IQWiG Reports – Commission No. A21-146

Nivolumab (gastric, gastrooesophageal junction or oesophageal adenocarcinoma) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Nivolumab (Adenokarzinome des Magens, des gastroösophagealen Übergangs oder des Ösophagus) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 25 February 2022). 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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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
5-FU	5-fluorouracil
ACT	appropriate comparator therapy
AE	adverse event
CPS	combined positive score
CTCAE	Common Terminology Criteria for Adverse Events
DBL	database lock
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-Ga	Functional Assessment of Cancer Therapy-Gastric
FISH	fluorescence in situ hybridization
FOLFOX	5-fluorouracil + folinic acid + oxaliplatin
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GaCS	gastric cancer subscale
HER2	human epidermal growth factor receptor 2
IHC	immunohistochemistry
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ISH	in situ hybridization
MedDRA	Medical Dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network
NGS	next generation sequencing
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
TPS	Tumour Proportion Score
XELOX	capecitabine + oxaliplatin

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 19 November 2021.

Research question

The aim of the present report is the assessment of the added benefit of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy in comparison with the appropriate comparator therapy (ACT) as first-line treatment of adult patients with human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic gastric, gastrooesophageal junction or oesophageal adenocarcinoma whose tumours express programmed cell death ligand 1 (PD-L1, combined positive score [CPS] ≥ 5).

The research questions shown in Table 2 result from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy

Research question	Subindication	ACT[a, b]
1	Adults with locally advanced or metastatic HER2-negative oesophageal adenocarcinoma that cannot be treated curatively and whose tumours express PD-L1 (CPS ≥ 5); first-line treatment	Treatment of physician's choice[c]
2	Adults with locally advanced or metastatic HER2-negative gastric or gastrooesophageal junction adenocarcinoma that cannot be treated curatively and whose tumours express PD-L1 (CPS ≥ 5); first-line treatment	▪ Cisplatin in combination with 5-fluorouracil ± folinic acid or ▪ cisplatin in combination with capecitabine or ▪ oxaliplatin in combination with 5-fluorouracil ± folinic acid[d] or ▪ oxaliplatin in combination with capecitabine or ▪ 5-fluorouracil ± folinic acid + oxaliplatin + docetaxel[e] (only for patients in good general condition and without relevant comorbidities)

a. Presented is the respective ACT specified by the GBA.
b. It is assumed for the present therapeutic indication that curative treatment with definitive radiochemotherapy is not an option for patients with unresectable cancer.
c. Guidelines mention several platinum- and fluoropyrimidine-based combination chemotherapies: S-1 (tegafur/gimeracil/oteracil) + cisplatin or capecitabine + cisplatin [XP], 5-fluorouracil+ cisplatin, 5-fluorouracil + oxaliplatin + folinic acid [FLO and FOLFOX], capecitabine + oxaliplatin, infusional 5-fluorouracil + folinic acid + cisplatin [PLF], epirubicin + cisplatin + capecitabine [ECX], epirubicin + oxaliplatin + capecitabine [EOX], epirubicin + cisplatin + infusional 5-fluorouracil [ECF], docetaxel + cisplatin + infusional 5-fluorouracil [DCF], 5-fluorouracil + oxaliplatin + epirubicin, infusional 5-fluorouracil + folinic acid + oxaliplatin + docetaxel [FLOT regimen]. However, only the drugs 5-fluorouracil and cisplatin are approved in the present therapeutic indication. There is a discrepancy between the drugs approved in the therapeutic indication and those recommended in guidelines. In the context of treatment of physician's choice, the G-BA considered the treatment options cited above to be suitable comparators.
d. According to the G-BA, the combination of infusional 5-fluorouracil + folinic acid + oxaliplatin (FLO and FOLFOX) is comprised by the ACT.
e. According to the G-BA, the combination of infusional 5-fluorouracil + folinic acid + oxaliplatin + docetaxel (FLOT) is comprised by the ACT.

ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; PD-L1: programmed cell death ligand 1

In the present benefit assessment, the following terms are used for the patient populations of the 2 research questions:

- Research question 1: oesophageal adenocarcinoma
- Research question 2: gastric or gastrooesophageal junction adenocarcinoma

The company initially followed the G-BA's specification of the ACT for both research questions. For research question 1, however, it additionally considered pembrolizumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy to be a relevant treatment option in the context of treatment of physician's choice, which was only approved after the specification of the ACT, according to the company. The company stated that it had chosen FOLFOX (5-fluorouracil [5-FU] + folinic acid + oxaliplatin) and XELOX (capecitabine + oxaliplatin) from the mentioned treatment options for both research questions.

Concurring with the G-BA's specification, the present assessment is conducted for research questions 1 and 2, each in comparison with the ACT specified by the G-BA. In accordance with this specification, pembrolizumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy is not part of the ACT.

Since the company considered all treatment options of the ACT for both research questions in its study search and selection and did not consider pembrolizumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy in the study selection, and the check of the completeness of the study pool did not reveal any additional relevant studies, the choice of the company has no consequences for the assessment.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

Study pool

For the benefit assessment of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy, the CheckMate 649 study is included, which compared the combination of nivolumab + chemotherapy (FOLFOX or XELOX) with chemotherapy (FOLFOX or XELOX). Due to its design and the patients included, the CheckMate 649 study is generally suitable for the derivation of conclusions on the added benefit of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy for the research questions 1 and 2 on the basis of subpopulations. However, the results of the study presented by the company in the dossier are incomplete in terms of content. An adequate assessment of the study data is therefore not possible, so that the results of the corresponding subpopulation of the CheckMate 649 study are not used in the benefit assessment for research question 1, and for research question 2 in the present situation only due to the large effect in overall survival.

Research questions 1 and 2

Study characteristics

The CheckMate 649 study is an ongoing, open-label RCT comparing nivolumab in combination with 2 different fluoropyrimidine- and platinum-based combination chemotherapy regimens, FOLFOX (5-FU + folinic acid + oxaliplatin) or XELOX (capecitabine + oxaliplatin), against FOLFOX or XELOX. It included adult patients with inoperable, (locally) advanced or

metastatic gastric, gastrooesophageal junction or distal oesophageal adenocarcinoma, without known positive HER2 status of their tumour, who have not yet received systemic therapy for advanced disease. Patients had to be in good general condition at study entry, corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.

The 2 relevant study arms, nivolumab + chemotherapy (FOLFOX or XELOX) and chemotherapy (FOLFOX or XELOX), included 1581 patients.

Treatment with nivolumab in the intervention arm was in compliance with the recommendations of the Summary of Product Characteristics (SPC). For treatment with the chemotherapy regimens FOLFOX and XELOX, no information on dosing for these treatment regimens is provided in the relevant SPCs. However, the chemotherapy regimens with the dosages used in the CheckMate 649 study are recommended according to current National Comprehensive Cancer Network (NCCN) guidelines.

The chemotherapy regimen (FOLFOX or XELOX) was chosen by the investigators before randomization.

Treatment of the study population was until disease progression, unacceptable toxicity, treatment discontinuation or a maximum treatment duration of 24 months. The maximum treatment duration applied to nivolumab, which could also be continued after disease progression until loss of clinical benefit, provided the patient tolerated the treatment. Switching to the treatment of the other study arm was not planned.

Primary outcomes of the study were overall survival and progression-free survival (PFS). Secondary outcomes were outcomes of the categories of morbidity, health-related quality of life and side effects.

Relevant subpopulations

The subpopulation of patients with oesophageal adenocarcinoma and PD-L1 expressing tumours with CPS ≥ 5 of the CheckMate 649 study is relevant for research question 1. This subpopulation comprises 56 patients in the intervention arm and 62 patients in the comparator arm. The subpopulation of patients with gastric or gastrooesophageal junction adenocarcinoma and PD-L1 expressing tumours with CPS ≥ 5 of the CheckMate 649 study is relevant for research question 2. This subpopulation comprises 417 patients in the intervention arm and 420 patients in the comparator arm.

However, the approval comprises only patients with HER2-negative tumours. Although patients with known positive HER2 status of the tumour were excluded from the CheckMate 649 study, the proportion of patients with HER2 status unknown or not reported at study entry was 27% in the subpopulation with oesophageal adenocarcinoma and 45% in the subpopulation with gastric or gastrooesophageal junction adenocarcinoma. For both patient populations, it is assumed on the basis of existing references that a total of > 80% had a negative

HER2 status. Therefore, the analyses of the above-mentioned subpopulations can be used. The uncertainty regarding the proportion of patients with HER2-negative tumours is taken into account when assessing the certainty of conclusions of the study results.

Data cut-offs

The CheckMate 649 study is an ongoing study. At the time of the benefit assessment, 3 data cut-offs are available. The first data cut-off from 27 May 2020 with database lock (DBL) on 10 July 2020, and the third data cut-off, conducted 1 year later on 27 May 2021 with DBL on 8 July 2021, were planned a priori. An additional data cut-off between the 2 planned data cut-offs was requested by the European Medicines Agency (EMA) (4 January 2021 with DBL on 16 February 2021).

Usability of the study results for the benefit assessment

The results of the CheckMate 649 study presented by the company in the dossier are incomplete in terms of content. An adequate assessment of the study data is therefore not possible, so that the results of the study are not usable in the benefit assessment for research question 1 overall, and for research question 2 in the present situation only due to the large effect in overall survival. This is mainly due to the lack of complete data on health-related quality of life, morbidity and side effects. This is explained below.

No complete data on health-related quality of life, morbidity and side effects

The final analysis for overall survival was carried out as planned with the third data cut-off, 24 months after randomization of the last patient. The company presented the analysis for overall survival for this (current) data cut-off, but not the analyses for the other outcomes of the categories of morbidity, health-related quality of life and side effects. For these outcomes, the company only presented analyses for the first data cut-off conducted 1 year earlier.

In principle, in accordance with the dossier template, complete analyses for all patient-relevant outcomes recorded must be conducted and provided for all of the data cut-offs relevant to the benefit assessment. The available data show that, in the subpopulation relevant to research question 1, up to 30% of patients in the intervention arm and up to 21% of patients in the comparator arm were still under observation at the time of the first data cut-off. In the subpopulation relevant to research question 2, up to 31% of patients in the intervention arm and up to 17% of patients in the comparator arm were still under observation at this time point. Thus, data of a relevant quantity can still become available for both research questions at the third data cut-off for the outcomes on morbidity, health-related quality of life and side effects.

Final assessment and consequences for both research questions

The data presented are incomplete in terms of content, especially due to the missing results on morbidity, health-related quality of life and side effects for the current third data cut-off. This aspect has a different impact on the assessment of the added benefit for the 2 research questions:

Research question 1

Due to the incomplete data, an adequate weighing of benefit and harm and thus an assessment of the added benefit of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy in comparison with the ACT is not possible for patients with oesophageal adenocarcinoma. The usable study results presented by the company for the outcome of overall survival are also not presented.

Research question 2

Due to the incomplete data, the data presented are usable for the benefit assessment for patients with gastric or gastrooesophageal junction adenocarcinoma in the present situation only due to the large effect in overall survival. The incompleteness of the content is taken into account in the overall conclusion on the added benefit of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy in comparison with the ACT.

