Nivolumab (oesophageal or gastro-oesophageal junction cancer, adjuvant)

Benefit assessment according to §35a SGB V[1] (expiry of the decision)

EXTRACT

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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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Part I: Benefit assessment

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I List of tables[2]

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AJCC	American Joint Committee on Cancer
BICR	blinded independent central review
CRT	chemoradiotherapy
CTCAE	Common Terminology Criteria for Adverse Events
DFS	disease-free survival
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ECS	oesophageal cancer subscale
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
FACT-E	Functional Assessment of Cancer Therapy-Esophageal
FACT-G	Functional Assessment of Cancer Therapy-General
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PD-L1	programmed cell death-ligand 1
PT	Preferred Term
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics
VAS	visual analogue scale

I 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 01 July 2025.

The company had already submitted a dossier for a previous benefit assessment of the drug to be assessed. That dossier was sent to IQWiG on 30 August 2021. In that procedure, by resolution of 17 February 2022, the G-BA limited the period of validity of the resolution to 1 October 2024. By resolution of 2 May 2024, the limited period of validity of the resolution was extended to 1 July 2025. The validity period was limited as further data relevant for the assessment of the added benefit were to be expected from the CA209-577 study, in particularly with regard to overall survival.

Research question

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

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of nivolumab

Therapeutic indication	**ACT**[a]
Adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy[b]	Watchful waiting
a. Presented is the 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 assumes that patients with ≥ R1 resection are not covered 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 to derive the added benefit. This concurred with the company's inclusion criteria.

Study pool and study design

CA209-577

Concurring with the company, the CA209-577 study was primarily used for the benefit assessment. CA209-577 is a completed 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 had to be in good general condition at enrolment, corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.

The CA209-577 study included a total of 794 patients, randomly allocated 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). Patients in the control arm received placebo treatment.

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

The data of the final data cut of 7 November 2024 were used for the benefit assessment.

Guideline-compliant prior therapy of the included patients

For patients with type III gastro-oesophageal junction carcinoma classified as gastric cancer or adenocarcinoma with T2N0 status, neoadjuvant CRT does not concur with the treatment recommendations of the guidelines. It can be assumed that only few patients in CA209-577 were concerned, however.

For patients with resectable adenocarcinoma with T3, T4 or N+ status, the treatment recommendations between the various current guidelines are partially discrepant. As the approach in the CA209-577 study for conducting neoadjuvant CRT was still in line with the recommendations of the S3 guidelines for oesophageal and gastric cancer, patients with adenocarcinoma with T3, T4 or N+ status in the study were assumed to have received guideline-compliant prior treatment.

Overall, based on the information available, it was assumed that neoadjuvant CRT not in compliance with the guidelines was used for only a few patients. There was therefore no consequence for the benefit assessment.

Implementation of the ACT

The G-BA specified watchful waiting as the ACT.

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

Although the examinations performed in the study did not fully represent the guideline recommendations, the examination regimen in CA209-577 was overall considered to be a sufficient approximation to the ACT of watchful waiting for this benefit assessment.

Subsequent therapies

A total of 86.0% of patients with recurrence received subsequent therapy in the intervention arm of CA209-577, compared with around 92% in the control arm. In both study arms, chemotherapy was most frequently used.

The extent of subsequent therapies used and the proportion of patients receiving chemotherapy in the CA209-577 study appeared appropriate. No information on the biomarkers programmed cell death-ligand 1 (PD-L1) or human epidermal growth factor receptor 2 (HER2) status at the time of subsequent therapy was available in the dossier. Therefore, the PD-L1 and HER2 tumour expression status at baseline were considered as an approximation.

At the time of study inclusion, 15% of patients in the control arm had a PD-L1 status ≥ 1%. Based on the information available, it cannot be assumed that the use of immunotherapies as subsequent therapy in the study deviated to a relevant extent from the guideline recommendations.

In the CA209-577 study, the proportion of HER2-positive carcinomas was around 8% at the time of study inclusion. In most patients, however, the HER2 status was unknown or not reported (66% in total). It was therefore unclear whether all patients who could have benefited from a subsequent therapy directed against HER2 actually received such therapy.

Despite the uncertainties described, the subsequent therapies used in the CA209-577 study were largely in line with guideline recommendations.

Risk of bias

The risk of bias across outcomes was rated as low for CA209-577.

For the results of the outcomes of overall survival and recurrence, the risk of bias was assessed as low in each case. The risk of bias of the results of the outcomes health status (EQ-5D visual analogue scale [VAS]), health-related quality of life and all results of outcomes in the side effects category, except discontinuation due to AEs, was assessed as high despite comparable observation periods, due to incomplete observations for potentially informative reasons.

Although the risk of bias for the outcome discontinuation due to AEs was low, the certainty of results for this outcome was limited. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome discontinuation due to AEs to be recorded. This means that, although AEs that would have led to discontinuation of therapy may occur after discontinuation for other reasons, the criterion of 'discontinuation' is no longer applicable to them. It was impossible to estimate how many AEs this affected.

Results

Mortality

Overall survival

There was no statistically significant difference between the treatment arms for the outcome overall survival. There is therefore no hint of an 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 disease-free survival), a statistically significant difference in favour of nivolumab in comparison with placebo was shown for both operationalizations. There is therefore an indication of an added benefit of nivolumab in comparison with watchful waiting.

Health status (EQ-5D VAS)

No statistically significant difference between the treatment arms was shown for health status, recorded using the EQ-5D VAS. However, there is an effect modification by the characteristic of sex. For men, there is a hint of greater harm of nivolumab in comparison with watchful waiting. For women, there is a hint of an added benefit of nivolumab in comparison with watchful waiting.

Health-related quality of life

No statistically significant difference between treatment arms was found for the outcome of health-related quality of life, recorded using the Functional Assessment of Cancer Therapy-Esophageal (FACT-E). There is therefore no hint of an 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, there is therefore no hint of greater or lesser harm of 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. There is therefore a hint of greater harm of nivolumab in comparison with watchful waiting.

Specific AEs

Immune-mediated SAEs

A statistically significant difference to the disadvantage of nivolumab compared with placebo was shown for the outcome of immune-mediated SAEs. There is therefore a hint of greater harm of nivolumab in comparison with watchful waiting.

