (6.4)	260	8 (3.1)	2.08 [0.98; 4.42]; 0.052
Immune-related severe AEs[c]	532	48 (9.0)	260	14 (5.4)	1.68 [0.94; 2.98]; 0.078
Infections and infestations (SOC, severe AEs[c])	532	40 (7.5)	260	8 (3.1)	2.44 [1.16; 5.14]; 0.014
Blood and lymphatic system disorders (SOC, severe AEs[c])	532	17 (3.2)	260	2 (0.8)	4.15 [0.97; 17.85]; 0.037

a. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [16]). Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.
b. Without recording of progression of the underlying disease.
c. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

On the basis of the available information, at most an indication, e.g. of an added benefit, can be determined for the outcome of recurrence; due to the high risk of bias or, for the outcome of discontinuation due to AEs, due to a limited certainty of results, at most hints can be determined for all other outcomes.

Mortality

Overall survival

There are no data on overall survival. According to the information provided by the company in Module 4 P, at the time point of the first data cut-off on 3 July 2020, the results of the interim analysis on overall survival were still "immature" and were not unblinded. The company did not make a respective statement for the second data cut-off, but also provided no analyses on overall survival. In the present situation, this is not appropriate. In addition, the statement of the company on the non-unblinding of the data on overall survival is not fully comprehensible, as the recurrence rate also includes the event "death without recurrence", for which unblinded data per treatment arm are available.

This results in no hint of added benefit of nivolumab in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

Recurrence

Operationalization

For the present benefit assessment, the proportion of patients with recurrence and, additionally, the time to recurrence of the disease were used for the outcome "recurrence".

Result

For the outcome of recurrence (operationalized as recurrence rate and DFS), a statistically significant difference in favour of nivolumab in comparison with placebo was shown for both operationalizations. This results in an indication of an added benefit of nivolumab in comparison with watchful waiting.

Health status (EQ-5D VAS)

The time to definitive deterioration by 15 points (scale range 0 – 100) is considered for the outcome of health status (EQ-5D VAS). There was no statistically significant difference between the treatment arms. This results in no hint of added benefit of nivolumab in comparison with watchful waiting; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life was recorded with the disease-specific instrument FACT-E. The time to definitive deterioration of the FACT-E total score by 15% of the scale range (scale range 0 – 176) is considered. There was no statistically significant difference between the treatment arms. This results in no hint of added benefit of nivolumab in comparison with watchful waiting; an added benefit is therefore not proven.

Side effects

SAEs and severe AEs

There was no statistically significant difference between the treatment arms for the outcomes of SAEs and severe AEs. In each case, this results in no hint of greater or lesser harm from nivolumab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference to the disadvantage of nivolumab compared with placebo was shown for the outcome of discontinuation due to AEs. This results in a hint of greater harm from nivolumab in comparison with watchful waiting.

Specific AEs

Immune-related SAEs and immune-related severe AEs

There was no statistically significant difference between the treatment arms for the outcomes of immune-related SAEs and immune-related severe AEs. In each case, this results in no hint

of greater or lesser harm from nivolumab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Infections and infestations (severe AES) and blood and lymphatic system disorders (severe AEs)
A statistically significant difference to the disadvantage of nivolumab in comparison with placebo was shown for each of the outcomes of infections and infestations (severe AEs) and blood and lymphatic system disorders (severe AEs). In each case, this results in a hint of greater harm from nivolumab versus watchful waiting.

2.4.4 Subgroups and other effect modifiers

The following potential effect modifiers are considered for the present assessment:

- age (< 65 years versus ≥ 65 years)
- sex (female versus male)
- pathologic lymph node status (ypN0 [negative] versus ≥ ypN1 [positive] versus unknown)

The selected characteristics were defined a priori. In the CA209-577 study, subgroup analyses were predefined only for DFS and overall survival, and partly for side effect outcomes. The dossier did not contain any interaction tests and subgroup analyses for the outcomes of health status (EQ-5D VAS) and health-related quality of life (FACT-E) for the response threshold of 15% of the respective scale range. There are also no subgroup analyses for immune-related severe AEs or immune-related SAEs.

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only results showing an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

Using the methods described above, the available subgroup results did not show any effect modifications.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.4 (see Table 17).

Determination of the outcome category for outcomes on morbidity and side effects

It cannot be inferred from the dossier for the outcomes of recurrence and discontinuation due to AEs whether they are serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

The outcome of recurrence is considered to be serious/severe. On the one hand, recurrence of the cancer can be life-threatening, and a recurrence shows that the attempt to cure a potentially life-threatening disease with the curative therapy approach has not been successful. On the other hand, the event of death without recurrence is a component of the outcome of recurrence. This allocation concurs with that of the company.

The outcome of discontinuation due to AEs was allocated to the outcome category of serious/severe side effects. The information provided by the company in Appendix 4 G shows that more than 50% of the AEs that led to treatment discontinuation were CTCAE grade ≥ 3 events. The company presented no assessment regarding the severity grade of this outcome.

