Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Nivolumab (new therapeutic indication: Gastric, gastro-oesophageal junction or oesophageal adenocarcinoma, CPS ≥ 5, HER2-negative, first-line, combination with fluoropyrimidine- and platinum-based combination chemotherapy)

of 19 May 2022

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient nivolumab (Opdivo) was listed for the first time on 5 July 2015 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 19 October 2021, Opdivo received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 16 November 2021, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction

with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient nivolumab with the new therapeutic indication (OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5.). The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 March 2022 on the G-BA website (www.g-ba.de), therefore initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of nivolumab compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of nivolumab.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Nivolumab (Opdivo) in accordance with the product information

OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5.

Therapeutic indication of the resolution (resolution of 19 May 2022):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with locally advanced or metastatic HER2-negative gastric, gastro-oesophageal junction or oesophageal adenocarcinoma which cannot be treated curatively and whose tumours express PD-L1 (combined positive score (CPS) ≥ 5); first-line therapy

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Appropriate comparator therapy for nivolumab in combination with FOLFOX (5-fluorouracil + folinic acid + oxaliplatin) or XELOX (capecitabine + oxaliplatin):

- Therapy according to doctor's instructions

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. In addition to nivolumab, the active ingredients tegafur / gimeracil / oteracil, capecitabine, cisplatin, 5-fluorouracil, folinic acid, doxorubicin, epirubicin, mitomycin, docetaxel and pembrolizumab are approved for the present indication.

Despite extensive clinical data, there is no approval for oxaliplatin for the present therapeutic indication, but the active ingredient is approved as combination therapy via other active ingredients (e.g. capecitabine, 5-fluorouracil).

on 2. A non-medicinal treatment option is not considered for the therapeutic indication in question.

on 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Tegafur/gimeracil/oteracil: Resolution of 20 December 2012
- Pembrolizumab: Resolution of 5 May 2022

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present therapeutic indication. The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a paragraph 7 SGB V.

Among the approved active ingredients listed under 1., only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of health care provision.

According to current guidelines and written statements of the scientific-medical societies, doublet or triplet chemotherapy containing platinum and fluoropyrimidine is indicated for patients with locally advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma with negative HER2 status. The general condition, age, concomitant diseases and comorbidity must be taken into account when selecting the treatment regimens. If a docetaxel-based triple combination is indicated, modified schemes should be preferred to the classical DCF regimen due to lower toxicity.

The guidelines mention various platinum and fluoropyrimidine-based combination chemotherapies[2,3,4,5]:

- S-1 (tegafur/ gimeracil/ oteracil) + cisplatin
- 5-fluorouracil (FU) + cisplatin
- 5-fluorouracil + oxaliplatin + folinic acid [FLO and FOLFOX]
- capecitabine + cisplatin [XP]
- 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 regime)

According to the scientific-medical societies and clinical experts in the written statement procedure on the present benefit assessment, gastric, gastro-oesophageal junction or oesophageal adenocarcinoma is also to be regarded as a histological entity. Against this background, no distinction is made in the healthcare context between the above-mentioned localisations with regard to the therapeutic approach in the context of systemic first-line therapy in the locally advanced or metastasised stage.

Overall, with the named treatment options, several treatment options are available for the treatment of patients with advanced HER2-negative gastric, gastro-oesophageal junction or oesophageal adenocarcinoma. However, only the active ingredients 5-fluorouracil, capecitabine, docetaxel, epirubicin, folinic acid and tegafur / gimeracil / oteracil have a marketing authorisation for the treatment of gastric adenocarcinoma. There is no marketing authorisation for cisplatin and oxaliplatin for gastric carcinoma despite extensive clinical data, but the active ingredients are approved as combination therapy via other active ingredients (e.g. capecitabine, docetaxel). The active ingredient

[2] Guideline program in oncology (German Cancer Society, German Cancer Aid, Association of the Scientific Medical Societies), 2019 Gastric carcinoma - Diagnosis and therapy of gastric and gastro-oesophageal junction adenocarcinoma; S3 guideline. Long version 2.0

[3] Guideline program in oncology (German Cancer Society, German Cancer Aid, Association of the Scientific Medical Societies), 2021 Diagnosis and therapy of squamous cell carcinomas and oesophageal adenocarcinoma; S3 guideline. Long version 3.0

[4] Alberta Health Services, 2020. Gastric cancer, version 5.

[5] National Institute for Health and Care Excellence (NICE), 2018. Oesophago-gastric cancer – Assessment and management in adults.

docetaxel is approved for the treatment of gastroesophageal junction adenocarcinomas. The active ingredients 5-fluorouracil, cisplatin and folinic acid are approved for the treatment of oesophageal adenocarcinoma. There is a discrepancy between the medicinal products approved in the therapeutic indication and those recommended in the guidelines.

The treatment options listed above in the guidelines are considered suitable comparators in the context of treatment as by the doctor's instructions. These combinations of active ingredients are equally suitable for the implementation of the appropriate comparator therapy. The additional benefit can be proven over one of the treatment options in a single-comparator study.

However, the possibility of the off-label use of the active ingredients in a clinical study does not allow any conclusions to be drawn about their appropriateness in the off-label use in the standard care of insured persons in the SHI system. Such an assessment would be reserved for the decision according to Section 35c SGB V. This does not affect an off-label prescription in specific cases according to the criteria of the established case law of the Federal Social Court on off-label use not regulated in the Pharmaceuticals Directive.