Immune-mediated severe AEs

There was no statistically significant difference between the treatment arms for the outcome of immune-mediated severe AEs. There is therefore no hint of greater or lesser harm of nivolumab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Skin and subcutaneous tissue disorders (AEs), 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 skin and subcutaneous tissue disorders (AEs), infections and infestations (severe AEs) and blood and lymphatic system disorders (severe AEs). In each case, there is therefore a hint of greater harm of nivolumab in comparison with 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, both positive and negative effects of nivolumab were shown in comparison with the ACT.

On the side of positive effects, there is an indication of a minor added benefit for the outcome recurrence, although the extent decreased compared with the 2nd data cut-off (4 January 2021). However, the advantage in the outcome recurrence is not apparent in a statistically significant advantage in the outcome overall survival.

On the other hand, there are hints of greater harm of differing, in some cases major extent for numerous outcomes in the side effects category.

In summary, there is no hint of an added benefit of nivolumab versus watchful waiting for adult patients with oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant CRT; an added benefit is therefore not proven.

Table 3 shows a summary of the probability and extent of the 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 adult patients with oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy[b]	Watchful waiting	Added benefit not proven[c]

a. Presented is the 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 [3]) after neoadjuvant chemoradiotherapy with R0 resection and residual pathologic disease. Since only patients with complete resection were included, the G-BA assumes that patients with ≥ R1 resection are not covered 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; G-BA: Federal Joint Committee

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

I 2 Research question

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

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of nivolumab

Therapeutic indication	**ACT[a]**
Adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy[b]	Watchful waiting

a. Presented is the 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 [3]) after neoadjuvant chemoradiotherapy with R0 resection and residual pathologic disease. Since only patients with complete resection were included, the G-BA assumes that patients with ≥ R1 resection are not covered 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 to derive the added benefit. This concurred with the company's inclusion criteria.

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on nivolumab (status: 6 May 2025)
- Bibliographical literature search on nivolumab (last search on 9 April 2025)
- Search of trial registries / trial results databases for studies on nivolumab (last search on 10 April 2025)
- Search on the G-BA website for nivolumab (last search on 24 April 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on nivolumab (last search on 14 July 2025); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant studies.

I 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 marketing authorization 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 [4]	Yes [5-7]	Yes [8,9]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial 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 included in this benefit assessment.

The study pool was consistent with that selected by the company.

I 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[b] carcinoma of the oesophagus or gastro-oesophageal junction ▪ after prior neoadjuvant chemoradiotherapy and R0 resection[c] ▪ with residual pathologic disease (≥ ypT1 or ≥ ypN1) ▪ 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, United States 7/2016–11/2024 ▪ 1st data cut-off[f]: 12 May 2020 ▪ 2nd data cut-off[g]: 4 Jan 2021 ▪ 3rd data cut-off[h]: 25 Jan 2022 ▪ 4th data cut-off[i]: 7 Nov 2024	Primary: disease-free survival Secondary: overall survival, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without taking into account 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 both squamous cell carcinoma and 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. 1st interim analysis: after 374 DFS events / 299 OS events.
g. As part of the marketing authorization process, an additional exploratory analysis on DFS was conducted at the request of the EMA.
h. 2nd interim analysis: final analysis of DFS after 440 events / 368 OS events.
i. Final analysis of OS.

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; OS: overall survival; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – 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 Maximum total treatment duration: 1 year	Placebo IV every 2 weeks, for 16 weeks From week 17: placebo IV every 4 weeks Maximum total treatment duration: 1 year
	Dose modification: ▪ No dose modification 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 gastro-oesophageal 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 **Allowed 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 protein-4; IV: intravenous; PD-L1/L2: programmed cell death-ligand 1/2; RCT: randomized controlled trial

CA209-577 is a completed 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 gastro-oesophageal junction at the time of initial diagnosis [3]. 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. According to the guidelines, neoadjuvant CRT is not recommended for this location [10-12], so that the exclusion of these patients appeared appropriate in the given therapeutic indication.

Programmed cell death-ligand 1 (PD-L1) expression of the tumour tissue had to be determined for study inclusion. This test had to be performed in a central laboratory; and the resected tumour tissue had to be obtained within 16 weeks prior to randomization, but after completed CRT. However, patients were included in the study regardless of their PD-L1 expression. PD-L1 expression was determined using a DAKO immunohistochemistry assay.

The CA209-577 study included a total of 794 patients, randomly allocated 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 (ypN0 versus ≥ ypN1), and histology (squamous cell carcinoma versus adenocarcinoma).

The study was conducted in 170 centres in 29 countries, including Russia. In June 2022, the participating study centres in Russia were closed due to increasing logistical challenges. Since only 15 patients had been included in these centres and all of them had already completed the 100-day follow-up after the last dose of the study medication at this time point, this had no consequences for the benefit assessment.

Treatment with nivolumab in the intervention arm was in compliance with the recommendations of the summary of product characteristics (SmPC) [13]. Correspondingly, dose adjustment was not allowed; treatment interruptions due to toxicity were possible and were largely in compliance with the SmPC [13]. Patients in the control arm received placebo treatment.

The study population was treated until recurrence, unacceptable toxicity, treatment discontinuation following the physician's or patient's decision, or until the scheduled completion of the study treatment after 1 year. The study did not provide for any switching between study arms. Subsequent therapies after recurrence of the disease were allowed without restrictions for patients in both study arms.

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

Guideline-compliant prior therapy of the included patients

CA209-577 included patients with stage II or stage III (classification per AJCC 7th edition) carcinoma of the oesophagus or gastro-oesophageal junction at the time of initial diagnosis. However, the current guidelines do not recommend neoadjuvant radiochemotherapy for all stage II and III tumours. This is explained below.

For patients with type III gastro-oesophageal junction carcinoma classified as gastric cancer or adenocarcinoma with T2N0 status, neoadjuvant CRT does not concur with the treatment recommendations of the guidelines [10-12,14]. However, it can be assumed that only a small number of patients in the CA209-577 study were affected by this, as only 5% of patients with type III gastro-oesophageal junction carcinoma were included. Furthermore, patients with T2N0 adenocarcinoma are only classified as stage II and thus met the study's inclusion criteria if the tumour also had a grade of differentiation of G3. Patients with a lower grade of differentiation are to be allocated to stage I [3]. The dossier did not contain any 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 was not assumed, however, that this was the case in a relevant proportion of patients.