Results on research question 1: oesophageal adenocarcinoma

No usable data are available for the assessment of the added benefit of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy in comparison with the ACT as first-line treatment of adult patients with HER2-negative advanced or metastatic oesophageal adenocarcinoma whose tumours express PD-L1 (CPS $\geq$ 5). Hence, there is no hint of an added benefit of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

Results on research question 2: gastric or gastrooesophageal junction adenocarcinoma

The current third data cut-off is relevant for the present benefit assessment. For this data cut-off, the company presented results exclusively for the outcome of overall survival. It presented results only for the first data cut-off for the other outcomes. This approach is not appropriate. The analyses for the first data cut-off presented by the company are not usable for the present assessment. Nevertheless, an added benefit can be derived in the present situation for the patients of research question 2 due to a large effect in the outcome of overall survival.

For the outcome of overall survival, there is a statistically significant difference in favour of nivolumab + chemotherapy (FOLFOX or XELOX) in comparison with chemotherapy (FOLFOX or XELOX); this results in an added benefit of major extent for this outcome.

It is not assumed that, taking into account the results of the first data cut-off, the data of the current data cut-off on the other outcomes, completely call into question the positive effect in the outcome of overall survival.

Based on this, an added benefit can be derived in this situation, but the extent of the added benefit cannot be estimated and is therefore non-quantifiable.

The certainty of conclusions of the study results is reduced due to the uncertainty described with regard to the proportion of patients with HER2-negative tumours, so that at most a hint can be derived.

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 combination with fluoropyrimidine- and platinum-based combination chemotherapy in comparison with the ACT is assessed as follows:

Research question 1: oesophageal adenocarcinoma:

No usable data are available for the assessment of the added benefit of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy in comparison with the ACT as first-line treatment of adult patients with HER2-negative advanced or metastatic oesophageal adenocarcinoma whose tumours express PD-L1 (CPS ≥ 5). Hence, there is no hint of an added benefit of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

Research question 2: gastric or gastrooesophageal junction adenocarcinoma

No complete data are available for the assessment of the added benefit of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy in comparison with the ACT as first-line treatment of adult patients with HER2-negative advanced or metastatic gastric or gastrooesophageal junction adenocarcinoma whose tumours express PD-L1 (CPS ≥ 5). Due to the large effect in overall survival, a hint of a non-quantifiable added benefit of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy in comparison with the ACT can still be derived in the present situation.

Table 3 shows a summary of probability and extent of the added benefit of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy.

[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 in combination with fluoropyrimidine- and platinum-based combination chemotherapy – probability and extent of added benefit

Research question	**Subindication**	**ACT**[a, b]	**Probability and extent of added benefit**
1	Adults with locally advanced or metastatic HER2-negative oesophageal adenocarcinoma that cannot be treated curatively and whose tumours express PD-L1 (CPS ≥ 5); first-line treatment	Treatment of physician's choice[c]	Added benefit not proven[d]
2	Adults with locally advanced or metastatic HER2-negative gastric or gastrooesophageal junction adenocarcinoma that cannot be treated curatively and whose tumours express PD-L1 (CPS ≥ 5); first-line treatment	▪ Cisplatin in combination with 5-fluorouracil ± folinic acid or ▪ cisplatin in combination with capecitabine or ▪ oxaliplatin in combination with 5-fluorouracil ± folinic acid[e] or ▪ oxaliplatin in combination with capecitabine or ▪ 5-fluorouracil ± folinic acid + oxaliplatin + docetaxel[f] (only for patients in good general condition and without relevant comorbidities)	Hint of non-quantifiable added benefit[g]

a. Presented is the respective ACT specified by the GBA.
b. It is assumed for the present therapeutic indication that curative treatment with definitive radiochemotherapy is not an option for patients with unresectable cancer.
c. Guidelines mention several platinum- and fluoropyrimidine-based combination chemotherapies: S-1 (tegafur/gimeracil/oteracil) + cisplatin or capecitabine + cisplatin [XP], 5-fluorouracil+ cisplatin, 5-fluorouracil + oxaliplatin + folinic acid [FLO and FOLFOX], capecitabine + oxaliplatin, infusional 5-fluorouracil + folinic acid + cisplatin [PLF], epirubicin + cisplatin + capecitabine [ECX], epirubicin + oxaliplatin + capecitabine [EOX], epirubicin + cisplatin + infusional 5-fluorouracil [ECF], docetaxel + cisplatin + infusional 5-fluorouracil [DCF], 5-fluorouracil + oxaliplatin + epirubicin, infusional 5-fluorouracil + folinic acid + oxaliplatin + docetaxel [FLOT regimen]. However, only the drugs 5-fluorouracil and cisplatin are approved in the present therapeutic indication. There is a discrepancy between the drugs approved in the therapeutic indication and those recommended in guidelines. In the context of treatment of physician's choice, the G-BA considered the treatment options cited above to be suitable comparators.
d. For those patients for whom FOLFOX (5-fluorouracil + folinic acid + oxaliplatin) or XELOX (capecitabine + oxaliplatin) is the suitable treatment of physician's choice.
e. According to the G-BA, the combination of infusional 5-fluorouracil + folinic acid + oxaliplatin (FLO and FOLFOX) is comprised by the ACT.
f. According to the G-BA, the combination of infusional 5-fluorouracil + folinic acid + oxaliplatin + docetaxel (FLOT) is comprised by the ACT.
g. The CheckMate 649 study included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.

ACT: appropriate comparator therapy; CPS: combined positive score; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor -2; PD-L1: programmed cell death ligand 1

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.

2.1 Research question

The aim of the present report is the assessment of the added benefit of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy in comparison with the ACT as first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastrooesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 (CPS ≥ 5).

The research questions shown in Table 4 result from the ACT specified by the G-BA.

Table 4:Research questions of the benefit assessment of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy

Research question	Subindication	ACT[a, b]
1	Adults with locally advanced or metastatic HER2-negative oesophageal adenocarcinoma that cannot be treated curatively and whose tumours express PD-L1 (CPS ≥ 5); first-line treatment	Treatment of physician's choice[c]
2	Adults with locally advanced or metastatic HER2-negative gastric or gastrooesophageal junction adenocarcinoma that cannot be treated curatively and whose tumours express PD-L1 (CPS ≥ 5); first-line treatment	▪ Cisplatin in combination with 5-fluorouracil ± folinic acid or ▪ cisplatin in combination with capecitabine or ▪ oxaliplatin in combination with 5-fluorouracil ± folinic acid[d] or ▪ oxaliplatin in combination with capecitabine or ▪ 5-fluorouracil ± folinic acid + oxaliplatin + docetaxel[e] (only for patients in good general condition and without relevant comorbidities)

a. Presented is the respective ACT specified by the GBA.
b. It is assumed for the present therapeutic indication that curative treatment with definitive radiochemotherapy is not an option for patients with unresectable cancer.
c. Guidelines mention several platinum- and fluoropyrimidine-based combination chemotherapies: S-1 (tegafur/gimeracil/oteracil) + cisplatin or capecitabine + cisplatin [XP], 5-fluorouracil+ cisplatin, 5-fluorouracil + oxaliplatin + folinic acid [FLO and FOLFOX], capecitabine + oxaliplatin, infusional 5-fluorouracil + folinic acid + cisplatin [PLF], epirubicin + cisplatin + capecitabine [ECX], epirubicin + oxaliplatin + capecitabine [EOX], epirubicin + cisplatin + infusional 5-fluorouracil [ECF], docetaxel + cisplatin + infusional 5-fluorouracil [DCF], 5-fluorouracil + oxaliplatin + epirubicin, infusional 5-fluorouracil + folinic acid + oxaliplatin + docetaxel [FLOT regimen]. However, only the drugs 5-fluorouracil and cisplatin are approved in the present therapeutic indication. There is a discrepancy between the drugs approved in the therapeutic indication and those recommended in guidelines. In the context of treatment of physician's choice, the G-BA considered the treatment options cited above to be suitable comparators.
d. According to the G-BA, the combination of infusional 5-fluorouracil + folinic acid + oxaliplatin (FLO and FOLFOX) is comprised by the ACT.
e. According to the G-BA, the combination of infusional 5-fluorouracil + folinic acid + oxaliplatin + docetaxel (FLOT) is comprised by the ACT.

ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; PD-L1: programmed cell death ligand 1

In the present benefit assessment, the following terms are used for the patient populations of the 2 research questions:

- Research question 1: oesophageal adenocarcinoma
- Research question 2: gastric or gastrooesophageal junction adenocarcinoma

In its dossier, the company referred to patients with oesophageal adenocarcinoma as the "oesophageal adenocarcinoma subpopulation", while patients with gastrooesophageal junction and gastric adenocarcinoma were summarized by the company as the "gastric carcinoma subpopulation".

The company initially followed the G-BA's specification of the ACT for both research questions. For research question 1, however, it additionally considered pembrolizumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy to be a relevant treatment option in the context of treatment of physician's choice, which was only approved after the specification of the ACT, according to the company. The company stated that it had chosen FOLFOX (5-FU + folinic acid + oxaliplatin) and XELOX (capecitabine + oxaliplatin) from the mentioned treatment options for both research questions.

Concurring with the G-BA's specification, the present assessment is conducted for research questions 1 and 2, each in comparison with the ACT specified by the G-BA. In accordance with this specification, pembrolizumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy is not part of the ACT.

Since the company considered all treatment options of the ACT for both research questions in its study search and selection and did not consider pembrolizumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy in the study selection, and the check of the completeness of the study pool did not reveal any additional relevant studies, the choice of the company has no consequences for the assessment.

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

2.2 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: 1 October 2021)
- bibliographical literature search on nivolumab (last search on 28 September 2021)
- search in trial registries/trial results databases for studies on nivolumab (last search on 1 October 2021)

- search on the G-BA website for nivolumab (last search on 1 October 2021)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab (last search on 3 December 2021); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant studies.

2.2.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) vs. chemotherapy (FOLFOX or XELOX)

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])
Study CA209-649 (CheckMate 649[d])	Yes	Yes	No	Yes [3,4]	Yes [5,6]	Yes [7,8]

a. Study for which the company was sponsor.
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: EPAR.
d. In the following tables, the study is referred to with this abbreviated form.

CSR: clinical study report; EPAR: European Public Assessment Report; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; G-BA: Federal Joint Committee; RCT: randomized controlled trial; XELOX: capecitabine + oxaliplatin

For the benefit assessment of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy, the CheckMate 649 study is included, which compared the combination of nivolumab + chemotherapy (FOLFOX or XELOX) with chemotherapy (FOLFOX or XELOX). This concurs with the company's study pool.

In the CheckMate 649 study, the combination of nivolumab with fluoropyrimidine- and platinum-based combination chemotherapy was only implemented as combination with FOLFOX or XELOX. Therefore, no data are available for the combination of nivolumab with other approved drugs within the framework of fluoropyrimidine- and platinum-based combination chemotherapy.

The CheckMate 649 study was to include both patients with distal oesophageal adenocarcinoma and those with gastric or gastrooesophageal junction adenocarcinoma.