In the present therapeutic indication, pembrolizumab is also approved in combination with platinum- and fluoropyrimidine-based chemotherapy. In the benefit assessment, no additional benefit was identified for the patient group of adults with locally advanced or metastatic HER2-negative adenocarcinoma of the oesophagus or of the gastroesophageal junction which cannot be treated curatively and whose tumours express PD-L1 expressing tumours (Combined Positive Score (CPS ≥ 10) compared to therapy as defined by the doctor's instructions. Pembrolizumab in combination with platinum- and fluoropyrimidine-based therapy is still a relatively new treatment option whose therapeutic significance cannot yet be conclusively assessed. Therefore, this treatment option is not currently determined as an appropriate comparator therapy.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

Change of the appropriate comparator therapy:

Originally, the appropriate comparator therapy was determined as follows:

a) Adults with locally advanced or metastatic HER2-negative adenocarcinoma of the oesophagus which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 5); first-line therapy

Appropriate comparator therapy for nivolumab in combination with FOLFOX (5-fluorouracil + folinic acid + oxaliplatin) or XELOX (capecitabine + oxaliplatin):

– Therapy according to doctor's instructions

The following treatment options are considered suitable comparators within the framework of therapy according to doctor's instructions:

- S-1 (tegafur/ gimeracil/ oteracil) + cisplatin,
- 5-fluorouracil + cisplatin,

- 5-fluorouracil + oxaliplatin + folinic acid (FLO and FOLFOX),
- capecitabine + cisplatin [XP],
- 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 regime).

b) Adults with locally advanced or metastatic HER2-negative gastric adenocarcinoma or HER2-negative gastroesophageal junction which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 5); first-line therapy

Appropriate comparator therapy for nivolumab in combination with FOLFOX (5-fluorouracil + folinic acid + oxaliplatin) or XELOX (capecitabine + oxaliplatin):

- cisplatin in combination with 5-fluorouracil +/- folinic acid

  or
- cisplatin in combination with capecitabine

  or
- oxaliplatin in combination with 5-fluorouracil +/- folinic acid

  or
- oxaliplatin in combination with capecitabine

  or
- 5-fluorouracil +/- folinic acid + oxaliplatin + docetaxel (only for patients in good general condition without relevant comorbidities)

Within the framework of the written statement procedure, the scientific-medical societies and clinical experts explained that subgrouping in the present indication is not meaningful, since gastric, gastro-oesophageal junction or oesophageal adenocarcinomas are one histological entity and the prognosis is comparable for the affected patients regardless of the tumour location. In healthcare context, no distinction is made between the localisations in systemic treatment.

Taking into account the statements of the scientific-medical societies and experts in the present procedure, the patients with gastric, gastro-oesophageal junction or oesophageal adenocarcinomas are combined into one patient population.

This change to the appropriate comparator therapy has no effects on the present assessment of the additional benefit, nor does it require the benefit assessment to be carried out again.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of nivolumab in combination with FOLFOX or XELOX is assessed as follows:

Hint of a considerable additional benefit

Justification:

For the evidence of an additional benefit, the pharmaceutical company submitted in the dossier the results of the still ongoing, open, randomised, controlled study CheckMate 649, in which nivolumab in combination with FOLFOX (5-fluorouracil + folinic acid + oxaliplatin) or XELOX (capecitabine + oxaliplatin), is compared with FOLFOX or XELOX.

The study included adults with inoperable, (locally) advanced or metastatic gastric, gastroesophageal junction or oesophageal adenocarcinoma who have not yet received systemic therapy for advanced disease. The patients had to have also a good general condition at start of the study, with an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1. Patients with a known positive HER2 status of their tumour were excluded from participation in the study. The study also included a percentage of patients for whom the HER2 status of their tumour was unknown or unreported at the time of enrolment.

A total of 1581 patients were included in the two relevant study arms. The relevant sub-population of patients with gastric, gastro-oesophageal junction or oesophageal adenocarcinoma with PD-L1 expression CPS ≥ 5 comprises a total of 955 patients, of whom 473 patients were treated in the intervention arm (nivolumab in combination with FOLFOX or XELOX) and 482 patients in the comparator arm (FOLFOX or XELOX).

The treatment with nivolumab in the intervention arm was carried out according to the requirements in the product information. For treatment with the chemotherapy regimens FOLFOX and XELOX, no information on the dosage for these treatment regimens is given in the corresponding product information. However, the chemotherapy regimens with the doses used in the CheckMate 649 study are recommended according to current National Comprehensive Cancer Network (NCCN) guidelines.

The decision on the choice of chemotherapy regimen (FOLFOX or XELOX) was determined by the principal investigators prior to randomisation.

The study population was treated until disease progression, unacceptable toxicity, treatment discontinuation or a maximum treatment duration of 24 months. The maximum treatment duration applies to nivolumab, which could also be passed on after disease progression until loss of clinical benefit, provided the patient tolerated the treatment. A changeover to the treatment of the other study arm was not planned.

The study, which is still ongoing, is being conducted at 175 study sites in 29 countries in Asia, Australia, Europe, North America and South America. Primary endpoints in the study are overall survival and progression-free survival (PFS). Secondary endpoints are endpoints in the categories morbidity, health-related quality of life and side effects.

At the time of the benefit assessment, 3 data cut-offs of the still ongoing CheckMate 649 study were available:

- 1. Data cut-off from 27.05.2020 with Database Lock (DBL) on 10.07.2020 (planned a priori)
- 2. Data cut-off from 04.01.2021 with DBL on 16.02.2021 (requested by the European Medicines Agency (EMA))
- 3. Data cut-off from 27.05.2021 with DBL on 08.07.2021 (planned a priori).

In the dossier on the current 3rd data cut-off, the pharmaceutical company published evaluations for the endpoint overall survival, but no evaluations for the other endpoints of the categories morbidity, health-related quality of life and side effects. For these endpoints, the pharmaceutical company submitted evaluations from the 1 year earlier 1st data cut-off. The pharmaceutical company justifies its action in the dossier with the fact that the 1st data cut-off was the relevant data cut-off for these endpoints, as the treatment at the 1st data cut-off had already ended for 91 % of the patients and considering the collection and evaluation of these endpoints at a later point in time, no significant gain in information could be expected.