For patients with resectable adenocarcinoma with T3, T4 or N+ status, the treatment recommendations between the various guidelines are partially discrepant. According to the S3 guideline on squamous-cell carcinoma and adenocarcinoma of the oesophagus, 2 equivalent treatment options are available for this patient group: neoadjuvant CRT and perioperative chemotherapy (preoperative chemotherapy followed by surgical resection and subsequent postoperative chemotherapy) [12]. The S3 guideline on gastric and gastro-oesophageal junction adenocarcinoma also names neoadjuvant CRT as an option for patients with T3 or T4 status [14]. In contrast, the European Society for Medical Oncology (ESMO) and the German Society for Haematology and Medical Oncology generally recommend perioperative chemotherapy in their guidelines [10,11]. Neoadjuvant CRT may be considered if perioperative chemotherapy is not an option for a patient. As the approach in the CA209 577 study for conducting neoadjuvant CRT was in line with the recommendations of the S3 guidelines for oesophageal and gastric cancer, patients with adenocarcinoma with T3, T4 or N+ status in the study were assumed to have received guideline-compliant prior treatment.

Overall, based on the information available, it was assumed that neoadjuvant CRT not in compliance with the guidelines was used for only a few patients. There was therefore no consequence for the benefit assessment.

Implementation of the ACT

The G-BA specified watchful waiting as the ACT.

The CA209-577 study used placebo as the comparator therapy. The study was not designed for a comparison with watchful waiting, but was 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, recording of weight and ECOG PS, and laboratory parameters during the treatment phase and at the start of each treatment cycle (see Table 7) as well as 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 on oesophageal carcinoma and the ESMO guideline, after-care should generally 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 [12,14,15]. In certain situations, structured after-care, which also includes regular imaging, should be offered according to the S3 guideline on oesophageal carcinoma [12], provided that treatment decisions can be derived from it. The patient's desire for information about their health status can also be a reason for structured after-care [12]. According to the S3 guideline on gastric cancer, structured after-care is recommended for all patients [14]. The recommendations of the ESMO guideline do not explicitly mention cross-sectional imaging [15].

The examinations performed in CA209-577 did not fully represent the guideline recommendations. This applied in particular to nutritional counselling or rehabilitative measures. On the other hand, cross-sectional imaging was performed regularly, which is not generally recommended for all patients across all guidelines. Overall, patients in the CA209-577 study received close and targeted examinations to assess their health status and detect local, regional and distant recurrences, so that the examination regimen was overall considered to be a sufficient approximation to the ACT of watchful waiting.

Data cut-offs

Four data cuts were available for the CA209-577 study:

- 1st data cut of 12 May 2020: DFS interim analysis / 1st interim analysis of overall survival, planned after the occurrence of 374 DFS events / 299 deaths
- 2nd data cut of 4 January 2021: additional exploratory analysis conducted during the marketing authorization process at the request of the European Medicines Agency (EMA)
- 3rd data cut of 25 January 2022: final DFS analysis / 2nd interim analysis of overall survival, planned after the occurrence of 440 DFS events / 368 deaths

- 4th data cut of 7 November 2024: final analysis of overall survival, planned after the occurrence of 460 deaths Amendment 4 of the study protocol (26 April 2024) stipulated that the final analysis could also be conducted after a follow-up period of ≥ 5 years if fewer than 460 deaths have occurred by then.

Analogous to the company's approach, the analyses on the final data cut-off (7 November 2024) were used for the benefit assessment.

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

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

Study **Outcome category** **Outcome**	**Planned follow-up**
CA209-577	
Mortality	
Overall survival	Until death or at most up to 5 years after end of treatment of the last patient
Morbidity	
Recurrence[a]	Until recurrence, at most up to 5 years after end of treatment of the last patient
Health status (EQ-5D VAS)	Up to 2 years after the last dose of the study medication
Health-related quality of life (FACT-E)[c]	Up to 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 up to 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 I 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 health-related quality of life and side effects were systematically shortened because they were only recorded for the period of treatment with the study medication (plus up to 128 days or 100 days).

However, to draw a reliable conclusion on the total study period or the time to patient death, it would also be necessary to record these outcomes for the total period, as was done for survival.

Table 9 shows the patient characteristics of the included study.

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

Study **Characteristic** **Category**	**nivolumab** **N[a] = 532**	**Placebo** **N[a] = 262**
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)
Gastro-oesophageal 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)

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

Study **Characteristic** **Category**	**nivolumab** **N[a] = 532**	**Placebo** **N[a] = 262**
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)
Pathologic tumour 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, n (%)		
≥ 1%	89 (17)	40 (15)
< 1%	374 (70)	196 (75)
Indeterminate/non-evaluable	69 (13)	26 (10)
HER2 tumour expression status at baseline, n (%)		
Positive	41 (8)	22 (8)
Negative	131 (25)	76 (29)
Unknown	2 (< 1)	0 (0)
Not reported	358 (67)	164 (63)
Treatment discontinuation[e], n (%)	272 (51)	144 (55)
Study discontinuation[f], n (%)	527 (99)	258 (99)

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 [3] used for study inclusion.
d. According to Siewert-Stein [16].
e. Frequent reasons for treatment discontinuation in the intervention arm vs. the control arm (percentages refer to randomized patients): disease recurrence (29% vs. 44%), toxicity (11% vs. 3%), patient request (6% vs. 2%). This includes 0% vs. < 1% of patients who never started treatment. Furthermore, 49% vs. 45% of the patients completed treatment as planned. The data also include patients who died during treatment with the study medication (intervention arm: < 1% vs. control arm: < 1%).
f. Frequent reasons for study discontinuation in the intervention arm vs. the control arm (percentages refer to randomized patients): not provided (39% vs. 35%), withdrawal of consent (6% vs. 4%), lost to follow-up (2% vs. 2%). The data additionally include patients who died during the course of the study (intervention arm: 52% vs. control arm: 59%).

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

Study Characteristic Category	nivolumab N[a] = 532	Placebo N[a] = 262
AJCC: American Joint Committee on Cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; HER2: human epidermal growth factor receptor 2; M: male; n: number of patients in the category; N: number of randomized patients; 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. The majority of patients had adenocarcinoma (71%) and 29% had squamous cell carcinoma. The carcinoma was located in the oesophagus in approx. 58% of patients and in the gastro-oesophageal junction in approx. 42%. Just over 50% of patients in both study arms discontinued therapy. In both treatment arms, the most frequent reasons for treatment discontinuation were disease recurrence (intervention arm: 29% versus control arm: 44%), followed by toxicity (11% versus 3%) and patient request (6% versus 2%).