On the basis of this study, the company assessed the added benefit for all patients with oesophageal, gastric or gastrooesophageal junction adenocarcinoma with PD-L1 expressing tumours (CPS ≥ 5) without differentiating between the individual research questions. The company presented separate results for the individual research questions as supplementary information.

The arguments put forward by the company are not suitable to adequately justify a joint consideration of the 2 patient populations (see Section 2.4.1, "Relevant subpopulations"). Deviating from the company's approach, the present assessment considers the corresponding subpopulations in accordance with the G-BA's research questions.

For research question 1, the study is only suitable for drawing conclusions on the added benefit of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy for the patient group for whom FOLFOX or XELOX represents a suitable treatment of physician's choice.

The CheckMate 649 study is generally rated as relevant for the present research questions. It is therefore included in the benefit assessment and characterized below. However, the results of the study presented by the company in the dossier are incomplete in terms of content. An adequate assessment of the study data is therefore not possible, so that the results of the corresponding subpopulation of the CheckMate 649 study are not used in the benefit assessment for research question 1, and for research question 2 in the present situation only due to the large effect in overall survival (see Sections 2.4.2 and 2.5.2).

2.3 Research question 1: oesophageal adenocarcinoma

2.3.1 Study characteristics

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

Table 6: Characteristics of the included study – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) vs. chemotherapy (FOLFOX or XELOX) (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CheckMate 649	RCT, open-label, parallel	Adult patients with inoperable, (locally) advanced or metastatic gastric, gastrooesophageal junction or distal oesophageal adenocarcinoma, without known positive HER2 status, who have not yet received systemic therapy for advanced disease	Nivolumab + chemotherapy (FOLFOX or XELOX)[b] (N = 789) Chemotherapy (FOLFOX or XELOX) (N = 792) Nivolumab + ipilimumab[c] (N = ND) Relevant subpopulations thereof: **Research question 1[d]:** Nivolumab + chemotherapy (FOLFOX or XELOX) (n = 56) Chemotherapy (FOLFOX or XELOX) (n = 62) **Research question 2[e]:** Nivolumab + chemotherapy (FOLFOX or XELOX) (n = 417) Chemotherapy (FOLFOX or XELOX) (n = 420)	Screening: up to 28 days Treatment: until disease progression[f], unacceptable toxicity, treatment discontinuation, or a maximum treatment duration of 24 months[g] Observation[h]: outcome-specific, at most until death, discontinuation of participation in the study or end of study	Argentina, Australia, Brazil, Canada, Chile, China, Colombia, Czech Republic, France, Germany, Greece, Hong Kong, Hungary, Israel, Italy, Japan, Mexico, Peru, Poland, Portugal, Romania, Russia, Singapore, South Korea, Spain, Taiwan, Turkey, United Kingdom, USA 10/2016–ongoing Data cut-offs: First data cut-off: 27 May 2020 (final PFS analysis) with DBL: 10 July 2020 Second data cut-off: 4 January 2021 (EMA request) with DBL: 16 February 2021 Third data cut-off: 27 May 2021 (final OS analysis) with DBL: 8 July 2021	Primary: overall survival, progression-free survival Secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the included study – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) vs. chemotherapy (FOLFOX or XELOX) (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant outcomes for this benefit assessment.
b. This treatment arm was added with Amendment 08 (7 December 2016); from Amendment 20 (11 June 2018) 1:1 randomization into this arm or the chemotherapy arm (FOLFOX or XELOX).
c. From 5 June 2018, no more patients were included for this arm. No information can be found on the number of randomized patients in this arm. The arm is not relevant for the assessment and is not presented in the following tables.
d. Patients with oesophageal adenocarcinoma with PD-L1 expression CPS ≥ 5.
e. Patients with gastric or gastrooesophageal junction adenocarcinoma with PD-L1 expression CPS ≥ 5.
f. Nivolumab could be continued after disease progression (assessed by the investigator according to RECIST version 1.1) until loss of clinical benefit, provided the patient tolerated the treatment.
g. Refers to nivolumab.
h. Outcome-specific information is provided in Table 8.

AE: adverse event; CPS: combined positive score, DBL: database lock; EMA: European Medicines Agency; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; N: number of randomized patients; ND: no data; OS: overall survival; PD-L1: programmed cell death ligand-1; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours; XELOX: capecitabine + oxaliplatin

Table 7: Characteristics of the intervention – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) vs. chemotherapy (FOLFOX or XELOX)

Study	Intervention	Comparison
CheckMate 649	**Nivolumab + FOLFOX** nivolumab 240 mg IV + oxaliplatin 85 mg/m² BSA + folinic acid 400 mg/m² BSA + 5-FU 400 mg/m² BSA IV, on day 1 of each cycle; + 5-FU 1200 mg/m² BSA IV continuous infusion daily on days 1 and 2, every 2 weeks or **Nivolumab + XELOX** nivolumab 360 mg IV on day 1 + oxaliplatin 130 mg/m² BSA IV on day 1 + capecitabine 1000 mg/m² BSA orally twice daily on days 1–14 every 3 weeks	**FOLFOX** oxaliplatin 85 mg/m² BSA + folinic acid 400 mg/m² BSA + 5-FU 400 mg/m² BSA IV, on day 1 of each cycle; + 5-FU 1200 mg/m² BSA IV continuous infusion daily on days 1 and 2, every 2 weeks or **XELOX** oxaliplatin 130 mg/m² BSA IV on day 1 + capecitabine 1000 mg/m² BSA orally twice daily on days 1–14 every 3 weeks
	▪ **Dose adjustments** ▪ nivolumab: no dose adjustment allowed (according to the SPC); interruption allowed in case of side effects ▪ chemotherapy: dose adjustments allowed according to SPCs or local standard ▪ if one of the therapy components was discontinued, the other(s) could also be continued as individual drug(s); if the chemotherapy components in the intervention arm were discontinued, nivolumab could be continued with dosages of 240 mg Q2W or 360 mg Q3W or 480 mg Q4W (the 480 mg dose only if the first dosing in the study was at least 6 months ago) ▪ switching between XELOX and FOLFOX within the study arms was not allowed	
	Permitted pretreatment ▪ adjuvant or neoadjuvant chemotherapy, radiotherapy and definitive radiochemotherapy for locally advanced disease ≥ 6 months prior to randomization ▪ palliative radiotherapy ≥ 2 weeks prior to randomization **Non-permitted pretreatment** ▪ targeted T-cell therapy ▪ systemic treatment with either corticosteroids (> 10 mg daily) or other immunosuppressive medications ≤ 14 days prior to randomization **Permitted concomitant treatment** corticosteroids: local administration (except in active autoimmune disease), as steroid replacement therapy (> 10 mg daily), as prophylaxis or treatment for allergies (for < 3 weeks) **Non-permitted concomitant treatment**[a] ▪ any antineoplastic treatment (e.g. surgery, chemotherapy, hormonal therapy, non-palliative radiotherapy or other drugs) ▪ herbal drugs, except marijuana and derivatives, if legal use for cancer treatment possible	

a. Except treatment of adverse side effects.

5-FU: 5-fluorouracil; BSA: body surface area; FOLFOX: 5-FU + folinic acid + oxaliplatin; IV: intravenous; Q2W: every 2 weeks, Q3W: every 3 weeks; Q4W: every 4 weeks; RCT: randomized controlled trial; XELOX: capecitabine + oxaliplatin

The CheckMate 649 study is an ongoing, open-label RCT comparing nivolumab in combination with 2 different fluoropyrimidine- and platinum-based combination chemotherapy regimens, FOLFOX (consisting of: 5-FU + folinic acid + oxaliplatin) or XELOX (consisting of: capecitabine + oxaliplatin), against FOLFOX or XELOX. It included adult patients with inoperable, (locally) advanced or metastatic gastric, gastrooesophageal junction or distal oesophageal adenocarcinoma, without known positive HER2 status of their tumour, who have not yet received systemic therapy for advanced disease. Patients had to be in good general condition at study entry, corresponding to an ECOG PS of 0 or 1.

Determination of PD-L1 expression of the tumour tissue was required for study inclusion. This test had to be performed in a central laboratory. However, patients were included in the study regardless of their PD-L1 expression. The PD-L1 expression on the tumour cells was determined using the Dako PD-L1 IHC 28-8 pharmDx assay.

Only 2 treatment arms were planned at the start of the study: nivolumab + ipilimumab versus chemotherapy (FOLFOX or XELOX). During the course of the study, the nivolumab + chemotherapy (FOLFOX or XELOX) intervention arm was added and recruitment to the nivolumab + ipilimumab intervention arm was stopped. Only the 2 study arms nivolumab + chemotherapy (FOLFOX or XELOX) and chemotherapy (FOLFOX or XELOX) are relevant for the present benefit assessment. These 2 study arms included 1581 patients. According to the company, the data presented in the dossier refer to patients who were randomized in parallel to the nivolumab + chemotherapy (FOLFOX or XELOX) intervention arm and the chemotherapy (FOLFOX or XELOX) comparator arm in a ratio of 1:1. Randomization was stratified by the following factors: PD-L1 expression of tumour cells (Tumour Proportion Score [TPS]: ≥ 1% versus < 1% including non-quantifiable), region (Asia versus North America [USA and Canada] versus rest of the world), ECOG PS (0 versus 1) and chemotherapy regimen (XELOX versus FOLFOX).

Treatment with nivolumab in the intervention arm was in compliance with the recommendations of the SPC [9]. Correspondingly, dose adjustment was not allowed; treatment interruptions due to toxicity were possible and were in compliance with the SPC [9]. With regard to the chemotherapy regimens FOLFOX (5-FU + folinic acid + oxaliplatin) and XELOX (capecitabine + oxaliplatin), it should be noted that these therapy regimens are not explicitly approved for the therapy of oesophageal carcinoma. [10-13]. Accordingly, the SPCs contain no information on the dosage for these treatment regimens. However, the combination of oxaliplatin with 5-FU and folinic acid as well as the combination of oxaliplatin with capecitabine within the framework of a treatment of physician's choice are considered suitable comparators in the present benefit assessment (see Table 4). The chemotherapy regimens with the dosages used in the CheckMate 649 study are recommended according to current NCCN guidelines [14,15].

The chemotherapy regimen (FOLFOX or XELOX) was chosen by the investigators before randomization.

Treatment of the study population was until disease progression, unacceptable toxicity, treatment discontinuation or a maximum treatment duration of 24 months. The maximum treatment duration applied to nivolumab (this is in compliance with the recommendations of the SPC), which could also be continued after disease progression until loss of clinical benefit, provided the patient tolerated the treatment. Switching to the treatment of the other study arm was not planned.

Primary outcomes of the study were overall survival and PFS. Secondary outcomes were outcomes of the categories of morbidity, health-related quality of life and side effects.