The IQWiG stated in the dossier assessment that, against this background, the results presented by the pharmaceutical company in the dossier are to be assessed as incomplete in terms of content. The information available in the dossier shows that at the time of the 1st data cut-off, depending on the treatment arm, 17 to 31% of patients were still under observation, so that for the endpoints on morbidity, health-related quality of life and side effects, the third data cut-off will add data of a relevant scope.

With its written statement, the pharmaceutical company submitted subsequently evaluations of the 3rd data cut-off for the endpoints on morbidity, health-related quality of life and side effects.

For the present benefit assessment, the results of the 3rd data cut-off are used, including the evaluations subsequently submitted by the pharmaceutical company.

Extent and probability of the additional benefit

Mortality

Overall survival is defined in the CheckMate 649 study as the time between randomisation and death, regardless of the underlying cause of death.

For the endpoint overall survival, there was a statistically significant difference in favour of nivolumab in combination with FOLFOX or XELOX for the relevant sub-population (PD-L1-positive population), the extent of which is assessed as a significant improvement in terms of prolongation of survival time.

Morbidity

Progression-free survival (PFS)

PFS is operationalised in the CheckMate 649 study as time from randomisation to disease progression according to RECIST criteria version 1.1 or death from any cause.

With nivolumab in combination with FOLFOX or XELOX, PFS was statistically significantly prolonged for the relevant sub-population (PD-L1 positive population) compared to FOLFOX or XELOX.

The PFS endpoint is a combined endpoint composed of endpoints of the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The morbidity component of “disease progression” is assessed according to RECIST criteria and thus not symptom-related, but by means of imaging procedures. Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient relevance of the endpoint PFS. The overall statement on the additional benefit remains unaffected.

Symptomatology

Data on disease symptomatology were not collected in the CheckMate 649 study.

Health status (EQ-5D, visual analogue scale)

General health status is assessed in the CheckMate 649 study using the EQ-5D visual analogue scale (VAS). The survey should be conducted in the study until death.

For this endpoint, the pharmaceutical company submitted responder analyses of the time to what he called "permanent deterioration". This was defined as a decrease in the corresponding score by at least the response criterion without a subsequent improvement above the response criterion (including 15% of the scale range) in one of the subsequent assessments. In addition, the pharmaceutical company submitted continuous analyses of the changes since the start of the study within the scope of sensitivity analyses.

Since the data on the responses show that the corresponding percentages after the end of treatment with the study medication become significantly lower in both arms and the data on the responses are only available separately for the period under treatment and the period after treatment, it cannot be conclusively assessed to what extent the presented responder analyses of the "time to permanent deterioration" are adequate. Against this background, the analyses on the "time to permanent deterioration" are not used for the present benefit assessment.

Since assessments conducted after the end of treatment were not taken into account in the continuous analyses of change since the start of the study, these analyses are also not used for the present benefit assessment.

<u>Quality of life</u>

Health-related quality of life is assessed in the CheckMate 649 study using the FACT-Ga (Functional Assessment of Cancer Therapy-Gastric). This comprises the FACT-G (FACT-General) and the gastric cancer-specific subscale GaCS (FACT-Gastric Cancer Subscale).

The planned follow-up duration for the FACT-Ga was 114 ± 14 days after the last dose of study medication. According to IQWiG's dossier assessment, it remained unclear on the basis of the benefit assessment dossier and the study documents whether the general part FACT-G was only collected during treatment or also up to 114 days after the last dose of the study medication. According to the information provided by the pharmaceutical company in the

context of the written statement procedure on the present benefit assessment, the FACT-G was only collected during treatment.

In the dossier for the benefit assessment, the pharmaceutical company submitted responder analyses on the time to what they called "permanent deterioration". IQWiG's dossier assessment pointed out that evaluations of the time to first-time or once-confirmed deterioration would be necessary, as without further information the evaluations of the time to "permanent deterioration" could not be interpreted.

Within the framework of the written statement procedure on the present benefit assessment, responder analyses of the time to first deterioration were submitted by the pharmaceutical company. These will be used for the present assessment.

There was a statistically significant advantage of nivolumab in combination with FOLFOX or XELOX for the endpoint FACT-Ga (total score) for the relevant sub-population (PD-L1 positive population). For the subscales PWB, SWB, EWB and FWB, there was no statistically significant difference between the treatment groups. For the GaCS subscale, no evaluations were available for the period over which the total score was calculated.

Side effects

Adverse events (AEs)

In the CheckMate 649 study, AEs occurred in both treatment groups in almost all patients enrolled. The results were only presented additionally.

Serious adverse events (SAEs) and severe adverse events (CTCAE grade ≥ 3)

For the endpoints of SAEs and severe AEs, there was no statistically significant difference between the treatment groups for the relevant sub-population.

Discontinuation due to AEs

For the endpoint discontinuation due to AEs, there was a statistically significant difference to the disadvantage of nivolumab in combination with FOLFOX or XELOX compared to FOLFOX or XELOX for the relevant sub-population.

Specific adverse events

For the specific AEs immune-mediated SAEs, immune-mediated severe AEs, skin and subcutaneous tissue disorders (SOC, AE), immune system disorders (SOC, AE), amylase elevated (PT, severe AE) and peripheral neuropathy (PT, severe AE), there was a statistically significant difference to the disadvantage of nivolumab in combination with FOLFOX or XELOX for the relevant sub-population.

In summary, a disadvantage of treatment with nivolumab in combination with FOLFOX or XELOX can be identified due to the negative effect in therapy discontinuations due to AEs. With regard to specific adverse events, there were in detail disadvantages of nivolumab in combination with FOLFOX or XELOX.

Overall assessment

For the benefit assessment of nivolumab in combination with FOLFOX or XELOX, data on the relevant sub-population from the open-label, randomised controlled CheckMate 649 study on mortality, morbidity, quality of life and side effects are available.

For the endpoint of overall survival, there is a statistically significant difference to the advantage of nivolumab in combination with FOLFOX or XELOX. The magnitude of the effect is assessed as a significant improvement.