Information on the course of the study

Table 10 shows the patients' mean/median treatment duration 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/outcome**	**nivolumab** **N = 532**	**Placebo** **N = 262**
CA209-577		
Treatment duration[a] [months]		
Median [min; max]	10.83 [< 0.1; 14.2]	8.99 [< 0.1; 15.0]
Mean (SD)	7.66 (ND)	7.71 (ND)
Observation period[b] [months]		
Overall survival, recurrences		
Median [min; max]	78.29 [60.1; 98.8]	78.39 [61.7; 96.7]
Mean (SD)	ND	
Health-related quality of life	ND	
Side effects	ND	

a. Based on patients who received at least one dose of the study medication (nivolumab arm N = 532; placebo arm N = 260).
b. Time between randomization and final data cut-off (7 November 2024).

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

At around 11 months, the median treatment duration in the intervention arm of the CA209-577 study was only slightly longer than in the control arm, where it was around 9 months. The median observation periods for the outcomes of overall survival and recurrences were comparable between the treatment arms (about 78 months). In Module 4 P of its dossier, the company again did not provide any information on the observation period for the outcome health status (morbidity) and for outcomes in the categories health-related quality of life and side effects (see also [17]).

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 (multipage table)

Study **Drug class** **Drug**	**Patients with subsequent therapy n (%)[a]**	
	Intervention **N = 532**	**Comparison** **N = 262**
CA209-577		
Patients with recurrence	285 (53.6)[b]	169 (64.5)[b]
Subsequent therapies in total[c]	245 (86.0)	156 (92.3)
Radiotherapy	83 (29.1)	68 (40.2)
Surgical intervention	61 (21.4)	37 (21.9)
Systemic therapy	199 (69.8)	132 (78.1)
Immunotherapy	29 (10.2)	39 (23.1)
Anti-PD-1	27 (9.5)	36 (21.3)
nivolumab	20 (7.0)	20 (11.8)
pembrolizumab	9 (3.2)	16 (9.5)
Anti-PDL-1	1 (0.4)	3 (1.8)
avelumab	0 (0)	3 (1.8)
Targeted therapy	30 (10.5)	23 (13.6)
ramucirumab	30 (10.5)	22 (13.0)
trastuzumab	21 (7.4)	16 (9.5)
Chemotherapy	197 (69.1)	127 (75.1)
capecitabine	38 (13.3)	29 (17.2)
carboplatin	14 (4.9)	13 (7.7)
cisplatin	37 (13.0)	20 (11.8)
docetaxel	16 (5.6)	10 (5.9)
fluorouracil	120 (42.1)	79 (46.7)
fluorouracil/leucovorin/oxaliplatin	16 (5.6)	9 (5.3)
gimeracil/oteracil/tegafur	8 (2.8)	3 (1.8)
Investigational antineoplastic drugs	8 (2.8)	8 (4.7)
irinotecan	36 (12.6)	26 (15.4)
oxaliplatin	113 (39.6)	73 (43.2)
paclitaxel	59 (20.7)	45 (26.6)
Not allocated	79 (27.7)	56 (33.1)
folinic acid	0 (0)	3 (1.8)
folic acid	9 (3.2)	5 (3.0)
leucovorin	52 (18.2)	34 (20.1)

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

Study Drug class Drug	Patients with subsequent therapy n (%)[a] Intervention N = 532	 Comparison N = 262

a. Institute's calculation; based on patients with recurrence (local recurrence, regional recurrence and distant metastases).
b. Discrepancy between information in Module 4 and Module 5 of the dossier. The data presented are from Module 4. Data in the clinical study report: patients with recurrence 282 (53.0%) vs. 168 (64.1%)
c. A patient may have received more than one type of subsequent therapy.

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. A total of 86% of patients with recurrence received subsequent therapy in the intervention arm of CA209-577, compared with around 92% in the control arm. Systemic therapy was the most common treatment in both study arms, with the proportion in the control arm (approx. 78% of patients with recurrence) being higher than in the intervention arm (approx. 70%). The majority of these patients received chemotherapy. Immunotherapy was used in about 10% of patients with recurrence in the intervention arm and in about 23% in the control arm. In both study arms, fewer than 10% of patients with recurrence received treatment with trastuzumab. In addition to systemic therapy, local procedures such as radiotherapy and/or surgery were also used as subsequent therapy.

Most recurrences were distant metastases (intervention arm: 72% versus control arm: 75%), but there was no information on the distribution of squamous cell carcinomas and adenocarcinomas. Depending on the PD-L1 status, the guidelines recommend chemotherapy, chemotherapy in combination with the immunotherapies pembrolizumab or nivolumab or a combination of nivolumab and ipilimumab for the first-line treatment of advanced squamous cell carcinoma that cannot be curatively treated [11,12]. According to the ESMO guideline, chemotherapy in combination with tislelizumab can also be used [10]. The first-line treatment of advanced adenocarcinoma that cannot be curatively treated is based on PD-L1 and human epidermal growth factor receptor 2 (HER2) status. While chemotherapy in combination with trastuzumab is recommended for HER2-positive adenocarcinomas, HER2-negative adenocarcinomas should be treated with chemotherapy or chemotherapy in combination with pembrolizumab or nivolumab, depending on their PD-L1 status, according to the guidelines [11,12]. In addition, local procedures can also be considered as subsequent therapy.

The guideline recommendations for the use of immunotherapies and HER2-targeted therapy with trastuzumab are based on described advantages in overall survival – in each case

compared with chemotherapy [12]. In various procedures concerning the given treatment situation, the G-BA determined indications of considerable added benefit for nivolumab (in combination with chemotherapy or ipilimumab) [18-20].

The extent of subsequent therapies used and the proportion of patients receiving chemotherapy in the CA209-577 study appeared appropriate. The predominant use of platinum compounds and fluorouracil also reflected the guideline recommendations. No information on the biomarkers PD-L1 or HER2 status at the time of subsequent therapy was available in the dossier. However, this information would be necessary to estimate the proportion of patients who would have been eligible for immunotherapy or targeted therapy with trastuzumab in accordance with the guideline recommendations. Therefore, the PD-L1 and HER2 tumour expression status at baseline were considered as an approximation.