Relevant subpopulations

The company explained that its assessment of the added benefit of nivolumab was across all research questions on the basis of the CheckMate 649 subpopulation that includes patients with CPS ≥ 5 regardless of tumour entity (oesophageal, gastric or gastrooesophageal junction adenocarcinoma) (referred to by the company as the "PD-L1-positive population"). Hence, this population comprised the subpopulations of the study relevant for research questions 1 and 2. The company justified this procedure by stating that the guideline recommendations for the treatment of the above-mentioned cancer entities largely correspond and the treatment results are comparable, and that the CheckMate 649 study also showed no proof of effect modification by location of the primary tumour. In the opinion of the company, the separate presentation according to the location of the primary tumour would therefore not provide any additional information, but would unnecessarily weaken the informative value of the evidence presented.

The argumentation of the company for pooling the patient populations of research questions 1 and 2 is not valid. Neither similar treatment recommendations nor a lack of relevant effect modification for the characteristic of location of the primary tumour are sufficient reasons to pool the populations. Guidelines also differentiate the populations according to location of the primary tumours. Thus, there are separate S3 guidelines for oesophageal carcinoma (squamous cell carcinoma and adenocarcinoma) and for gastric and gastrooesophageal junction adenocarcinoma [16,17].

The subpopulation of patients with oesophageal adenocarcinoma and PD-L1 CPS ≥ 5 is relevant for answering research question 1. The subpopulation of patients with gastric or gastrooesophageal junction adenocarcinoma and PD-L1 CPS ≥ 5 is relevant for answering research question 2. In addition, the approval comprises only patients with HER2-negative tumours (see section below).

Patients with HER2-negative adenocarcinoma

In the therapeutic indication to be assessed, nivolumab is approved for patients with HER2-negative adenocarcinoma [9]. Although patients with known positive HER2 status of the tumour were excluded from the CheckMate 649 study, the proportion of patients with HER2 status unknown or not reported at study entry was 27% in the subpopulation with oesophageal

adenocarcinoma (see also Table 9) and 45% in the subpopulation with gastric or gastrooesophageal junction adenocarcinoma (see also Table 13).

In Module 4 Q, the company presented results for all patients with PD-L1 expressing tumours with CPS ≥ 5 and additionally for the 2 subpopulations (depending on the research question). In this context, it considered not only the patients with HER2-negative tumours, but also the 42.4% (based on the "PD-L1-positive population") with HER2 status unknown or not reported. The company explained its approach by stating that the proportion of HER2-negative patients with known HER2 status for the present therapeutic indication was 76.9% and referred to a Dutch cohort study [18]. The company further explained that applying this proportion to the HER2-undetermined patients (i.e. patients whose HER2 status was unknown or not reported at the time of inclusion in the study) resulted in a total of 89.5% HER2-negative patients in the CheckMate 649 study. Since this proportion was greater than 80%, the company considered the total study population. The company additionally stated that this conclusion was supported by the analysis of the HER2 amplification status using next generation sequencing (NGS) in the study. According to the company, it was possible to perform this analysis in 49.1% of the HER2-undetermined patients, of which 86.3% had the status "not amplified" and could therefore be considered negative. Furthermore, the company referred to an observational study in Germany [19], which found a proportion of 31.5% of HER2-undetermined patients in all patients with gastric adenocarcinoma, including gastrooesophageal junction adenocarcinoma (minus the HER2-positive patients). In the opinion of the company, the proportion of 42.4% of HER2-undetermined patients in the present CheckMate 649 study therefore is not an argument against the transferability of the study results to the German health care context.

Such a high proportion of patients with unknown HER2 status cannot be assumed in today's everyday health care. For oesophageal, gastric or gastrooesophageal junction adenocarcinoma, the HER2 status is to be tested before starting palliative drug therapy because an HER2-positive status is considered a positive predictive factor for a potential therapy with the drug trastuzumab [16,17]. With regard to the analysis of HER2 amplification using NGS conducted in the CheckMate 649 study, the company did not provide any information on the validity of this method for determining HER2 status in oesophageal, gastric or gastrooesophageal junction adenocarcinoma. Current S3 guidelines mention immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) as methods to determine HER2 status [16,17]. The NCCN guidelines recommend IHC, FISH and in situ hybridization (ISH) for testing HER2 status and describe them as the gold standard, while they recommend testing with NGS only in exceptional cases due to limitations [14,15]. Irrespective of the fact that the validity of the HER2 status determined by NGS is unclear and these analyses are not taken into account in the present assessment, the HER2 status remains undetermined in half of the patients with HER2 status unknown or not reported at baseline (see also Table 9 and Table 13).

In order to estimate the proportion of patients with HER2-positive status among those with HER2 status unknown or not reported in the relevant subpopulations per research question, the sources of the company and other sources are used. Based on these sources, the following

percentages of patients with HER2-positive tumours are possible at population level for the following locations of advanced or metastatic adenocarcinoma:

- oesophagus: up to about 30% [15,18,20]
- stomach: up to about 23% (up to 33% for the intestinal subtype) [14,16,18]
- gastrooesophageal junction: up to about 33% [15,16,18]

Even assuming a proportion of up to 40% of HER2-positive patients among patients with HER2 status unknown or not reported, the total proportion of HER2-negative patients in these subpopulations would still be over 80%. For this reason, it seems adequate in the present situation to use the results of the respective subpopulation without limitation to derive the added benefit for research question 1 and for research question 2 [1]. The subpopulations of the CheckMate 649 study for research question 1 and research question 2 presented by the company are therefore relevant for the benefit assessment. However, the certainty of conclusions of the results of the CheckMate 649 study regarding the subpopulation relevant for the respective research questions is reduced, because there is uncertainty regarding the proportion of patients with HER2-negative tumours.

Subpopulation of the CheckMate 649 study relevant for the assessment of research question 1

The subpopulation of patients with oesophageal adenocarcinoma and PD-L1 expressing tumours with CPS ≥ 5 of the CheckMate 649 study is relevant for research question 1. For this patient population, it is assumed that > 80% have a negative HER2 status (see Section above). This subpopulation comprises 56 patients in the intervention arm and 62 patients in the comparator arm.

Data cut-offs and analyses

The CheckMate 649 study is an ongoing study. At the time of the benefit assessment, 3 data cut-offs are available (see also Table 12). The first data cut-off from 27 May 2020 with DBL on 10 July 2020, and the third data cut-off, conducted 1 year later on 27 May 2021 with DBL on 8 July 2021, were planned a priori. An additional data cut-off between the 2 planned data cut-offs was requested by the EMA (4 January 2021 with DBL on 16 February 2021).

In Module 4 Q of the dossier, the company presented analyses for all outcomes for the first planned data cut-off. It additionally presented the analyses for overall survival for the second planned data cut-off (third data cut-off). Thus, in deviation from the specification in the dossier template [21], no analyses for all outcomes relevant for the benefit assessment are available for the current data cut-off. The company did not sufficiently justify that no important additional information can be expected from the third data cut-off compared with the other data cut-offs. As a result, the data submitted by the company are incomplete in terms of content (for a detailed description, see Section 2.4.2.2).

Planned duration of 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 observation – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) vs. chemotherapy (FOLFOX or XELOX)

Study Outcome category Outcome	Planned follow-up observation
CheckMate 649	
Mortality	
Overall survival	Until death
Morbidity	
Health status (EQ-5D VAS)	Until death
Health-related quality of life (FACT-Ga)[a]	Up to 114 [± 14] days after the last dose of study medication[b]
Side effects (all outcomes in the category of side effects)	Up to 114 [± 14] days after the last dose of study medication[c]

a. Only the general part FACT-G is relevant for the patients of research question 1, as the indication-specific FACT-GaCS scale has not been validated for this patient population (see Section 2.4.2.2).
b. Inconsistent information within the study documents and Module 4 Q. It is unclear whether the general part FACT-G was only recorded during treatment or also until the second follow-up visit (114 days after the last dose of study medication). After that, only the abbreviated version FACT-G7, which only includes 7 of the 27 items of the FACT-G, and the indication-specific scale FACT-GaCS were recorded. Neither alone nor in combination with the FACT-GaCS scale is the FACT-G7 suitable for representing health-related quality of life (see Section 2.4.2.2).
c. Inconsistent information within the study documents and Module 4 Q. It is unclear whether side effects were recorded up to 100 or 114 (±14) days after the last dose of the study medication.

FACT-G: Functional Assessment of Cancer Therapy-General; FACT-Ga: Functional Assessment of Cancer Therapy-Gastric; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; GaCS: gastric cancer subscale; RCT: randomized controlled trial; VAS: visual analogue scale; XELOX: capecitabine + oxaliplatin

The observation periods for the outcomes of the outcome category 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 114 [±14] days). For these outcomes, data are therefore available only for the shortened observation period. Data on the entire study duration or until death are missing.

For the outcome category of health-related quality of life, it is unclear due to inconsistent information within the study documents and Module 4 Q of the dossier whether the general part Functional Assessment of Cancer Therapy-General (FACT-G) was only recorded during treatment or also until the second follow-up visit (114 days after treatment discontinuation). After that, only the abbreviated version FACT-G7, which only includes 7 of the 27 items of the FACT-G, and the indication-specific scale FACT-gastric cancer subscale (GaCS) were recorded.

Characteristics of the study population

Table 9 shows the characteristics of the patients with oesophageal adenocarcinoma in the included study.

Table 9: Characteristics of the study population – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) vs. chemotherapy (FOLFOX or XELOX), oesophageal adenocarcinoma (multipage table)

Study **Characteristic** **Category**	**Nivolumab + chemotherapy (FOLFOX or XELOX)** **N[a] = 56**	**Chemotherapy (FOLFOX or XELOX)** **N[a] = 62**
CheckMate 649		
Age [years], mean (SD)	64 (10)	63 (11)
Age group, n (%)		
< 65 years	25 (45)	34 (55)
≥ 65 years to < 75 years	24 (43)	17 (27)
≥ 75 years	7 (13)	11 (18)
Sex [F/M], %	21/79	19/81
Family origin n (%)		
Asian	1 (2)	1 (2)
White	53 (95)	59 (95)
Other	2 (4)	2 (3)
Region, n (%)		
Asia	1 (2)	1 (2)
North America	20 (36)	28 (45)
Rest of the world	35 (63)	33 (53)
ECOG PS, n (%)		
0	25 (45)	30 (48)
1	31 (55)	32 (52)
Disease status, n (%)		
Locally recurrent/advanced	1 (2)	1 (2)
Metastatic	55 (98)	61 (98)
Prior surgery related to current cancer, n (%)		
Yes	11 (20)	15 (24)
No	45 (80)	47 (76)
Prior radiotherapy, n (%)		
Yes	14 (25)	13 (21)
No	42 (75)	49 (79)
Laurén classification, n (%)		
Intestinal type	21 (38)	25 (40)
Diffuse type	10 (18)	11 (18)
Mixed type	5 (9)	2 (3)
Unknown	20 (36)	24 (39)
Time between first diagnosis and randomization, n (%)		
< 6 months	47 (84)	43 (69)
6 months to < 1 year	1 (2)	4 (6)
≥ 1 year	8 (14)	15 (24)

Table 9: Characteristics of the study population – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) vs. chemotherapy (FOLFOX or XELOX), oesophageal adenocarcinoma (multipage table)