Table 17: Extent of added benefit at outcome level: nivolumab vs. watchful waiting (multipage table)

Outcome category **Outcome**	**Nivolumab vs. placebo** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	No data available[c]	Lesser/added benefit not proven
Morbidity		
Recurrence		Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ Added benefit; extent: "considerable"
Recurrence rate	50.4% vs. 65.3% RR: 0.77 [0.69; 0.87] $p < 0.001$ Probability: "indication"	
Disease-free survival	22.41 vs. 10.35 months HR: 0.67 [0.55; 0.81] $p < 0.001$ Probability: "indication"	
Health status (EQ-5D VAS)	39.10 vs. NA months HR: 1.11 [0.75; 1.64] $p = 0.607$	Lesser/added benefit not proven
Health-related quality of life		
FACT-E	NA vs. NA HR: 0.98 [0.57; 1.68] $p = 0.933$	Lesser/added benefit not proven
Side effects		
SAEs	32.5% vs. 31.2% RR: 0.99 [0.82; 1.21] $p = 0.961$	Greater/lesser harm not proven
Severe AEs	40.2% vs. 36.2% RR: 1.04 [0.87; 1.23] $p = 0.736$	Greater/lesser harm not proven
Discontinuation due to AEs	13.7% vs. 5.8% RR: 2.38 [1.39; 4.06] RR: 0.42 [0.25; 0.72][d] $p < 0.001$ Probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk $\geq 5\%$ Greater harm, extent: "major"
Immune-related SAEs	6.4% vs. 3.1% RR: 2.08 [0.98; 4.42] $p = 0.052$	Greater/lesser harm not proven
Immune-related severe AEs	9.0% vs. 5.4% RR: 1.68 [0.94; 2.98] $p = 0.078$	Greater/lesser harm not proven

Table 17: Extent of added benefit at outcome level: nivolumab vs. watchful waiting (multipage table)

Outcome category **Outcome**	**Nivolumab vs. placebo** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Infections and infestations (severe AEs)	7.5% vs. 3.1% RR: 2.44 [1.16; 5.14] RR: 0.41 [0.19; 0.86][d] p = 0.014 Probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm; extent: considerable
Blood and lymphatic system disorders (severe AEs)	3.2% vs. 0.8% RR: 4.15 [0.97; 17.85] RR: 0.24 [0.06; 1.03][d] p = 0.037 Probability: "hint"	Outcome category: serious/severe side effects greater harm[e], extent: "minor"[f]

a. Probability is stated whenever a statistically significant and relevant effect is present.
b. Estimations of effect size are made depending on the outcome category, with different limits according to the upper limit of the confidence interval (CI_u).
c. According to the information provided by the company in Module 4 P, at the time point of the first data cut-off on 3 July 2020, the results of the interim analysis on overall survival were still "immature" and were not unblinded.
d. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e. The result of the statistical test is decisive for the derivation of the added benefit.
f. Discrepancy between CI and p-value; the extent is rated as "minor".

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; FACT-E: Functional Assessment of Cancer Therapy-Esophageal; HR: hazard ratio; NA: not achieved; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

Table 18 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of nivolumab in comparison with watchful waiting

Positive effects	Negative effects
Morbidity Serious/severe symptoms/late complications ▪ Recurrence: indication of an added benefit – extent: "considerable"	
	Serious/severe side effects ▪ Discontinuation due to AEs: hint of greater harm – extent "major" ▪ Infections and infestations (severe AEs): hint of greater harm – extent: "considerable" ▪ Blood and lymphatic system disorders (severe AEs): hint of greater harm – extent: "minor"
There are no data on overall survival. According to the information provided by the company in Module 4 P, at the time point of the first data cut-off on 3 July 2020, the results of the interim analysis on overall survival were still "immature" and were not unblinded.	
AE: adverse event	

Overall, there are positive and negative effects of different extent, with the probability of an indication for the positive effect, and a hint for each of the negative effects.

A positive effect of nivolumab in comparison with watchful waiting with the extent "considerable" was shown for the outcome of recurrence. In contrast, there are negative effects from nivolumab in comparison with watchful waiting in the category of serious/severe side effects. Here, greater harm of major extent was shown for the outcome of discontinuation due to AEs. There is greater harm of minor extent for one of the 2 specific AEs, and of considerable extent for the other.

No data are available for overall survival. However, overall survival of the patients is of particular importance in the present oncological indication. The lack of these data is not appropriate in the present situation and is not sufficiently justified by the company. However, it can be assumed that the results on overall survival would only have an influence on the overall conclusion on added benefit if a disadvantage of nivolumab was shown. Based on the available information (e.g. results on SAEs, data on subsequent therapies), there are no hints that such a disadvantage in comparison with watchful waiting is to be expected. The EMA also described in its assessment report that it considered a detrimental effect of nivolumab on overall survival as very unlikely [9]. The resulting uncertainties are considered in the balancing regarding the added benefit and, together with the negative effects, result in a downgrading of the extent.

In summary, there is an indication of a minor added benefit of nivolumab versus the ACT of watchful waiting for adult patients with oesophageal or gastrooesophageal junction cancer who have residual pathologic disease following prior neoadjuvant CRT.

The result of the assessment of the added benefit of nivolumab in comparison with the ACT is summarized in Table 19.

Table 19: Nivolumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adjuvant treatment of carcinoma of the oesophagus or the gastroesophageal junction in adults with pathological residual disease after prior neoadjuvant chemoradiotherapy[b]	Watchful waiting	Indication of minor added benefit[c]

a. Presented is the respective ACT specified by the GBA.
b. The CA209-577 study included both patients with adenocarcinoma and patients with squamous cell carcinoma in stages II and III (per AJCC 7th edition) after neoadjuvant chemoradiotherapy with R0 resection and residual pathologic disease. Since only patients with complete resection were included, the G-BA assumed that patients with ≥ R1 resection were not comprised by the therapeutic indication.
c. Only patients with an ECOG PS of 0 or 1 were included in the CA209-577 study. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.

ACT: appropriate comparator therapy; AJCC: American Joint Committee on Cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which, based on the results of the CA209-577 study, derived an indication of considerable added benefit of nivolumab in comparison with the ACT of watchful waiting for patients with oesophageal or gastrooesophageal junction cancer who have residual pathologic disease following prior neoadjuvant CRT.

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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