The use of immunotherapy as subsequent therapy in case of a positive PD-L1 status would have been particularly beneficial for patients in the control arm, as they had not yet received any immunotherapy. At the time of study inclusion, 15% of patients in the control arm had a PD-L1 status ≥ 1%. Based on the information available, it cannot be assumed that the use of immunotherapies as subsequent therapy in the study deviated to a relevant extent from the guideline recommendations.

According to the S3 guideline, the HER2 status should be determined before palliative systemic therapy of adenocarcinoma [12]. In the CA209-577 study, the proportion of HER2-positive carcinomas was around 8% at the time of study inclusion. In most patients, however, the HER2 status was unknown or not reported (66% in total). No information was available on whether further molecular diagnostics were performed after recurrence. It was therefore unclear whether all patients who could have benefited from a subsequent therapy directed against HER2 actually received such therapy.

Despite the uncertainties described, the subsequent therapies used in the CA209-577 study were largely 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	Absence of other 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 was rated as low for CA209-577.

Transferability of the study results to the German health care context

The company considered the results of the CA209-577 study to be transferable to the German health care context. It justified this assessment with the good comparability with the target population in Germany in terms of demographic and disease-specific characteristics.

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

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
  - Overall survival
- Morbidity
  - Recurrence
  - Health status, recorded using the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
  - measured using the FACT-E total score
- Side effects
  - Serious adverse events (SAEs)
  - Severe AEs, operationalized as Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3
  - Discontinuation due to AEs
  - Immune-mediated AEs (SAEs and severe AEs)
  - Other specific AEs, if any

The selection of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4).

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-mediated SAEs[c]	Immune-mediated severe AEs[b, c]	Skin and subcutaneous tissue disorders (PT, AEs)	Infections and infestations (SOC, severe AEs[b])	Blood and lymphatic system disorders (SOC, severe AEs[b])
CA209-577	Yes	Yes	Yes	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.

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 outcome of recurrence

The outcome of recurrence was a composite outcome and included the components of local recurrence, regional recurrence, distant metastases and death (without recurrence). The results of the operationalizations 'proportion of patients with recurrence' (hereinafter referred to as 'recurrence rate') and 'disease-free survival' are presented for the outcome of recurrence.

According to the study protocol, the diagnosis of recurrence was based on cytological/pathological findings and/or imaging techniques as evaluated by the investigator. Although Amendment 05 of the study protocol (24 August 2016) provided for the option of a blinded independent central review (BICR) at the discretion of the sponsor, the company's dossier only contained evaluations by the investigator. The EMA explicitly recommends assessment using BICR, particularly for oncological studies whose treatment arms have different toxicity profiles, and criticized the lack of a BICR in the European Public Assessment Report on nivolumab [21,22].

It should be noted that, despite the blinding in the CA209-577 study, due to the toxicity profile of nivolumab, the investigator might have recognized the treatment group some of the

patients were assigned to, which could have influenced the recording of the outcome recurrence. Overall, however, it was not assumed that this was the case for a relevant proportion of patients.

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 Functional Assessment of Cancer Therapy-Esophageal (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 were 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. In Module 4 P, the company again did not provide any information on the outcome-specific observation period. However, based on the available information on treatment and observation period (Table 10), the planned follow-up (Table 8) and the comparable response rates to the questionnaires between the arms, it was assumed that the median observation periods for the EQ-5D VAS and the FACT-E were sufficiently comparable between the treatment arms. In situations with comparable observation periods, definitive deterioration can be a suitable operationalization. However, further methodological aspects must be taken into account, which are described below.

Operationalization of definitive deterioration

The company operationalized definitive deterioration 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 or without subsequent recordings. Accordingly, patients for whom no data were available after an initial deterioration were also rated as having definite deterioration. In the previous benefit assessment procedure for this therapeutic indication [17], the company had not presented any information on how many patients with a first deterioration and without any further data were assessed as having a definitive deterioration. For the present benefit assessment, however, the company presented relevant data in Module 4 P.

The information on the outcome health status (EQ-5D VAS) in the company's dossier showed that the majority (approx. 59%) of patients with a result in the intervention arm were included in the analysis with a single deterioration at the last available recording without subsequent recording (due to death or other reasons); in the control arm, the figure was 55.0%. While it

could be assumed that patients who died after a single deterioration had confirmed deterioration, this was unclear in cases without subsequent recording for reasons other than death. The latter applied to a comparable proportion of patients with event in both study arms (intervention arm: 35% versus control arm: 28%).

The analyses of the FACT-E also included mostly patients with event in both study arms for whom no more data were available after a single deterioration (intervention arm: 63% versus control arm: 70%). While the proportions of missing data due to death and other reasons were comparable in the intervention arm, the proportion of deceased patients clearly predominated in the control arm, at 60.0%. Consequently, the proportion of patients with a single deterioration at the last available recording without subsequent recordings for reasons other than death was higher in the intervention arm than in the control arm (30% versus 13%).

Overall, the analyses presented for the EQ-5D VAS and FACT-E included a relevant number of patients with a single deterioration. It was therefore not appropriate to speak of a 'definitive deterioration' in this situation. Rather, the operationalization chosen by the company represented a combination of single deterioration and confirmed deterioration. Due to the shortened observation period of both outcomes compared with the total observation period, conclusions could only be drawn about the shortened observation period.

Response criteria

The responder analyses were not prespecified for the outcomes health status (EQ-5D VAS) and health-related quality of life (FACT-E) in the study protocol. The company used a deterioration of at least 15% of the respective scale range of the instrument as the response criterion. This meets the requirements for response criteria for reflecting with sufficient certainty a change that is perceivable for patients, as described in the General Methods of the Institute [1].

Summary

Despite the limitations described above, the responder analyses presented by the company for the outcomes EQ-5D VAS and FACT-E were used for the benefit assessment to represent the deterioration that occurred over the shortened observation period.

Notes on the side effect outcomes

Types of analysis

The company again presented only time-to-event analyses for all side effects outcomes. Time-to-event analyses are of particular relevance in group comparisons with different mean observation periods [1]. However, due to the comparable treatment durations (see Table 10), it was assumed in the given situation that the observation periods (see Table 8) between the study arms were also comparable. In the assessment of side effects, the number of patients

in whom an event occurred is primarily relevant. 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, this assessment, like the first assessment, used the relative risk (RR).