Study Characteristic Category	**Nivolumab + chemotherapy (FOLFOX or XELOX) N[a] = 56**	**Chemotherapy (FOLFOX or XELOX) N[a] = 62**
Peritoneal metastases, n (%)		
Yes	7 (13)	3 (5)
No	49 (88)	55 (89)
Not reported	0 (0)	4 (6)
Liver metastases, n (%)		
Yes	26 (46)	31 (50)
No	30 (54)	27 (44)
Not reported	0 (0)	4 (6)
HER2 status at study entry, n (%)		
Negative	40 (71)	46 (74)
Positive	0 (0)	0 (0)
Unknown	0 (0)	0 (0)
Not reported	16 (29)	16 (26)
HER2 status/amplification[b], n (%)		
Negative	45 (80[c])	52 (84[c])
Positive	2 (4)	0 (0)
Unknown	0 (0)	0 (0)
Not reported	9 (16[c])	10 (16[c])
Treatment discontinuation (third data cut-off), n (%)	ND[d]	ND[d]
Study discontinuation (third data cut-off), n (%)	ND[e]	ND[e]

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. According to the company, the HER2 amplification status was subsequently analysed using next generation sequencing. The company considered a number of ≥ 4 copies of the HER2 gene in the analysis to be HER2-amplified.
c. Institute's calculation.
d. The information provided by the company shows that 52 out of 55 (95%) and 57 out of 59 (97%) of the patients with at least one dose of the study medication in the intervention and comparator arm, respectively, are "no longer on study medication" (minus those who, according to the company, have "completed treatment according to protocol"). It is assumed that these are patients for whom all drugs of the study medication have been discontinued. Common reasons were (intervention vs. comparator arm): disease progression (75% vs. 63%) and AEs (15% vs. 19%).
e. The company only provided information on how many patients discontinued the study "at the end of study medication" (24% vs. 12%). The most common reason for study discontinuation in these patients was death (20% vs. 7%). It is unclear how many patients discontinued the study in total by the time of the data cut-off.

ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; HER2: human epidermal growth factor receptor 2; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus; XELOX: capecitabine + oxaliplatin

The mean age of the patients with oesophageal adenocarcinoma was 64 and 63 years. The clear majority of patients were men of white family origin. 47% of the patients had an ECOG PS of 0, and 53% an ECOG PS of 1. Almost all patients (98%) had metastases. The time between first diagnosis and randomization was less than 6 months for the majority of the patients in both study arms of the relevant subpopulation. According to the approval, only patients with negative HER2 status are comprised by the present therapeutic indication. In the relevant subpopulation, the proportion of patients with negative HER2 status at study entry was 73%. For the other patients, the HER2 status was unknown or not reported. This is discussed in Section 2.4.1 on "Patients with HER2-negative adenocarcinoma".

Data on the proportion of patients with discontinuation of one drug component are not available. It is inferred from the available information that about 96% of the patients had discontinued all treatment components by the third data cut-off. The company presented no information on how many patients had discontinued the study by the third data cut-off. It only provided information on how many patients discontinued the study at the end of treatment.

Information on the course of the study

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

Table 10: Information on the course of the study – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) vs. chemotherapy (FOLFOX or XELOX), oesophageal adenocarcinoma

Study **Duration of the study phase** **Outcome category**	**Nivolumab + chemotherapy (FOLFOX or XELOX)** **N = 55**	**Chemotherapy (FOLFOX or XELOX)** **N = 59**
CheckMate 649 (third data cut-off)		
Treatment duration [months]		
Median [min; max]	6.08 [0.1; 28.9]	4.24 [0.1; 35.6]
Mean (SD)	8.31 (6.91)	5.55 (6.13)
Observation period [months]		
Overall survival[a]		
Median [min; max]	11.20 [0.9; 47.1]	10.68 [1.3; 37.4]
Mean (SD)	15.91 (11.62)	12.84 (9.27)
Morbidity (health status – EQ-5D VAS)	ND	ND
Health-related quality of life (FACT-G)	ND	ND
Side effects	ND	ND

a. Information on how the observation period was calculated is not available.

FACT-G: Functional Assessment of Cancer Therapy-General; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; max: maximum; min: minimum; N: number of patients with at least one dose of the study medication; ND: no data; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; XELOX: capecitabine + oxaliplatin

The median treatment duration for patients with oesophageal adenocarcinoma in the intervention arm (nivolumab + chemotherapy [FOLFOX or XELOX]) was 6.08 months, markedly longer than the median treatment duration in the comparator arm (chemotherapy [FOLFOX or XELOX]) of 4.24 months. The company provided information on the observation period only for the outcome of overall survival. No information on the observation period is available for the outcome categories of morbidity, health-related quality of life and side effects. Whereas the outcome of health status was to be observed until death, the observation period for the outcomes on health-related quality of life and side effects was linked to the end of treatment (plus 114 days) (see Table 8). For these outcomes, conclusions can therefore be drawn only regarding the time up to 114 days after treatment. Based on the information on the treatment duration plus 114 days, the median observation period was 9.8 months in the intervention arm and 8.0 months in the comparator arm. Hence, the observation periods for these outcomes were shortened in comparison with overall survival. Data for the entire observation period are missing for these outcomes.

In addition, there are also differences in the observation periods of the outcomes corresponding to the differences in the treatment durations between the study arms. This data situation influences the interpretability of the outcomes with shorter observation period (see Section 2.4.2.2).

Information on subsequent therapies

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

Table 11: Information on subsequent therapies – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) vs. chemotherapy (FOLFOX or XELOX), oesophageal adenocarcinoma

Study **Drug class** **Drug**	**Patients with subsequent therapy n (%)**	
	Nivolumab + FOLFOX or XELOX **N = 56**	**FOLFOX or XELOX** **N = 62**
CheckMate 649 (third data cut-off)		
Total	26 (46.4)	34 (54.8)
Radiotherapy	8 (14.3)	7 (11.3)
Surgical intervention	1 (1.8)	1 (1.6)
Systemic therapy	21 (37.5)	33 (53.2)
Immunotherapy	1 (1.8)	7 (11.3)
Anti-PD1	0 (0)	7 (11.3)
Nivolumab	0 (0)	1 (1.6)
Pembrolizumab	0 (0)	6 (9.7)
Other immunotherapy	1 (1.8)	0 (0)
Investigational immunotherapy	1 (1.8)	0 (0)
Targeted therapy	7 (12.5)	9 (14.5)
Olaparib	1 (1.8)	0 (0)
Ramucirumab	7 (12.5)	9 (14.5)
Other systemic cancer therapy – investigational drugs	1 (1.8)	1 (1.6)
Investigational antineoplastic drug	1 (1.8)	1 (1.6)
Other systemic cancer therapy – chemotherapy	19 (33.9)	31 (50.0)
Capecitabine	0 (0)	4 (6.5)
Carboplatin	3 (5.4)	2 (3.2)
Cisplatin	0 (0)	2 (3.2)
Docetaxel	0 (0)	4 (6.5)
Fluorouracil	9 (16.1)	14 (22.6)
Irinotecan	9 (16.1)	12 (19.4)
Oxaliplatin	2 (3.6)	5 (8.1)
Paclitaxel	13 (23.2)	16 (25.8)
Not assigned	8 (14.3)	13 (21.0)

FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; n: number of patients with subsequent therapy; N: number of analysed patients; PD-1: programmed cell death 1; RCT: randomized controlled trial; XELOX: capecitabine + oxaliplatin

After discontinuation of the study medication, 46% of the patients in the intervention arm and 55% of the patients in the comparator arm received subsequent therapy. In both study arms, this was mostly a systemic therapy – the majority of patients received other chemotherapeutic agents.

Limitations regarding subsequent therapies cannot be inferred from the study documents. Switching to the treatment of the other study arm was not planned.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - health status, surveyed using the EQ-5D VAS
- Health-related quality of life
  - FACT-G
- Side effects
  - serious adverse events (SAEs)
  - severe adverse events (AEs), operationalized as Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3
  - discontinuation due to AEs
  - immune-related SAEs
  - immune-related severe AEs
  - further specific AEs, if any

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

As the results presented by the company for research question 1 are not used (see the following Section 2.4.2.2), the risk of bias across outcomes and the outcome-specific risk of bias is not assessed for the results of the CheckMate 649 study for this research question.

2.3.2.2 Usability of the study results for the benefit assessment

The results of the CheckMate 649 study presented by the company in the dossier are incomplete in terms of content. An adequate assessment of the study data is therefore not possible, so that the results of the study are not usable in the benefit assessment for research question 1 overall, and for research question 2 in the present situation only due to the large effect in overall survival. This is explained below.

No complete data on health-related quality of life, morbidity and side effects

In Module 4 Q of the dossier, the company presented analyses for different data cut-offs for the different outcome categories. Table 12 shows the data cut-offs and the results reported for them per outcome category.

Table 12: Analyses presented by the company for the CheckMate 649 study per data cut-off and outcome category

Data cut-off	Mortality	Morbidity	Health-related quality of life	Side effects
First data cut-off from 27 May 2020[a] with DBL on 10 July 2020	x	x	x	x
Second data cut-off from 4 January 2021[b] with DBL on 16 February 2021	–	–	–	–
Third data cut-off from 27 May 2021[c] with DBL on 8 July 2021	x	–	–	–

a. Planned final analysis for the outcome of PFS and planned interim analysis for the outcome of overall survival.
b. Data cut-off requested by the EMA; results for the total population were presented for the outcomes of overall survival, PFS, objective response rate, and duration of response.
c. Planned final analysis for the outcome of overall survival.

DBL: database lock; EMA: European Medicines Agency; PFS: progression-free survival

The final analysis for overall survival was carried out as planned with the third data cut-off, 24 months after randomization of the last patient. The company presented the analysis for overall survival for this (current) data cut-off, but not the analyses for the other outcomes of the categories of morbidity, health-related quality of life and side effects. For these outcomes, the company only presented analyses for the first data cut-off conducted 1 year earlier. It justified this with the fact that at this point in time, treatment had already been completed for 91% of the patients (related to the "PD-L1-positive population") and, taking into account the recording and analysis of these outcomes, no significant gain in information could be expected at a later point in time.

In principle, in accordance with the dossier template [21], complete analyses for all patient-relevant outcomes recorded must be conducted and provided for all of the data cut-offs relevant to the benefit assessment. The argumentation of the company that no important gain in information for the outcomes on morbidity, health-related quality of life and side effects could be expected after the time point of the first data cut-off is not valid. For the assessment of whether there can be a significant gain in information from a more up-to-date data cut-off, only the proportion of patients under observation is relevant and not, as the company argues, the proportion of patients under treatment. Thus, the outcomes on health-related quality of life and side effects were to be observed up to 114 days after the end of treatment, and health status even until death (see Table 8). The available data show that, in the subpopulation relevant to research question 1, up to 30% of patients in the intervention arm and up to 21% of patients in

the comparator arm were still under observation at the time of the first data cut-off. In the subpopulation relevant to research question 2, up to 31% of patients in the intervention arm and up to 17% of patients in the comparator arm were still under observation at this time point. Thus, data of a relevant quantity can still become available for both research questions at the third data cut-off for the outcomes on morbidity, health-related quality of life and side effects.