Data on disease symptomatology were not collected in the CheckMate 649 study.

No usable data on health status are available from the CheckMate 649 study.

With regard to health-related quality of life (assessed by FACT-Ga), there is an advantage of nivolumab in combination with FOLFOX or XELOX.

There were no statistically significant differences in side effects between the treatment groups with regard to the endpoints serious AEs, severe adverse events (CTCAE grade ≥ 3). For the endpoint discontinuation due to AEs, there is a disadvantage of nivolumab in combination with FOLFOX or XELOX. In detail, the specific AEs show negative effects of nivolumab in combination with FOLFOX or XELOX compared to FOLFOX or XELOX.

The overall results show a significant improvement in overall survival. In addition, there are advantages in health-related quality of life. On the other hand, there are disadvantages in the endpoint discontinuation due to AEs, as well as in the specific AEs in detail. As a result, a considerable additional benefit is found for nivolumab in combination with FOLFOX or XELOX compared to FOLFOX or XELOX.

Reliability of data (probability of additional benefit)

The present CheckMate 649 study is a randomised, controlled, open-label study.

The risk of bias across all endpoints is rated as low for the study.

However, the reliability of data of the results is reduced across all endpoints, as a percentage of patients had unknown or unreported HER2 status at time of enrolment, resulting in uncertainties regarding the percentage of patients with HER2-negative adenocarcinomas.

The risk of bias is rated as low for overall survival.

The risk of bias for the endpoint health-related quality of life is rated as high, on the one hand because a high percentage of patients was not considered in the evaluation and on the other hand because of the lack of blinding of the study. For the endpoint discontinuation due to AEs, an increased risk of bias is also derived due to the open study design.

These limitations lead to the reliability of data of the additional benefit being classified overall as "hint".

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient nivolumab:

"OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with HER2-negative

advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5.)."

For the benefit assessment, the pharmaceutical company submits the results of the CheckMate 649 study, an open-label, randomised, controlled study in which nivolumab in combination with FOLFOX (5-fluorouracil + folinic acid + oxaliplatin) or XELOX (capecitabine + oxaliplatin) is compared against FOLFOX or XELOX. The comparator therapy in the study corresponds to the appropriate comparator therapy.

For the endpoint overall survival, nivolumab showed a statistically significant advantage, the magnitude of which was assessed as a significant improvement.

In the endpoint category morbidity, no data suitable for the benefit assessment are available.

There is a significant advantage with regard to health-related quality of life (assessed using FACT-Ga).

In terms of side effects, there are disadvantages in the endpoint discontinuation due to AEs, as well as in detail in the specific AEs.

Relevant uncertainties arise with regard to the percentage of patients with HER2-negative adenocarcinomas, as a percentage of patients had an unknown or unreported HER2 status at time of enrolment. In addition, there is a high risk of bias in the data on health-related quality of life, which is why the overall reliability of data regarding the additional benefit identified is classified as a "hint".

As a result, the G-BA found a hint of considerable additional benefit for nivolumab compared with the appropriate comparator therapy.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA bases its resolution on the information from the addendum to the benefit assessment prepared by IQWiG. It must be taken into account that an underestimation must be assumed here. On the one hand, this results from an excessive restriction of the target population to patients who receive palliative first-line therapy based on the distribution of patients among different therapy options. On the other hand, patients who have already received therapy at an earlier stage and may suffer a progression were not taken into account.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Opdivo (active ingredient: nivolumab) at the following publicly accessible link (last access: 4 March 2022):
https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf

Treatment with nivolumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, internal medicine and gastroenterology, and specialists participating in the Oncology Agreement experienced in the treatment of adults with gastric, gastroesophageal junction or oesophageal carcinoma.

In accordance with the Medicines Agency requirements regarding additional risk minimisation measures, the pharmaceutical company must provide healthcare professionals and patients with a patient card. The patient card contains, in particular, instructions on the management of immune-mediated side effects potentially occurring with nivolumab as well as on infusion-related reactions. The prescribing doctors must discuss the risks of therapy with nivolumab with the patients.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 May 2022).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information. The annual treatment costs shown refer to the first year of treatment.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Nivolumab in combination with 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX 4)				
Nivolumab	1 x every 14 days	26.1	1	26.1
5-fluorouracil	1 x on day 1 and 2 of a 14 day cycle	26.1	2	52.2
Folinic acid	1 x on day 1 and 2 of a 14 day cycle	26.1	2	52.2
Oxaliplatin	1 x on day 1 of a 14 day cycle	26.1	1	26.1
Nivolumab in combination with 5-fluorouracil + folinic acid + oxaliplatin (mod. FOLFOX 6)				
Nivolumab	1 x every 14 days	26.1	1	26.1

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
5-fluorouracil	1 x on day 1 of a 14 day cycle	26.1	1	26.1
Folinic acid	1 x on day 1 of a 14 day cycle	26.1	1	26.1
Oxaliplatin	1 x on day 1 of a 14 day cycle	26.1	1	26.1
Nivolumab in combination with capecitabine + oxaliplatin (XELOX)				
Nivolumab	1 x every 21 days	17.4	1	17.4
Capecitabine	2 x on day 1 - 14 of a 21 day cycle	17.4	14	243.6
Oxaliplatin	1 x on day 1 of a 21 day cycle	17.4	1	17.4
Appropriate comparator therapy				
Therapy according to doctor's instructions[6]:				
Cisplatin + 5-fluorouracil				
Cisplatin	1 x on day 1 of a 21-day cycle	17.4	1	17.4
5-fluorouracil	1 x on day 1 - 5 of a 21-day cycle	17.4	5	87
Cisplatin + 5-fluorouracil + folinic acid				
Cisplatin	1 x on day 1 of a 21-day cycle	17.4	1	17.4
5-fluorouracil	1 x on day 1 - 5 of a 21-day cycle	17.4	5	87
Folinic acid	1 x on day 1 of a 21-day cycle	17.4	1	17.4