Immune-mediated AEs, immune-mediated severe AEs and immune-mediated SAEs

In Appendix 4 G of the dossier, the company provided supplementary analyses on AEs of special interest predefined in the statistical analysis plan (immune-mediated AEs, select AEs and further AEs of special interest). In addition, analyses of severe events (operationalized as CTCAE grade ≥ 3) and serious events were available for these outcomes. In the dossier, the company stated that the AEs of special interest it referred to as immune-mediated AEs, with the exception of endocrine immune-mediated AEs, were events requiring immunomodulatory therapy. This operationalization was unsuitable for fully representing immune-mediated AEs. The outcome of AEs of special interest, which the company referred to as 'select AEs', however, was a selection of Preferred Terms (PTs) that are typical immune-mediated AEs and that could require immunosuppressant treatment (e.g. with corticosteroids), but not necessarily so. In addition, it presented the list of PTs that were included as events in the analysis of the "select AEs".

In addition to the operationalization using select AEs, the outcome referred to by the company as AE of special interest also potentially included other immune-mediated PTs (e.g. in particular myocarditis, uveitis, rhabdomyolysis and pancreatitis). It would therefore make sense to consider both the PTs of the PT collection referred to by the company as select AEs and those of the AEs of special interest in the analyses of immune-mediated AEs. In the given data situation, however, only few events occurred in this category. Therefore, the company's approach remained without consequence for this benefit assessment. Overall, the company's operationalization of the select AEs was considered a sufficient approximation to the immune-mediated AEs and was used for the benefit assessment. Both severe AEs (CTCAE grade ≥ 3) and SAEs were considered.

I 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-mediated SAEs[c]	Immune-mediated severe AEs[b, c]	Skin and subcutaneous tissue disorders (SOC, AEs)	Infections and infestations (SOC, severe AEs[b])	Blood and lymphatic system disorders (SOC, severe AEs[b])
CA209-577	L	L	L	H[d]	H[d]	H[d]	H[d]	L[e]	H[d]	H[d]	H[d]	H[d]	H[d]

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. Incomplete observations for potentially informative reasons.
e. 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

For the results of the outcomes of overall survival and recurrence, the risk of bias was assessed as low in each case. The risk of bias of the results of the outcomes health status (EQ-5D VAS), health-related quality of life (FACT-E) and all results of outcomes in the side effects category, except discontinuation due to AEs, was assessed as high despite comparable observation periods. This was due to incomplete observations for potentially informative reasons, as the discontinuation of observation for these outcomes was linked to the end of treatment with the study medication. The observation period was thus controlled by treatment discontinuation, which was largely determined by disease progression.

Although the risk of bias for the outcome discontinuation due to AEs was low, the certainty of results for this outcome was limited. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome discontinuation due to AEs to be recorded. This means that, although AEs that would have led to discontinuation of therapy may occur after discontinuation for other reasons, the criterion of ‘discontinuation’ is no longer applicable to them. It was impossible to estimate how many AEs this affected.

I 4.3 Results

Table 15 and Table 16 summarize the results of the comparison of nivolumab with placebo in adult patients with oesophageal or gastro-oesophageal 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.

The available Kaplan-Meier curves on the presented time-to-event analyses can be found in I Appendix B of the full dossier assessment. Results on common AEs, SAEs, severe AEs, and discontinuations due to AEs are presented in I Appendix C of the full dossier assessment. A list of the occurred categories of immune-mediated AEs, immune-mediated severe AEs (CTCAE grade ≥ 3) and immune-mediated SAEs is presented as supplementary information in I Appendix D of the full dossier assessment.

Table 15: Results (mortality and morbidity, time-to-event) – 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**
CA209-577					
Mortality					
Overall survival	532	51.71 [41.03; 61.63] 299 (56.2)	262	35.25 [30.72; 48.76] 162 (61.8)	0.85 [0.70; 1.03]; 0.106[a]
Morbidity					
Recurrence					
Recurrence rate	532	– 334 (62.8)[b]	262	– 185 (70.6)[b]	RR: 0.89 [0.81; 0.98][c]; 0.030[d]
Local recurrence	532	– 39 (7.3)	262	– 15 (5.7)	–
Regional recurrence	532	– 41 (7.7)[b]	262	– 27 (10.3)	–
Distant metastases	532	– 205 (38.5)[b]	262	– 127 (48.5)[b]	–
Death without recurrence	532	– 49 (9.2)[b]	262	– 16 (6.1)[b]	–
Disease-free survival	532	21.26 [16.62; 29.50] 334 (62.8)[b]	262	10.81 [8.31; 14.32] 185 (70.6)[b]	0.76 [0.63; 0.91]; 0.003[a]
Health status (EQ-5D VAS – time to first deterioration[e, f])	497	NA [50.92; NC] 106 (21.3)	247	NA 40 (16.2)	1.30 [0.90; 1.88]; 0.160[a]

Table 15: Results (mortality and morbidity, time-to-event) – RCT, direct comparison: nivolumab vs. placebo (multipage table)

Study Outcome category Outcome	nivolumab N	nivolumab Median time to event in months [95% CI] Patients with event n (%)	Placebo N	Placebo Median time to event in months [95% CI] Patients with event n (%)	nivolumab vs. placebo HR [95% CI]; p-value
Health-related quality of life					
FACT-E (time to deterioration[g, f])	484	NA 40 (8.3)	248	NA 20 (8.1)	1.02 [0.60; 1.75][a]; 0.956[h]
Physical wellbeing	495	NA 80 (16.2)	250	NA 38 (15.2)	1.14 [0.77; 1.68][a]
Social/family wellbeing	495	18.00 [16.85; NC] 65 (13.1)	250	NA [15.90; NC] 31 (12.4)	1.03 [0.67; 1.60][a]
Emotional wellbeing	492	NA [16.16; NC] 85 (17.3)	249	NA 37 (14.9)	1.20 [0.81; 1.77][a]
Functional wellbeing	493	16.46 [16.16; NC] 87 (17.6)	249	NA [16.13; NC] 35 (14.1)	1.22 [0.82; 1.82][a]
Oesophageal cancer subscale	494	NA 59 (11.9)	249	NA [57.10; NC] 32 (12.9)	1.01 [0.65; 1.57][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. Discrepancy between information in the company's dossier. The deviations have no impact on the effect estimate for disease-free survival. Data in the clinical study report: recurrence rate 329 (61.8%) vs. 183 (69.8%), regional recurrence rate 39 vs. 27, distant metastases 204 vs. 126, death without recurrence 47 vs. 15.
c. 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.
d. Institute's calculation (unconditional exact test [23]).
e. A score decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
f. The operationalization represents a combination of single deterioration and confirmed deterioration (see Section I 4.1).
g. A score decrease by ≥ 26.4 points from baseline is considered a clinically relevant deterioration (scale range: 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.