Analyses on patient-reported outcomes of the categories of morbidity and health-related quality of life

General

The company presented event time analyses for all patient-reported outcomes. These were operationalized as time to so-called "definitive deterioration". "Definitive deterioration" was defined as a decrease of the corresponding score by at least the response criterion without subsequent improvement above the response criterion in one of the following recordings. Among other things, in accordance with the General Methods of the Institute [1], the company also presented analyses in which the response criterion corresponded to 15% of the scale range of an instrument.

The recording on health-related quality of life was discontinued 114 days after the end of treatment (see Table 8). The company presented no information on the observation period for health-related quality of life. The estimated median observation periods for the outcome on health-related quality of life show that the observation period for this outcome was markedly shortened in comparison with overall survival. Thus, the median observation periods for overall survival were 11.2 months (intervention arm) and 10.7 months (comparator arm) in the subpopulation relevant to research question 1, and 14.3 months (intervention arm) and 10.8 months (comparator arm) in the subpopulation relevant to research question 2 (see Table 10 and Table 14). In contrast, the median observation periods for health-related quality of life calculated on the basis of the information on treatment duration plus 114 days were 9.8 months (intervention arm) and 8.0 months (comparator arm) in the subpopulation relevant to research question 1, and 11.1 months (intervention arm) and 8.5 months (comparator arm) in the subpopulation relevant to research question 2 (see also Table 10 and Table 14).

On the one hand, this results in the problem that the observation period of the outcome of health-related quality of life does not cover the entire observation period. It is therefore not appropriate to speak of a "definitive deterioration" in this situation. Rather, this is only a deterioration confirmed over the shortened observation period.

On the other hand, the differences in the treatment duration and thus also in the observation periods between the treatment arms mean that a sustained deterioration across all follow-up values is potentially more difficult to achieve in the intervention arm with longer observation (nivolumab + chemotherapy [FOLFOX or XELOX]). In addition, the analysis also included patients who had deteriorated once at the last documentation time and for whom no confirmatory value was available at all.

The analyses presented on health-related quality of life cannot be interpreted without further information. In order to be able to interpret the data in the present situation, additional analyses of the first-time deterioration or the once-confirmed first-time deterioration would be necessary.

The company would have to submit Kaplan-Meier curves and subgroup analyses for the event time analyses presented, including those with the response criterion of 15% of the scale range relevant for the benefit assessment. These are not available.

The analysis of the outcome of overall survival also considered recordings that were not conducted until after the respective data cut-off, but before the DBL. For the other outcomes relevant to this benefit assessment, it is assumed that only the recordings made until the respective data cut-off were included in the analyses presented by the company in Module 4 Q of the dossier. As the company only described in Module 4 Q of the dossier that the time points of the DBL are given for the data cut-offs without providing any further information in this regard, this remains unclear.

Health-related quality of life

In the study, health-related quality of life was recorded with the Functional Assessment of Cancer Therapy-Gastric (FACT-Ga). The FACT-Ga comprises the FACT-G and the GaCS. For the FACT-Ga total score, the company presented analyses of the time period during the therapy phase. As already described in Section 2.4.1, it is unclear whether the observation for the FACT-G took place until the end of treatment or up to 114 [± 14] days afterwards (until the second follow-up visit). If recordings also took place after the end of treatment, these should also be taken into account in the analysis. In the subsequent survival follow-up, only the FACT G7 (an abbreviated version of the FACT-G) and the GaCS were recorded, but not the complete FACT-Ga. However, FACT-G7 and GaCS are unsuitable for representing the complex construct of health-related quality of life.

Regardless of the usability of the available results, the total score for the general part FACT-G is relevant for the patients of research question 1, as the indication-specific scale is only validated for patients with gastric cancer. The FACT-Ga total score is relevant for patients of research question 2. These also include patients with gastrooesophageal junction adenocarcinoma, but since these only constitute about 20% of the patients in the relevant subpopulation for research question 2, the results of the total subpopulation can be considered (assuming availability of usable results).

Analyses on the outcomes of the category of side effects

The company provided Kaplan-Meier curves for the overall rates of AEs (AEs, SAEs, severe AEs, discontinuation due to AEs), but not for the analyses at the level of the System Organ Class (SOC) or Preferred Terms (PTs) of the Medical Dictionary for Regulatory Activities (MedDRA).

For the outcomes of immune-related AEs, severe AEs and SAEs, the operationalization of the company-specific MedDRA PT collection from the outcome of specific AEs ("select AE") is considered relevant. This is a selection of SOCs and 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. For immune-related AEs, the company presented neither results at PT level nor Kaplan-Meier curves for the overall rates, the upper and lower categories or at PT level. In addition, for immune-related AEs, the company presented only subgroup analyses at the AE level but not for severe AEs or SAEs.

As for the morbidity and health-related quality of life outcomes, it is also unclear for the side effect outcomes whether the analysis included recordings conducted after the respective data cut-off but before the DBL.

In addition, it should be noted that the company did not provide any information on observation periods for the outcome category of side effects. For this outcome category, the observation period likewise covers only a part of the entire observation period. On the basis of these data, conclusions could therefore be drawn only for the shortened time period under treatment (plus 114 days follow-up observation). Data for the entire observation period are missing.

Final assessment and consequences for both research questions

Overall, the deficiencies in the dossier described above are considered to be serious. The data presented are incomplete in terms of content, especially due to the missing results on morbidity, health-related quality of life and side effects for the current third data cut-off. This aspect has a different impact on the assessment of the added benefit for the 2 research questions:

Research question 1

Due to the incomplete data, an adequate weighing of benefit and harm and thus an assessment of the added benefit of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy in comparison with the ACT is not possible for patients with oesophageal adenocarcinoma. The usable study results presented by the company for the outcome of overall survival are also not presented.

Research question 2

Due to the incomplete data, the data presented are usable for the benefit assessment for patients with gastric or gastrooesophageal junction adenocarcinoma in the present situation only due to the large effect in overall survival. The incompleteness of the content is taken into account in the overall conclusion on the added benefit of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy in comparison with the ACT (see Section 2.5.2.2).

2.3.3 Probability and extent of added benefit

No usable data are available for the assessment of the added benefit of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy in comparison with the ACT as first-line treatment of adult patients with HER2-negative advanced or metastatic oesophageal adenocarcinoma whose tumours express PD-L1 (CPS ≥ 5). Hence, there is no hint of an added benefit of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

The assessment described above deviates from that of the company, which derived an indication of major added benefit for all patients in the therapeutic indication, regardless of the different tumour entities. Even if the 2 subpopulations were considered separately, in the opinion of the company there would be a major added benefit in each case in the overall view.

2.4 Research question 2: gastric or gastrooesophageal junction adenocarcinoma

2.4.1 Study characteristics

The study characteristics, information on data cut-offs and the planned duration of follow-up observation in the CheckMate 649 study are described in detail in Section 2.4.1. The operationalizations of the subpopulations relevant for research questions 1 and 2 for the present benefit assessment are also described there.

The subpopulation of patients with gastric or gastrooesophageal junction adenocarcinoma and PD-L1 expressing tumours with CPS ≥ 5 of the CheckMate 649 study is relevant for research question 2. For this patient population, it is assumed that > 80% have a negative HER2 status (see Section 2.4.1 “Patients with HER2-negative adenocarcinoma”). This subpopulation comprises 417 patients in the intervention arm and 420 patients in the comparator arm. The uncertainty regarding the proportion of patients with HER2-negative tumours is addressed in Section 2.5.2.2.

In the CheckMate 649 study, the investigators determined before randomization whether the patients received FOLFOX (5-FU + folinic acid + oxaliplatin) or XELOX (capecitabine + oxaliplatin). For treatment with the chemotherapy regimens FOLFOX and XELOX, no information on dosing for these treatment regimens is provided in the relevant SPCs [10-13]. The chemotherapy regimens with the dosages used in the CheckMate 649 study are recommended according to current NCCN guidelines, however [14,15].

Characteristics of the study population

Table 13 shows the characteristics of the patients with gastric or gastrooesophageal adenocarcinoma in the included study.

Table 13: Characteristics of the study population – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) vs. chemotherapy (FOLFOX or XELOX), gastric or gastrooesophageal junction adenocarcinoma (multipage table)

Study Characteristic Category	**Nivolumab + chemotherapy (FOLFOX or XELOX) N[a] = 417**	**Chemotherapy (FOLFOX or XELOX) N[a] = 420**
CheckMate 649		
Age [years], mean (SD)	61 (12)	60 (12)
Age group, n (%)		
< 65 years	241 (58)	252 (60)
≥ 65 years to < 75 years	127 (30)	130 (31)
≥ 75 years	49 (12)	38 (9)
Sex [F/M], %	31/69	29/71
Family origin n (%)		
Asian	118 (28)	116 (28)
White	275 (66)	268 (64)
Other	24 (6)	36 (9)
Region, n (%)		
Asia	116 (28)	110 (26)
North America	47 (11)	42 (10)
Rest of the world	254 (61)	268 (64)
ECOG PS, n (%)		
0	169 (41)	173 (41)
1	248 (59)	246 (59)
Unknown	0 (0)	1 (< 1)
Location of primary tumour at first diagnosis, n (%)		
Stomach	333 (80)	334 (80)
Gastrooesophageal junction	84 (20)	86 (20)
Disease status, n (%)		
Locally recurrent/advanced	18 (4)	20 (5)
Metastatic	399 (96)	400 (95)
Prior surgery related to current cancer, n (%)		
Yes	86 (21)	90 (21)
No	331 (79)	330 (79)
Prior radiotherapy, n (%)		
Yes	30 (7)	29 (7)
No	387 (93)	391 (93)
Laurén classification, n (%)		
Intestinal type	150 (36)	151 (36)
Diffuse type	127 (30)	130 (31)
Mixed type	32 (8)	28 (7)
Unknown	108 (26)	111 (26)

Table 13: Characteristics of the study population – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) vs. chemotherapy (FOLFOX or XELOX), gastric or gastrooesophageal junction adenocarcinoma (multipage table)

Study Characteristic Category	**Nivolumab + chemotherapy (FOLFOX or XELOX)** **N[a] = 417**	**Chemotherapy (FOLFOX or XELOX)** **N[a] = 420**
Time between first diagnosis and randomization, n (%)		
< 6 months	352 (84)	363 (86)
6 months to < 1 year	8 (2)	17 (4)
≥ 1 year	57 (14)	40 (10)
Peritoneal metastases, n (%)		
Yes	94 (23)	93 (22)
No	309 (74)	316 (75)
Not reported	14 (3)	11 (3)
Liver metastases, n (%)		
Yes	165 (40)	186 (44)
No	238 (57)	223 (53)
Not reported	14 (3)	11 (3)
HER2 status at study entry, n (%)		
Negative	232 (56)	225 (54)
Positive	3 (< 1)	4 (< 1)
Unknown	2 (< 1)	3 (< 1)
Not reported	180 (43)	188 (45)
HER2 status/amplification[b], n (%)		
Negative	308 (74[c])	314 (75[c])
Positive	16 (4[c])	14 (3[c])
Unknown	1 (< 1[c])	0 (0)
Not reported	92 (22[c])	92 (22[c])
Treatment discontinuation (third data cut-off), n (%)	ND[d]	ND[d]
Study discontinuation (third data cut-off), n (%)	ND[e]	ND[e]

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. According to the company, the HER2 amplification status was subsequently analysed using next generation sequencing. The company considered a number of ≥ 4 copies of the HER2 gene in the analysis to be HER2-amplified.
c. Institute's calculation.
d. The information provided by the company shows that 361 out of 413 (87%) and 396 out of 406 (98%) of the patients with at least one dose of the study medication in the intervention and comparator arm, respectively, are "no longer on study medication" (minus those who, according to the company, have "completed treatment according to protocol"). It is assumed that these are patients for whom all drugs of the study medication have been discontinued. Common reasons were (intervention vs. comparator arm): disease progression (63% vs. 71%) and AEs (16% vs. 11%).
e. The company only provided information on how many patients discontinued the study "at the end of study medication" (19% vs. 22%). The most common reason for study discontinuation in these patients was death (15% vs. 14%). It is unclear how many patients discontinued the study in total by the time of the data cut-off.