[6] The costs are presented for the active ingredients that are each approved for at least one of the present localisations. The following medicinal product combinations are only approved for the treatment of gastric carcinoma: Cisplatin + capecitabine (XP), oxaliplatin + 5-fluorouracil + folinic acid (FOLFOX-4 and mod. FOLFOX-6), oxaliplatin + 5-fluorouracil + folinic acid (FLO), oxaliplatin + capecitabine (XELOX) , docetaxel + cisplatin + 5-fluorouracil (DCF), docetaxel + oxaliplatin + infusional 5-fluorouracil + folinic acid (FLOT), epirubicin + cisplatin + capecitabine (ECX), epirubicin + oxaliplatin + capecitabine (EOX), epirubicin + cisplatin + 5-fluorouracil (ECF), epirubicin + oxaliplatin + 5-fluorouracil and S-1 (tegafur/gimeracil/oteracil) + cisplatin.

Cisplatin + capecitabine (XP)				
Cisplatin	1 x every 21 days	17.4	1	17.4
Capecitabine	2 x on day 1 - 14 of a 21 day cycle	17.4	14	243.6
Oxaliplatin + 5-fluorouracil + folinic acid (FOLFOX-4)				
Oxaliplatin	1 x on day 1 of a 14 day cycle	26.1	1	26.1
5-fluorouracil	1 x on day 1 and 2 of a 14 day cycle	26.1	2	52.2
Folinic acid	1 x on day 1 and 2 of a 14 day cycle	26.1	2	52.2
Oxaliplatin + 5-fluorouracil + folinic acid (mod. FOLFOX-6)				
Oxaliplatin	1 x on day 1 of a 14 day cycle	26.1	1	26.1
5-fluorouracil	1 x on day 1 of a 14 day cycle	26.1	1	26.1
Folinic acid	1 x on day 1 of a 14 day cycle	26.1	1	26.1
Oxaliplatin + 5-fluorouracil + folinic acid (FLO)				
Oxaliplatin	1 x on day 1 of a 14 day cycle	26.1	1	26.1
5-fluorouracil	1 x on day 1 of a 14 day cycle	26.1	1	26.1
Folinic acid	1 x on day 1 of a 14 day cycle	26.1	1	26.1
Oxaliplatin + capecitabine (XELOX)				
Oxaliplatin	1 x on day 1 of a 21 day cycle	17.4	1	17.4
Capecitabine	2 x on day 1 - 14 of a 21 day cycle	17.4	14	243.6
Docetaxel + cisplatin + 5-fluorouracil (DCF)				
Docetaxel	1 x on day 1 of a 21 day cycle	17.4	1	17.4
Cisplatin	1 x on day 1 of a 21 day cycle	17.4	1	17.4
5-fluorouracil	1 x on day 1 - 5 of a 21-day cycle	17.4	5	87
Docetaxel + oxaliplatin + 5-fluorouracil + folinic acid (FLOT)				

Docetaxel	1 x on day 1 of a 14 day cycle	26.1	1	26.1
Oxaliplatin	1 x on day 1 of a 14 day cycle	26.1	1	26.1
5-fluorouracil	1 x on day 1 of a 14 day cycle	26.1	1	26.1
Folinic acid	1 x on day 1 of a 14 day cycle	26.1	1	26.1
Epirubicin + cisplatin + capecitabine (ECX)				
Epirubicin	1 x on day 1 of a 21 day cycle	17.4	1	17.4
Cisplatin	1 x on day 1 of a 21 day cycle	17.4	1	17.4
Capecitabine	2 x daily per 21-day cycle	17.4	21	365[7]
Epirubicin + oxaliplatin + capecitabine (EOX)				
Epirubicin	1 x on day 1 of a 21 day cycle	17.4	1	17.4
Oxaliplatin	1 x on day 1 of a 21 day cycle	17.4	1	17.4
Capecitabine	2 x daily per 21-day cycle	17.4	21	365[7]
Epirubicin + cisplatin + 5-fluorouracil (ECF)				
Epirubicin	1 x on day 1 of a 21 day cycle	17.4	1	17.4
Cisplatin	1 x on day 1 of a 21 day cycle	17.4	1	17.4
5-fluorouracil	1 x daily per 21-day cycle	17.4	21	365[7]
Epirubicin + oxaliplatin + 5-fluorouracil				
Epirubicin	1 x on day 1 of a 21 day cycle	17.4	1	17.4
Oxaliplatin	1 x on day 1 of a 21 day cycle	17.4	1	17.4
5-fluorouracil	1 x daily per 21-day cycle	17.4	21	365[7]
S-1 (tegafur/ gimeracil/ oteracil) + cisplatin				

[7] Since a maximum treatment duration of 365 days is assumed for the year, the calculated figure of 365.4 days is rounded down.

S-1 (tegafur/ gimeracil/ oteracil)	2 x on day 1 - 21 of a 28 day cycle	13	21	273.0
Cisplatin	1 x per 28-day cycle for 6 cycles	6	1	6.0

Consumption:

For the cost representation only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

For dosages depending on body weight or body surface, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body height: 1,72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916).[8]