CI: confidence interval; FACT-E: Functional Assessment of Cancer Therapy-Esophageal; HR: hazard ratio; IRT: interactive response technology; n: number of patients with event (at least one); N: number of analysed patients; PD-L1: programmed cell death-ligand 1; RCT: randomized controlled trial; RR: relative risk; VAS: visual analogue scale; ypN: pathologic lymph node status after neoadjuvant therapy

Table 16: Results (side effects, dichotomous) – 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	515 (96.8)	260	241 (92.7)	–
SAEs[b]	532	175 (32.9)	260	82 (31.5)	1.04 [0.84; 1.30]; 0.736
Severe AEs[b, c]	532	220 (41.4)	260	95 (36.5)	1.13 [0.94; 1.37]; 0.196
Discontinuation due to AEs[b]	532	74 (13.9)	260	16 (6.2)	2.26 [1.34; 3.81]; 0.001
Immune-mediated AEs (supplementary information)	532	379 (71.2)	260	144 (55.4)	–
Immune-mediated SAEs	532	36 (6.8)	260	8 (3.1)	2.20 [1.04; 4.66][d]; 0.034
Immune-mediated severe AEs[c]	532	48 (9.0)	260	14 (5.4)	1.68 [0.94; 2.98][d]; 0.090
Skin and subcutaneous tissue disorders (SOC, AEs)	532	209 (39.3)	260	62 (23.8)	1.65 [1.29; 2.10][d]; < 0.001
Infections and infestations (SOC, severe AEs[c])	532	45 (8.5)	260	10 (3.8)	2.20 [1.13; 4.30][d]; 0.017
Blood and lymphatic system disorders (SOC, severe AEs[c])	532	20 (3.8)	260	2 (0.8)	4.89 [1.15; 20.75][d]; 0.017

a. Institute's calculation (unconditional exact test, CSZ method according to [citation]).
b. Without progression of the underlying disease (several PTs of the SOC 'neoplasms benign, malignant and unspecified [including cysts and polyps]' according to the company's list).
c. Operationalized as CTCAE grade ≥ 3.
d. Institute's calculation of RR and CI (asymptotic).

AE: adverse event; CI: confidence interval; 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; RR: relative risk; SAE: serious adverse event

On the basis of the available information, at most indications, e.g. of an added benefit, can be determined for the outcomes of overall survival and recurrence; for all other outcomes, 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.

Mortality

There was no statistically significant difference between the treatment arms for the outcome overall survival. There is therefore no hint of an 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 disease-free survival), a statistically significant difference in favour of nivolumab in comparison with placebo was shown for both operationalizations. There is therefore an indication of an added benefit of nivolumab in comparison with watchful waiting.

Health status (EQ-5D VAS)

No statistically significant difference between the treatment arms was shown for health status, recorded using the EQ-5D VAS. There was an effect modification for the characteristic of sex, however (see Section I 4.4). For men, there is a hint of greater harm of nivolumab in comparison with watchful waiting. For women, there is a hint of an added benefit of nivolumab in comparison with watchful waiting.

Health-related quality of life

No statistically significant difference between treatment arms was found for the outcome of health-related quality of life, recorded using the FACT-E. There is therefore no hint of an 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, there is therefore no hint of greater or lesser harm of 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. There is therefore a hint of greater harm of nivolumab in comparison with watchful waiting.

Specific AEs

Immune-mediated SAEs

A statistically significant difference to the disadvantage of nivolumab compared with placebo was shown for the outcome of immune-mediated SAEs. There is therefore a hint of greater harm of nivolumab in comparison with watchful waiting.

Immune-mediated severe AEs

There was no statistically significant difference between the treatment arms for the outcome of immune-mediated severe AEs. There is therefore no hint of greater or lesser harm of nivolumab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Skin and subcutaneous tissue disorders (AEs), 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 skin and subcutaneous tissue disorders (AEs), infections and infestations (severe AEs) and blood and lymphatic system disorders (severe AEs). In each case, there is therefore a hint of greater harm of nivolumab in comparison with watchful waiting.

I 4.4 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account for this 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.

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

For the outcome category of side effects, the company considered the time to event, using the hazard ratio (HR) as the effect measure. The subgroup analyses conducted by the company for this outcome category were also based on the HR. In contrast to the approach of the company, this assessment used analyses of the number of patients with event with the RR effect measure for the side effect outcomes to derive the added benefit. Analyses based on the RR were therefore also preferable for the subgroup analyses. This benefit assessment therefore examined whether, using the HR, there was a significant effect modification at the 0.2 level. If this was the case, an interaction test was performed using the Q test, based on the RR.

The results are presented in Table 17. The Kaplan-Meier curves on the subgroup results are presented in I Appendix B of the full dossier assessment.

Table 17: Subgroups (morbidity, time to event) – RCT, direct comparison: nivolumab vs. placebo

Study Outcome Characteristic Subgroup	nivolumab N	nivolumab Median time to event in months [95% CI] Patients with event n (%)	Placebo N	Placebo Median time to event in months [95% CI] Patients with event n (%)	nivolumab vs. placebo HR [95% CI][a]	nivolumab vs. placebo p-value[a]
CA209-577						
Health status (EQ-5D VAS – time to deterioration[b])						
Sex						
Male	418	NA [50.63; NC] 97 (23.2)	212	NA 29 (13.7)	1.77 [1.17; 2.68]	0.008
Female	79	NA [48.66; NC] 9 (11.4)	35	NA [27.01; NC] 11 (31.4)	0.31 [0.13; 0.75]	0.014
Total					Interaction[c]:	< 0.001

a. Cox model adjusted for value at baseline.
b. An EQ-5D VAS score decrease of ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
c. Based on Cox model adjusted for baseline value, subgroup and treatment*subgroup interaction term.

CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; VAS: visual analogue scale

Morbidity

Health status (EQ-5D VAS)

There was an effect modification by the characteristic of sex for the outcome of health status, recorded using the EQ-5D VAS.

A statistically significant difference to the disadvantage of nivolumab compared with placebo was shown for men. There was a hint of greater harm from nivolumab in comparison with watchful waiting.