Table 13: Characteristics of the study population – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) vs. chemotherapy (FOLFOX or XELOX), gastric or gastrooesophageal junction adenocarcinoma (multipage table)

Study Characteristic Category	Nivolumab + chemotherapy (FOLFOX or XELOX)	Chemotherapy (FOLFOX or XELOX)
	N[a] = 417	N[a] = 420

ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; HER2: human epidermal growth factor receptor 2; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus; XELOX: capecitabine + oxaliplatin

The mean age of the patients with gastric or gastrooesophageal junction adenocarcinoma was 61 and 60 years. In both treatment arms, about 70% were men and 30% women. 28% were of Asian and 65% of white family origin. 41% of the patients had an ECOG PS of 0, and 59% an ECOG PS of 1. In the relevant subpopulation, 80% of the patients had gastric adenocarcinoma and 20% gastrooesophageal junction adenocarcinoma. Almost all patients (96%) had metastases. The time between first diagnosis and randomization was less than 6 months for the majority of the patients in both study arms of the relevant subpopulation. According to the approval, only patients with negative HER2 status are comprised by the present therapeutic indication. In the relevant subpopulation, the proportion of patients with negative HER2 status at study entry was 55%. Few patients (< 1%) had a positive HER2 status in deviation from the inclusion criteria. For the other patients, the HER2 status was unknown or not reported. This is discussed in Section 2.4.1 on “Patients with HER2-negative adenocarcinoma”.

Data on the proportion of patients with discontinuation of one drug component are not available. It is inferred from the available information that 87% (intervention arm) and 98% (comparator arm) of the patients had discontinued all treatment components by the third data cut-off. The company presented no information on how many patients had discontinued the study by the third data cut-off. It only provided information on how many patients discontinued the study at the end of treatment.

Information on the course of the study

Table 14 shows the mean/median treatment duration of the patients with gastric or gastrooesophageal junction adenocarcinoma and the mean/median observation period for individual outcomes.

Table 14: Information on the course of the study – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) vs. chemotherapy (FOLFOX or XELOX), gastric or gastrooesophageal junction adenocarcinoma

Study **Duration of the study phase** **Outcome category**	**Nivolumab + chemotherapy (FOLFOX or XELOX)** **N = 413**	**Chemotherapy (FOLFOX or XELOX)** **N = 406**
CheckMate 649 (third data cut-off)		
Treatment duration [months]		
Median [min; max]	7.36 [0.1; 44.3]	4.70 [0.1; 42.9]
Mean (SD)	10.29 (8.75)	6.83 (7.06)
Observation period [months]		
Overall survival[a]		
Median [min; max]	14.26 [0.6; 49.5]	10.79 [0.1; 45.5]
Mean (SD)	17.34 (12.06)	13.42 (10.41)
Morbidity (health status – EQ-5D VAS)	ND	ND
Health-related quality of life (FACT-Ga)	ND	ND
Side effects	ND	ND

a. Information on how the observation period was calculated is not available.

FACT-Ga: Functional Assessment of Cancer Therapy-Gastric; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; max: maximum; min: minimum; N: number of patients with at least one dose of the study medication; ND: no data; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; XELOX: capecitabine + oxaliplatin

The median treatment duration for patients with gastric or gastrooesophageal junction adenocarcinoma in the intervention arm (nivolumab + chemotherapy [FOLFOX or XELOX]) was 7.36 months, markedly longer than the median treatment duration in the comparator arm (chemotherapy [FOLFOX or XELOX]) of 4.70 months. The company provided information on the observation period only for the outcome of overall survival. No information on the observation period is available for the outcome categories of morbidity, health-related quality of life and side effects. Whereas the morbidity outcome was to be observed until death, the observation period for the outcomes on health-related quality of life and side effects was linked to the end of treatment (plus 114 days) (see Table 8). For these outcomes, conclusions can therefore be drawn only regarding the time up to 114 days after treatment. Based on the information on the treatment duration plus 114 days, the median observation period was 11.1 months in the intervention arm and 8.5 months in the comparator arm. Hence, the observation periods for these outcomes were shortened in comparison with overall survival. Data for the entire observation period are missing for these outcomes.

In addition, there are also differences in the observation periods of the outcomes corresponding to the differences in the treatment durations between the study arms of both studies. This data situation influences the interpretability of the outcomes with shorter observation period (see Section 2.4.2.2).

Information on subsequent therapies

Table 15 shows the subsequent therapies patients with gastric or gastrooesophageal junction adenocarcinoma received after discontinuing the study medication.

Table 15: Information on subsequent therapies – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) vs. chemotherapy (FOLFOX or XELOX), gastric or gastrooesophageal junction adenocarcinoma (multipage table)

Study **Drug class** **Drug**	**Patients with subsequent therapy n (%)**	
	Nivolumab + chemotherapy (FOLFOX or XELOX) **N = 417**	**Chemotherapy (FOLFOX or XELOX)** **N = 420**
CheckMate 649 (third data cut-off)		
Total	169 (40.5)	172 (41.0)
Radiotherapy	18 (4.3)	21 (5.0)
Surgical intervention	11 (2.6)	6 (1.4)
Systemic therapy	153 (36.7)	164 (39.0)
Immunotherapy	9 (2.2)	38 (9.0)
Anti-PD1	9 (2.2)	33 (7.9)
Nivolumab	6 (1.4)	16 (3.8)
Pembrolizumab	2 (0.5)	15 (3.6)
Toripalimab	1 (0.2)	2 (0.5)
Anti-PD-L1	0 (0)	4 (1.0)
Atezolizumab	0 (0)	4 (1.0)
Other immunotherapy	0 (0)	2 (0.5)
Investigational immunotherapy	0 (0)	1 (0.2)
Tumour necrosis factor	0 (0)	1 (0.2)
Targeted therapy	62 (14.9)	65 (15.5)
Aflibercept	1 (0.2)	0 (0)
Apatinib	10 (2.4)	17 (4.0)
Bevacizumab	0 (0)	2 (0.5)
Cabozantinib	0 (0)	1 (0.2)
Crenolanib	1 (0.2)	0 (0)
Crizotinib	0 (0)	1 (0.2)
Endostar	0 (0)	1 (0.2)
Erdafitinib	1 (0.2)	0 (0)
Ibrutinib	1 (0.2)	1 (0.2)
Ramucirumab	46 (11.0)	41 (9.8)
Regorafenib	0 (0)	1 (0.2)
Selumetinib	0 (0)	1 (0.2)
Trastuzumab	5 (1.2)	4 (1.0)
Other systemic cancer therapy – investigational drugs	17 (4.1)	21 (5.0)
Investigational antineoplastic drug	17 (4.1)	21 (5.0)

Table 15: Information on subsequent therapies – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) vs. chemotherapy (FOLFOX or XELOX), gastric or gastrooesophageal junction adenocarcinoma (multipage table)

Study **Drug class** **Drug**	**Patients with subsequent therapy n (%)**	
	Nivolumab + chemotherapy (FOLFOX or XELOX) **N = 417**	**Chemotherapy (FOLFOX or XELOX)** **N = 420**
Other systemic cancer therapy – chemotherapy	150 (36.0)	156 (37.1)
Antineoplastic	3 (0.7)	0 (0)
Capecitabine	19 (4.6)	10 (2.4)
Carboplatin	2 (0.5)	2 (0.5)
Cisplatin	10 (2.4)	11 (2.6)
Docetaxel	12 (2.9)	14 (3.3)
Doxorubicin	0 (0)	1 (0.2)
Epirubicin	0 (0)	2 (0.5)
Etoposide	1 (0.2)	1 (0.2)
Floxuridine	0 (0)	1 (0.2)
Fluoropyrimidine	0 (0)	1 (0.2)
Fluorouracil	40 (9.6)	56 (13.3)
S-1	9 (2.2)	15 (3.6)
Herbal anti-cancer agents	0 (0)	1 (0.2)
Irinotecan	49 (11.8)	64 (15.2)
Methotrexate	1 (0.2)	0 (0)
Oxaliplatin	18 (4.3)	26 (6.2)
Paclitaxel	82 (19.7)	93 (22.1)
Raltitrexed	3 (0.7)	6 (1.4)
Tegafur	1 (0.2)	1 (0.2)
Temozolomide	0 (0)	1 (0.2)
Tipiracil/trifluridine	1 (0.2)	2 (0.5)
Tipiracil	0 (0)	1 (0.2)
Not assigned	32 (7.7)	47 (11.2)

FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; n: number of patients with subsequent therapy; N: number of analysed patients; PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; XELOX: capecitabine + oxaliplatin

After discontinuation of the study medication, 41% of the patients in both treatment arms received subsequent therapy. In both treatment arms, this was mostly a systemic therapy – the majority of patients received other chemotherapeutic agents.

Limitations regarding subsequent therapies cannot be inferred from the study documents. Switching to the treatment of the other study arm was not planned.

Risk of bias across outcomes (study level)

Table 16 shows the risk of bias across outcomes (risk of bias at study level).

Table 16: Risk of bias across outcomes (study level) – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) vs. chemotherapy (FOLFOX or XELOX), gastric or gastrooesophageal junction adenocarcinoma

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			
CheckMate 649	Yes	Yes	No	No	Yes	Yes	Low

FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; RCT: randomized controlled trial; XELOX: capecitabine + oxaliplatin

The risk of bias across outcomes is rated as low for the CheckMate 649 study.

Transferability of the study results to the German health care context

From the point of view of the company, the results of the CheckMate 649 study are readily transferable to the German health care context, as the study was also conducted in Germany and in Western industrialized countries (Europe and North America) with similar population groups and approximately 69% were of white family origin.