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Nivolumab in combination with 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX-4)					
Nivolumab	240 mg	240 mg	2 x 120 mg	26.1	52.2 x 120 mg
5-fluorouracil	400 mg/ m^2 = 760 mg	760 mg	1 x 1,000 mg	52.2	52.2 x 1,000 mg
	600 mg/m^2 = 1,140 mg	1,140 mg	1 x 2,500 mg		52.2 x 2,500 mg
Folinic acid	200 mg/ m^2 = 380 mg	380 mg	1 x 400 mg	52.2	52.2 x 400 mg
Oxaliplatin	85 mg/ m^2 = 161.5 mg	161.5 mg	1 x 200 mg	26.1	26.1 x 200 mg
Nivolumab in combination with 5-fluorouracil + folinic acid + oxaliplatin (mod. FOLFOX-6)					
Nivolumab	240 mg	240 mg	2 x 120 mg	26.1	52.2 x 120 mg
5-fluorouracil	400 mg/ m^2 = 760 mg	760 mg	1 x 1,000 mg	26.1	26.1 x 1,000 mg
	2,400 mg/ m^2 = 4,560 mg	4,560 mg	1 x 5000 mg		26.1 x 5000 mg
Folinic acid	400 mg/ m^2 = 760 mg	760 mg	1 x 800 mg	26.1	26.1 x 800 mg

[8] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Oxaliplatin	85 mg/ m^2 = 161.5 mg	161.5 mg	1 x 200 mg	26.1	26.1 x 200 mg
Nivolumab in combination with capecitabine + oxaliplatin (XELOX)					
Nivolumab	360 mg	360 mg	3 x 120 mg	17.4	52.2 x 120 mg
Capecitabine	1,000 mg/m^2 = 1,800 mg	3,600 mg	6 x 500 mg + 4 x 150 mg	243.6	1,461.6 x 500 mg + 974.4 x 150 mg
Oxaliplatin	130 mg/ m^2 = 247 mg	247 mg	1 x 200 mg + 1 x 50 mg	17.4	17.4 x 200 mg + 17.4 x 50 mg

Appropriate comparator therapy					
Therapy according to doctor's instructions[9]:					
Cisplatin + 5-fluorouracil					
5-fluorouracil	800 mg/m^2 = 1,520 mg	1,520 mg	1 x 2,500 mg	87	87 x 2,500 mg
Cisplatin	80 mg/m^2 = 152 mg	152 mg	1 x 100 mg + 1 x 50 mg + 1 x 10 mg	17.4	17.4 x 100 mg + 17.4 x 50 mg + 17.4 x 10 mg
Cisplatin + 5-fluorouracil + folinic acid					
Cisplatin	80 mg/m^2 = 152 mg	152 mg	1 x 100 mg + 1 x 50 mg + 1 x 10 mg	17.4	17.4 x 100 mg + 17.4 x 50 mg + 17.4 x 10 mg
5-fluorouracil	800 mg/m^2	1,520 mg	1 x 2,500 mg	87	87 x 2,500 mg

[9] The costs are presented for the active ingredients that are each approved for at least one of the present localisations. The following medicinal product combinations are only approved for the treatment of gastric carcinoma: Cisplatin + capecitabine (XP), oxaliplatin + 5-fluorouracil + folinic acid (FOLFOX-4 and mod. FOLFOX-6), oxaliplatin + 5-fluorouracil + folinic acid (FLO), oxaliplatin + capecitabine (XELOX), docetaxel + cisplatin + 5-fluorouracil (DCF), docetaxel + oxaliplatin + infusional 5-fluorouracil + folinic acid (FLOT), epirubicin + cisplatin + capecitabine (ECX), epirubicin + oxaliplatin + capecitabine (EOX), epirubicin + cisplatin + 5-fluorouracil (ECF), epirubicin + oxaliplatin + 5-fluorouracil and S-1 (tegafur/gimeracil/oteracil) + cisplatin.

	= 1,520 mg				
Folinic acid	400 mg/ m^2 = 760 mg	760 mg	1 x 800 mg	17.4	17.4 x 800 mg
Cisplatin + capecitabine (XP)					
Cisplatin	80 mg/m^2 = 152 mg	152 mg	1 x 100 mg + 1 x 50 mg + 1 x 10 mg	17.4	17.4 x 100 mg + 17.4 x 50 mg + 17.4 x 10 mg
Capecitabine	1,000 mg/m^2 = 1,800 mg	3,600 mg	6 x 500 mg + 4 x 150 mg	243.6	1,461.6 x 500 mg + 974.4 x 150 mg
Oxaliplatin + 5-fluorouracil + folinic acid (FOLFOX-4)					
Oxaliplatin	85 mg/ m^2 = 161.5 mg	161.5 mg	1 x 200 mg	26.1	26.1 x 200 mg
5-fluorouracil	400 mg/ m^2 = 760 mg	760 mg	1 x 1,000 mg	52.2	52.2 x 1,000 mg
	600 mg/m^2= 1,140 mg	1,140 mg	1 x 2,500 mg		52.2 x 2,500 mg
Folinic acid	200 mg/ m^2 = 380 mg	380 mg	1 x 400 mg	52.2	52.2 x 400 mg
Oxaliplatin + 5-fluorouracil + folinic acid (mod. FOLFOX 6)					
Oxaliplatin	85 mg/ m^2 = 161.5 mg	161.5 mg	1 x 200 mg	26.1	26.1 x 200 mg
5-fluorouracil	400 mg/ m^2 = 760 mg	760 mg	1 x 1,000 mg	26.1	26.1 x 1,000 mg
	2,400 mg/ m^2 = 4,560 mg	4,560 mg	1 x 5000 mg		26.1 x 5000 mg
Folinic acid	400 mg/ m^2 = 760 mg	760 mg	1 x 800 mg	26.1	26.1 x 800 mg
Oxaliplatin + 5-fluorouracil + folinic acid (FLO)					
Oxaliplatin	85 mg/ m^2 = 161.5 mg	161.5 mg	1 x 200 mg	26.1	26.1 x 200 mg
5-fluorouracil	2,600 mg/ m^2 = 4,940 mg	4940 mg	1 x 5000 mg	26.1	26.1 x 5000 mg
Folinic acid	200 mg/ m^2 = 380 mg	380 mg	1 x 400 mg	26.1	26.1 x 400 mg
Oxaliplatin + capecitabine (XELOX)					
Oxaliplatin	130 mg/ m^2 = 247 mg	247 mg	1 x 200 mg +	17.4	17.4 x 200 mg +