A statistically significant difference in favour of nivolumab in comparison with placebo was shown for women. There is a hint of an added benefit of nivolumab in comparison with watchful waiting.

I 5 Probability and extent of added benefit

The probability and extent of 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 IQWiG General Methods [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.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Chapter I 4 (see Table 18).

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

For the following symptom outcome(s), it could not be inferred from the dossier whether they were serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Recurrence

The outcome of recurrence was 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 was a component of the outcome of recurrence.

Health status (EQ-5D VAS)

For the outcome health status (recorded using the EQ-5D VAS), insufficient information was available to allow a severity category classification of serious or severe. This outcome was therefore assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Discontinuation due to AEs

The outcome of discontinuation due to AEs was assigned to the outcome category of serious/severe side effects. The information provided by the company in Appendix 4 G showed that more than 50% of the AEs that led to treatment discontinuation were CTCAE grade ≥ 3 events.

Table 18: Extent of added benefit at outcome level: nivolumab vs. watchful waiting (multipage table)

Outcome category **Outcome** **Subgroup**	**nivolumab vs. watchful waiting** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	51.71 vs. 35.25 months HR: 0.85 [0.70; 1.03]; p = 0.106	Lesser benefit/added benefit not proven
Morbidity		
Recurrence		Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Added benefit, extent: “minor”
Recurrence rate	62.8% vs. 70.6% RR: 0.89 [0.81; 0.98]; p = 0.030 Probability: indication	
Disease-free survival	21.26 vs. 10.81 months HR: 0.76 [0.63; 0.91]; p = 0.003 Probability: indication	
Outcomes with shortened observation period		
Morbidity		
Health status (EQ-5D VAS – time to deterioration)		
Sex		
Male	NA vs. NA HR: 1.77 [1.17; 2.68]; HR: 0.56 [0.37; 0.85][c]; p = 0.008 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Lesser benefit, extent: “minor”
Female	NA vs. NA HR: 0.31 [0.13; 0.75]; p= 0.014 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ Added benefit, extent: considerable
Health-related quality of life		
FACT-E (time to deterioration)	NA vs. NA HR: 1.02 [0.60; 1.75]; p = 0.956	Lesser benefit/added benefit not proven

Table 18: Extent of added benefit at outcome level: nivolumab vs. watchful waiting (multipage table)

Outcome category **Outcome** **Subgroup**	**nivolumab vs. watchful waiting** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Side effects		
SAE	32.9% vs. 31.5% RR: 1.04 [0.84; 1.30]; p = 0.736	Greater/lesser harm not proven
Severe AEs	41.1% vs. 36.5% RR: 1.13 [0.94; 1.37]; p = 0.196	Greater/lesser harm not proven
Discontinuation due to AEs	13.9% vs. 6.2% RR: 2.26 [1.34; 3.81]; RR: 0.44 [0.26; 0.746][c]; p = 0.001 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: major
Immune-mediated SAEs	6.8% vs. 3.1% RR: 2.20 [1.04; 4.66]; RR: 0.45 [0.21; 0.96][c]; p = 0.034 Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: minor
Immune-mediated severe AEs	9.0% vs. 5.4% RR: 1.68 [0.94; 2.98]; p = 0.090	Greater/lesser harm not proven
Skin and subcutaneous tissue disorders (AEs)	39.3% vs. 23.8% RR: 1.65 [1.29; 2.10]; RR: 0.61 [0.48; 0.78][c]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: considerable
Infections and infestations (severe AEs)	8.5% vs. 3.8% RR: 2.20 [1.13; 4.30]; RR: 0.45 [0.23; 0.88][c]; p = 0.017 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)	3.8% vs. 0.8% RR: 4.89 [1.15; 20.75]; RR: 0.20 [0.05; 0.87][c]; p = 0.017 Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm, extent: considerable

Table 18: Extent of added benefit at outcome level: nivolumab vs. watchful waiting (multipage table)

Outcome category **Outcome** **Subgroup**	**nivolumab vs. watchful waiting** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category and the scale of the outcome, the effect size is estimated with different limits based on the upper limit of the confidence interval (CI_u). c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit. d. If the CI for the SMD is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived. AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; FACT-E: Functional Assessment of Cancer Therapy-Esophageal; HR: hazard ratio; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale		

I 5.2 Overall conclusion on added benefit

Table 19 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 19: Positive and negative effects from the assessment of nivolumab in comparison with watchful waiting

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Morbidity Serious/severe symptoms/late complications ▪ Recurrence: indication of an added benefit – extent: minor	–
Outcomes with shortened observation period	
Morbidity Non-serious/non-severe symptoms/late complications ▪ Health status (EQ-5D VAS) ▫ Sex (female) hint of an added benefit – extent: considerable	Morbidity Non-serious/non-severe symptoms/late complications ▪ Health status (EQ-5D VAS) ▫ Sex (male) hint of lesser benefit – extent: minor
–	Serious/severe side effects ▪ Discontinuation due to AEs: hint of greater harm – extent: major ▪ Infections and infestations (severe AEs), blood and lymphatic system disorders (severe AEs): hint of greater harm – extent considerable ▪ Immune-mediated SAEs: hint of greater harm – extent: minor
	Non-serious/non-severe side effects ▪ Skin and subcutaneous tissue disorders (AEs): hint of greater harm – extent: considerable
AE: adverse event; SAE: serious adverse event; VAS: visual analogue scale	

Overall, both positive and negative effects of nivolumab were shown in comparison with the ACT.

On the side of positive effects, there is an indication of a minor added benefit for the outcome recurrence, although the extent decreased compared with the 2nd data cut-off (4 January 2021). However, the advantage in this outcome is not apparent in a statistically significant advantage in the outcome overall survival.

On the other hand, there are hints of greater harm of differing, in some cases major extent for numerous outcomes in the side effects category.

In summary, there is no hint of an added benefit of nivolumab versus watchful waiting for adult patients with oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant CRT; an added benefit is therefore not proven.

The result of the assessment of the added benefit of nivolumab in comparison with the ACT is summarized in Table 20.

Table 20: Nivolumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy[b]	Watchful waiting	Added benefit not proven[c]

a. Presented is the 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 [3]) after neoadjuvant chemoradiotherapy with R0 resection and residual pathologic disease. Since only patients with complete resection were included, the G-BA assumes that patients with ≥ R1 resection are not covered 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; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit of nivolumab in comparison with the ACT.

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

I 6 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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