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

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - health status recorded with the EQ-5D VAS
- Health-related quality of life
  - FACT-Ga
- Side effects

- SAEs
- severe AEs, operationalized as CTCAE grade ≥ 3
- discontinuation due to AEs
- immune-related SAEs
- immune-related severe AEs
- further specific AEs, if any

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

2.4.2.2 Derivation of an added benefit is only possible due to the large effect in overall survival

As described in Section 2.4.2.2, the results of the CheckMate 649 study presented by the company in the dossier are incomplete in terms of content. The current third data cut-off is relevant for the present benefit assessment. For this data cut-off, the company presented results exclusively for the outcome of overall survival. It presented results only for the first data cut-off for the other outcomes. This approach is not appropriate. The analyses for the first data cut-off presented by the company are not usable for the present assessment. Nevertheless, an added benefit can be derived in the present situation for the patients of research question 2 due to a large effect in the outcome of overall survival.

The results on the outcome of overall survival for research question 2 are presented in the following Table 17.

Table 17: Results (mortality) – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) vs. chemotherapy (FOLFOX or XELOX), gastric or gastrooesophageal junction adenocarcinoma

Study **Outcome category** **Outcome**	**Nivolumab + chemotherapy (FOLFOX or XELOX)**		**Chemotherapy (FOLFOX or XELOX)**		**Nivolumab + chemotherapy (FOLFOX or XELOX) vs. chemotherapy (FOLFOX or XELOX)**
	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]**
CheckMate 649 (third data cut-off)					
Mortality					
Overall survival	417	14.5 [13.1; 16.3] 319 (76.5)	420	11.1 [10.0; 12.5] 362 (86.2)	0.68 [0.59; 0.79]; < 0.001

a. HR and CI: Cox proportional hazards model; p-value: log-rank test; each unstratified.

CI: confidence interval; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; XELOX: capecitabine + oxaliplatin

For the outcome of overall survival, there is a statistically significant difference in favour of nivolumab + chemotherapy (FOLFOX or XELOX) in comparison with chemotherapy (FOLFOX or XELOX); this results in an added benefit of major extent for this outcome [1].

It is not assumed that, taking into account the results of the first data cut-off (see supplementary information in Appendix C of the full dossier assessment), the data of the current data cut-off on the other outcomes, completely call into question the positive effect in the outcome of overall survival.

Based on this, an added benefit can be derived in this situation, but the extent of the added benefit cannot be estimated and is therefore non-quantifiable.

The certainty of conclusions of the study results is reduced due to the uncertainty described in Section 2.4.1 with regard to the proportion of patients with HER2-negative tumours, so that at most a hint can be derived.

2.4.3 Probability and extent of added benefit

No complete data are available for the assessment of the added benefit of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy in comparison with the ACT as first-line treatment of adult patients with HER2-negative advanced or metastatic gastric or gastrooesophageal junction adenocarcinoma whose tumours express

PD-L1 (CPS ≥ 5). Due to the large effect in overall survival, a hint of a non-quantifiable added benefit of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy in comparison with the ACT can still be derived in the present situation.

The assessment described above deviates from that of the company, which derived an indication of major added benefit for all patients in the therapeutic indication, regardless of the different tumour entities. Even if the 2 subpopulations were considered separately, in the opinion of the company there would be a major added benefit in each case in the overall view.

2.5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy in comparison with the ACT is summarized in Table 18.

Table 18: Nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy – probability and extent of added benefit

Research question	Subindication	ACT[a, b]	Probability and extent of added benefit
1	Adults with locally advanced or metastatic HER2-negative oesophageal adenocarcinoma that cannot be treated curatively and whose tumours express PD-L1 (CPS ≥ 5); first-line treatment	Treatment of physician's choice[c]	Added benefit not proven[d]
2	Adults with locally advanced or metastatic HER2-negative gastric or gastrooesophageal junction adenocarcinoma that cannot be treated curatively and whose tumours express PD L1 (CPS ≥ 5); first-line treatment	▪ Cisplatin in combination with 5-fluorouracil ± folinic acid or ▪ cisplatin in combination with capecitabine or ▪ oxaliplatin in combination with 5-fluorouracil ± folinic acid[e] or ▪ oxaliplatin in combination with capecitabine or ▪ 5-fluorouracil ± folinic acid + oxaliplatin + docetaxel[f] (only for patients in good general condition and without relevant comorbidities)	Hint of non-quantifiable added benefit[g]

a. Presented is the respective ACT specified by the GBA.
b. It is assumed for the present therapeutic indication that curative treatment with definitive radiochemotherapy is not an option for patients with unresectable cancer.
c. Guidelines mention several platinum- and fluoropyrimidine-based combination chemotherapies: S-1 (tegafur/gimeracil/oteracil) + cisplatin or capecitabine + cisplatin [XP], 5-fluorouracil+ cisplatin, 5-fluorouracil + oxaliplatin + folinic acid [FLO and FOLFOX], capecitabine + oxaliplatin, infusional 5-fluorouracil + folinic acid + cisplatin [PLF], epirubicin + cisplatin + capecitabine [ECX], epirubicin + oxaliplatin + capecitabine [EOX], epirubicin + cisplatin + infusional 5-fluorouracil [ECF], docetaxel + cisplatin + infusional 5-fluorouracil [DCF], 5-fluorouracil + oxaliplatin + epirubicin, infusional 5-fluorouracil + folinic acid + oxaliplatin + docetaxel [FLOT regimen]. However, only the drugs 5-fluorouracil and cisplatin are approved in the present therapeutic indication. There is a discrepancy between the drugs approved in the therapeutic indication and those recommended in guidelines. In the context of treatment of physician's choice, the G-BA considered the treatment options cited above to be suitable comparators.
d. For those patients for whom FOLFOX (5-fluorouracil + folinic acid + oxaliplatin) or XELOX (capecitabine + oxaliplatin) is the suitable treatment of physician's choice.
e. According to the G-BA, the combination of infusional 5-fluorouracil + folinic acid + oxaliplatin (FLO and FOLFOX) is comprised by the ACT.
f. According to the G-BA, the combination of infusional 5-fluorouracil + folinic acid + oxaliplatin + docetaxel (FLOT) is comprised by the ACT.
g. The CheckMate 649 study included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.

ACT: appropriate comparator therapy; CPS: combined positive score; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor -2; PD-L1: programmed cell death ligand 1

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.

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Bristol Myers Squibb. A Randomized, Multicenter, Open-Label, Phase 3 Study of Nivolumab Plus Ipilimumab or Nivolumab in Combination with Oxaliplatin Plus Fluoropyrimidine versus Oxaliplatin Plus Fluoropyrimidine in Subjects with Previously Untreated Advanced or Metastatic Gastric or Gastroesophageal Junction Cancer; study CA209649; Primary Clinical Study Report [unpublished]. 2020.

4. Bristol Myers Squibb. Nivolumab (BMS-936558) in Combination with Chemotherapy; study CA209649; Ad Hoc Report [unpublished]. 2021.

5. Bristol-Myers Squibb. Efficacy Study of Nivolumab Plus Ipilimumab or Nivolumab Plus Chemotherapy Against Chemotherapy in Stomach Cancer or Stomach/Esophagus Junction Cancer [online]. 2021 [Accessed: 01.02.2022]. URL: https://ClinicalTrials.gov/show/NCT02872116.

6. Bristol-Myers Squibb. A Randomized, Multicenter, Open-Label, Phase 3 Study of Nivolumab plus Ipilimumab or Nivolumab in Combination with Oxaliplatin plus Fluoropyrimidine versus Oxaliplatin plus Fluoropyrimidine in Subjects with Previously Untreated Advanced or Metastatic Gastric or Gastroesophageal Junction Cancer [online]. [Accessed: 10.12.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-001018-76.

7. Janjigian YY, Shitara K, Moehler M et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet 2021; 398: 27-40. https://dx.doi.org/10.1016/s0140-6736(21)00797-2.

8. European Medicines Agency. Assessment report. OPDIVO; nivolumab; Procedure No. EMEA/H/C/003985/II/0096; 16.09.2021 [online]. 2021. URL: https://www.ema.europa.eu/en/medicines/human/EPAR/opdivo.

9. Bristol Myers Squibb. OPDIVO 10 mg/ml Konzentrat zur Herstellung einer Infusionslösung [online]. 2021 [Accessed: 20.01.2022]. URL: https://www.fachinfo.de.

10. Medac. Capecitabin medac 150/500 mg Filmtabletten [online]. 2021 [Accessed: 26.11.2021]. URL: https://www.fachinfo.de.

11. Pfizer. Fachinformation Leucovorin 10 mg/ml Lösung zur Injektion/Infusion. Stand: Mai 2021 [online]. 2021. URL: https://www.fachinfo.de.

12. Sanofi Genzyme. ELOXATIN 5 mg/ml Konzentrat zur Herstellung einer Infusionslösung [online]. 2019 [Accessed: 26.11.2021]. URL: https://www.fachinfo.de.

13. Ribosepharm. Ribofluor [online]. 2017 [Accessed: 26.11.2021]. URL: https://www.fachinfo.de.

14. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Gastric Cancer, Version 5.2021 [online]. 2021. URL: https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf.

15. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Esophageal and Esophagogastric Junction Cancers, Version 4.2021 [online]. 2021. URL: https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf.

16. Leitlinienprogramm Onkologie der Awmf, Deutsche Krebsgesellschaft, Deutsche Krebshilfe. S3-Leitlinie Magenkarzinom - Diagnostik und Therapie der Adenokarzinome des Magens und ösophagogastralen Übergangs, Langversion 2.0. Stand: August 2019 [online]. 2019. URL: https://www.awmf.org/uploads/tx_szleitlinien/032-009l_S3_Magenkarzinom_Diagnostik_Therapie_Adenokarzinome_oesophagogastraler_Uebergang_2019-12.pdf.

17. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF). S3-Leitlinie; Diagnostik und Therapie der Plattenepithelkarzinome und Adenokarzinome des Ösophagus; Langversion 3.0; Oktober 2021; AWMF Registernummer: 021/023OL [online]. 2021 [Accessed: 18.02.2022]. URL: https://www.leitlinienprogramm-onkologie.de/leitlinien/oesophaguskarzinom/.

18. Dijksterhuis WPM, Verhoeven RHA, Meijer SL et al. Increased assessment of HER2 in metastatic gastroesophageal cancer patients: a nationwide population-based cohort study. Gastric Cancer 2020; 23: 579-590. https://dx.doi.org/10.1007/s10120-020-01039-7.

19. Baretton G, Kreipe HH, Schirmacher P et al. HER2 testing in gastric cancer diagnosis: insights on variables influencing HER2-positivity from a large, multicenter, observational study in Germany. Virchows Arch 2019; 474: 551-560. https://dx.doi.org/10.1007/s00428-019-02541-9.

20. Langer R, Rauser S, Feith M et al. Assessment of ErbB2 (Her2) in oesophageal adenocarcinomas: summary of a revised immunohistochemical evaluation system, bright field double in situ hybridisation and fluorescence in situ hybridisation. Mod Pathol 2011; 24(7): 908-916. https://dx.doi.org/10.1038/modpathol.2011.52.

21. Gemeinsamer Bundesausschuss. Dossier zur Nutzenbewertung gemäß § 35a SGB V; Modul 4; Dokumentvorlage, Version vom 21.02.2019 [online]. 2019 [Accessed: 27.01.2022]. URL: https://www.g-ba.de/downloads/17-98-4825/2019-02-21_Anl2_6_Modul4.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects/a21-146.html.