			1 x 50 mg		17.4 x 50 mg
Capecitabine	1,000 mg/m² = 1,800 mg	3,600 mg	6 x 500 mg + 4 x 150 mg	243.6	1,461.6 x 500 mg + 974.4 x 150 mg
Docetaxel + cisplatin + 5-fluorouracil (DCF)					
Docetaxel	75 mg/ m² = 142.5 mg	142.5 mg	2 x 80 mg	17.4	34.8 x 80 mg
Cisplatin	75 mg/ m² = 142.5 mg	142.5 mg	1 x 100 mg + 1 x 50 mg	17.4	17.4 x 100 mg + 17.4 x 50 mg
5-fluorouracil	750 mg/m² = 1,425 mg	1,425 mg	1 x 2500 mg	87	87 x 2500 mg
Docetaxel + oxaliplatin + 5-fluorouracil + folinic acid (FLOT)					
Docetaxel	50 mg/ m² = 95 mg	95 mg	1 x 80 mg + 1 x 20 mg	26.1	26.1 x 80 mg + 26.1 x 20 mg
Oxaliplatin	85 mg/ m² = 161.5 mg	161.5 mg	1 x 200 mg	26.1	26.1 x 200 mg
5-fluorouracil	2,600 mg/ m² = 4,940 mg	4,940 mg	1 x 5000 mg	26.1	26.1 x 5000 mg
Folinic acid	200 mg/ m² = 380 mg	380 mg	1 x 400 mg	26.1	26.1 x 400 mg
Epirubicin + cisplatin + capecitabine (ECX)					
Epirubicin	50 mg/ m² = 95 mg	95 mg	1 x 100 mg	17.4	17.4 x 100 mg
Cisplatin	60 mg/ m² = 114 mg	114 mg	1 x 100 mg + 2 x 10 mg	17.4	17.4 x 100 mg + 34.8 x 10 mg
Capecitabine	625 mg/ m² = 1187.5 mg	2375 mg	4 x 500 mg + 4 x 150 mg	365	1,460 x 500 mg + 1460 x 150 mg
Epirubicin + oxaliplatin + capecitabine (EOX)					
Epirubicin	50 mg/ m² = 95 mg	95 mg	1 x 100 mg	17.4	17.4 x 100 mg
Oxaliplatin	130 mg/ m² = 247 mg	247 mg	1 x 200 mg + 1 x 50 mg	17.4	17.4 x 200 mg + 17.4 x 50 mg
Capecitabine	625 mg/ m² = 1187.5 mg	2375 mg	4 x 500 mg + 4 x 150 mg	365	1,460 x 500 mg +

					1460 x 150 mg
Epirubicin + cisplatin + 5-fluorouracil (ECF)					
Epirubicin	50 mg/ m² = 95 mg	95 mg	1 x 100 mg	17.4	17.4 x 100 mg
Cisplatin	60 mg/ m² = 114 mg	114 mg	1 x 100 mg + 2 x 10 mg	17.4	17.4 x 100 mg + 34.8 x 10 mg
5-fluorouracil	200 mg/m² = 380 mg	380 mg	1 x 500 mg	365	365 x 500 mg
Epirubicin + oxaliplatin + 5-fluorouracil					
Epirubicin	50 mg/ m² = 95 mg	95 mg	1 x 100 mg	17.4	17.4 x 100 mg
Oxaliplatin	130 mg/ m² = 247 mg	200 mg	1 x 200 mg + 1 x 50 mg	17.4	17.4 x 200 mg + 17.4 x 50 mg
5-fluorouracil	200 mg/m² = 380 mg	380 mg	1 x 500 mg	365	365 x 500 mg

S-1 (tegafur/ gimeracil/ oteracil) + cisplatin					
S-1 (tegafur/ gimeracil/ oteracil)	25 mg/ m² = 47.5 mg	47.5 mg	2 x 20 mg + 1 x 15 mg	273	546 x 20 mg + 273 x 15 mg
Cisplatin	75 mg/m² = 142.5 mg	142.5 mg	1 x 100 mg + 1 x 50 mg	6	6 x 100 mg + 6 x 50 mg

Costs:

Costs of the medicinal products:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Nivolumab 120 mg	1 CIS	€ 1,546.93	€ 1.77	€ 85.05	€ 1,460.11
Capecitabine 150 mg[10]	120 FCT	€ 54.11	€ 1.77	€ 3.39	€ 48.95
Capecitabine 500 mg[10]	120 FCT	€ 151.81	€ 1.77	€ 11.11	€ 138.93
5-Fluorouracil 1,000 mg[10]	1 SFI	€ 16.64	€ 1.77	€ 0.42	€ 14.45
5-Fluorouracil 2,500 mg[10]	1 SFI	€ 23.56	€ 1.77	€ 0.97	€ 20.82
5-Fluorouracil 5,000 mg[10]	1 SFI	€ 33.99	€ 1.77	€ 1.80	€ 30.42
Folinic acid 400 mg[10]	1 SFI	€ 165.46	€ 1.77	€ 12.19	€ 151.50
Folinic acid 800 mg[10]	1 SFI	€ 304.62	€ 1.77	€ 23.20	€ 279.65
Oxaliplatin 200 mg[11]	1 CIS	€ 399.29	€ 1.77	€ 18.41	€ 379.11
Oxaliplatin 50 mg[12]	1 CIS	€ 164.89	€ 1.77	€ 7.29	€ 155.83
Oxaliplatin 200 mg[12]	1 CIS	€ 628.26	€ 1.77	€ 29.28	€ 597.21
Appropriate comparator therapy					
Capecitabine 150 mg[10]	120 FCT	€ 54.11	€ 1.77	€ 3.39	€ 48.95
Capecitabine 500 mg[10]	120 FCT	€ 151.81	€ 1.77	€ 11.11	€ 138.93
Cisplatin 10 mg[13]	1 CIS	€ 18.56	€ 1.77	€ 0.35	€ 16.44
Cisplatin 50 mg[13]	1 CIS	€ 47.70	€ 1.77	€ 4.61	€ 41.32
Cisplatin 100 mg[13]	1 CIS	€ 84.10	€ 1.77	€ 9.22	€ 73.11
Cisplatin 10 mg[14]	1 CIS	€ 17.49	€ 1.77	€ 0.30	€ 15.42
Cisplatin 100 mg[14]	1 CIS	€ 76.55	€ 1.77	€ 3.10	€ 71.68
Docetaxel 80 mg	1 CIS	€ 415.86	€ 1.77	€ 19.20	€ 394.89
Epirubicin 100 mg	1 CIS	€ 300.81	€ 1.77	€ 13.74	€ 285.30
5-Fluorouracil 500 mg10	1 IIS	€ 14.13	€ 1.77	€ 0.23	€ 12.13
5-Fluorouracil 2,500 mg10	1 SFI	€ 23.56	€ 1.77	€ 0.97	€ 20.82
5-Fluorouracil 5,000 mg[10]	1 SFI	€ 33.99	€ 1.77	€ 1.80	€ 30.42
Folinic acid 400 mg[10]	1 SFI	€ 165.46	€ 1.77	€ 12.19	€ 151.50
Folinic acid 800 mg[10]	1 SFI	€ 304.62	€ 1.77	€ 23.20	€ 279.65
Oxaliplatin 200 mg[11]	1 CIS	€ 399.29	€ 1.77	€ 18.41	€ 379.11
Oxaliplatin 50 mg[12]	1 CIS	€ 164.89	€ 1.77	€ 7.29	€ 155.83
Oxaliplatin 200 mg[12]	1 CIS	€ 628.26	€ 1.77	€ 29.28	€ 597.21
S-1(tegafur/gimeracil/oteracil) 20 mg	84 HC	€ 455.06	€ 1.77	€ 24.57	€ 428.72

[10] Fixed reimbursement rate

[11] Cheapest proprietary medicinal product for dosage 161.5 mg / day. Only the 200 mg potency is available on the German market from the manufacturer in question

[12] Cheapest proprietary medicinal products for dosage 247 mg / day. In addition to the 200 mg potency, the 50 mg potency is also available on the German market from the manufacturer in question.

[13] Cheapest proprietary medicinal products for cisplatin dosing concerning the medicinal product combinations cisplatin + 5-fluorouracil, cisplatin + 5-fluorouracil + folinic acid, cisplatin + capecitabine (XP), docetaxel + cisplatin + 5-fluorouracil (DCF) and S-1 (tegafur/gimeracil/oteracil) + cisplatin.

[14] Cheapest proprietary medicinal products for cisplatin dosing concerning the medicinal product combinations epirubicin + cisplatin + capecitabine (ECX) and epirubicin + cisplatin + 5-fluorouracil (ECF).

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
S-1(tegafur/gimeracil/oteracil) 15 mg	84 HC	€ 344.11	€ 1.77	€ 18.43	€ 323.91
Abbreviations: FCT = film-coated tablets; HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; IIS = injection/infusion solution; SFI = solution for injection					

LAUER-TAXE® last revised: 1 May 2022

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I to the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5a SGB V, when a non-prescription medicinal product is dispensed invoiced according Section 300, a medicinal product sale price applies to the insured person in the amount of the sale price of the pharmaceutical company plus the surcharges according to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the valid version of 31 December 2003.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Medicinal product to be assessed							
Appropriate comparator therapy							
Cisplatin - all combination regimens							
Antiemetic treatment							
In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin. The product information does not provide any specific information why the necessary costs cannot be quantified.							
Cisplatin – Cisplatin in combination with 5-fluorouracil - Cisplatin in combination with 5-fluorouracil and folinic acid							

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
- Cisplatin in combination with capecitabine (XP) – Docetaxel + cisplatin + 5-fluorouracil (DCF) – Epirubicin + cisplatin + capecitabine (ECX) – Epirubicin + cisplatin + 5-fluorouracil (ECF)							
Hydration/ diuresis							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	17.4	€ 158.51
Sodium chloride 0.9% infusion solution, 3 l - 4,4 l/day	10 x 1,000 ml INF	€ 35.47	€ 1.77	€ 1.12	€ 32.58	17.4	€ 170.07 - € 263.11
	10 x 500 ml INF	€ 22.72	€ 1.14	€ 0.69	€ 20.89		
Cisplatin – S-1 (tegafur/gimeracil/oteracil) + cisplatin							
Hydration/ diuresis							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	6	€ 54.66
Sodium chloride 0.9% infusion solution, 3 l - 4,4 l/day	10 x 1,000 ml INF	€ 35.47	€ 1.77	€ 1.12	€ 32.58	6	€ 58.64 - € 90.73
	10 x 500 ml INF	€ 22.72	€ 1.14	€ 0.69	€ 20.89		
Abbreviation: INF = infusion solution							

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost

representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 12 January 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy defined by the G-BA took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 27 April 2021.

On 16 November 2021, the pharmaceutical company submitted a dossier for the benefit assessment of nivolumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 18 November 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient nivolumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 25 February 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 1 March 2022. The deadline for submitting written statements was 22 March 2022.

The oral hearing was held on 11 April 2022.

By letter dated DD. Month YYYY, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addenda prepared by the IQWiG was submitted to the G-BA on 28 April 2022 and 6 May 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 10 May 2022, and the proposed resolution was approved.

At its session on 19 May 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	25 August 2020	Determination of the appropriate comparator therapy
Working group Section 35a	27 April 2021	New determination of the appropriate comparator therapy
Working group Section 35a	6 April 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	11 April 2022	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	21 April 2022 4 May 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	10 May 2022	Concluding discussion of the draft resolution
Plenum	19 May 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 19 May 2022

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken