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)

Pembrolizumab (change to the therapeutic indication: oesophageal or gastro-oesophageal junction carcinoma, PD-L1 expression ≥ 10 (CPS), first-line, combination with platinum and fluoropyrimidine-containing chemotherapy)
Pembrolizumab (new therapeutic indication: gastric or gastro-oesophageal junction adenocarcinoma, PD-L1 expression ≥ 1, HER2-, first-line, combination with fluoropyrimidine and platinum-containing chemotherapy)

of 20 June 2024

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 pembrolizumab (Keytruda) was listed for the first time on 15 August 2015 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

The active ingredient pembrolizumab received the marketing authorisation for the new therapeutic indication "Keytruda, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus or HER2-negative gastro-oesophageal junction adenocarcinoma, in adults whose tumours express PD-L1 with a CPS ≥ 10" on 24 June 2021. As part of the extension of the marketing authorisation of 23 November 2023 for the new therapeutic indication to be assessed here "Gastric or gastro-oesophageal junction adenocarcinoma, PD-L1 expression ≥ 1, HER2-, first-line, combination with fluoropyrimidine and platinum-containing chemotherapy)", the product information for pembrolizumab was, among other things, amended to the effect that the information in section 4.1. on the indication "Oesophageal carcinoma" with reference to "HER2-negative gastro-oesophageal junction adenocarcinoma" was deleted and moved to the indication with the heading "Gastric

orgastro-oesophageal junction (GEJ) adenocarcinoma".[1] The findings of the benefit assessment resolution of 5 May 2022 (resolution (g-ba.de)) on the active ingredient pembrolizumab (new therapeutic indication: oesophageal or gastro-oesophageal junction carcinoma, PD-L1 expression ≥ 10 (CPS), first-line, combination with fluoropyrimidine and platinum-containing chemotherapy) for sub-population b1) "Adults with locally advanced or metastatic HER2-negative oesophageal or gastro-oesophageal junction adenocarcinoma which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10); first-line therapy" were updated by the present resolution of 20 June 2024 for patients with locally advanced unresectable or metastatic HER2-negative gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 (CPS ≥ 1) or supplemented with regard to patients with PD-L1 expression < 10. This relationship is clarified in the information on the active ingredient pembrolizumab for the therapeutic indication "Oesophageal or gastro-oesophageal junction carcinoma, PD-L1 expression ≥ 10 (CPS), first-line, combination with fluoropyrimidine and platinum-containing chemotherapy)" by means of a footnote.

On 23 May 2023, the pharmaceutical company submitted an application for postponement of the date for the start of the benefit assessment procedure for pembrolizumab in the therapeutic indication "for first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma" in accordance with Section 35a paragraph 5b SGB V.

The pharmaceutical company expected marketing authorisation extensions for the active ingredient pembrolizumab within the period specified in Section 35a paragraph 5b SGB V for multiple therapeutic indications at different times.

In its session on 6 July 2023, the G-BA approved the application pursuant to Section 35a paragraph 5b SGB V and postponed the relevant date for the start of the benefit assessment and the submission of a dossier for the benefit assessment for the therapeutic indication in question to four weeks after the marketing authorisation of the last therapeutic indication of the therapeutic indications covered by the application, at the latest six months after the first relevant date. The marketing authorisation for the last therapeutic indication covered by the application in accordance with Section 35a, paragraph 5b SGB V "for first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma" was granted within the 6-month period.

For the therapeutic indication in question here "for first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma", pembrolizumab received the extension of the marketing authorisation 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 from 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, 12.12.2008, sentence 7) on 23 November 2023. In accordance with the resolution of 6 July 2023, the benefit assessment of the active ingredient pembrolizumab in this new therapeutic indication thus began at the latest within four weeks after the last marketing authorisation of pembrolizumab on 11 December 2023 in the therapeutic indication "for first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma", as well as 6 months after the first relevant date, i.e. at the latest on 23 February 2024.

[1] https://www.ema.europa.eu/en/documents/variation-report/keytruda-h-c-003820-ii-0117-epar-assessment-report-variation_en.pdf

On 29 December 2023, the pharmaceutical company submitted a dossier in due time in accordance with Section 4, paragraph 3, number 3 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 2 of the Rules of Procedure of the G-BA (VerfO) for the combination of active ingredients pembrolizumab in combination with trastuzumab as well as fluoropyrimidine and platinum-containing chemotherapy with the therapeutic indication "for first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma".

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 April 2024 on the G-BA website (www.g-ba.de), thus 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 pembrolizumab compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. 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 pembrolizumab.

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 Pembrolizumab (Keytruda) in accordance with the product information

KEYTRUDA, in combination with fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

Therapeutic indication of the resolution (resolution of 20.06.2024):

see the approved therapeutic indication

1 General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1.2 Appropriate comparator therapy

Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours express PD-L1 with a CPS ≥ 1; first-line therapy

Appropriate comparator therapy for pembrolizumab in combination with fluoropyrimidine and platinum-containing chemotherapy:

- cisplatin + capecitabine

  or

- oxaliplatin + capecitabine

  or

- cisplatin + S-1 (tegafur/ gimeracil/ oteracil)

  or

- cisplatin + 5-fluorouracil (only for patients with adenocarcinoma of the oesophagus)

  or

- cisplatin + 5-fluorouracil + folinic acid (only for patients with adenocarcinoma of the oesophagus)

  or

- epirubicin + cisplatin + capecitabine

  or

- epirubicin + cisplatin + 5-fluorouracil

  or

- epirubicin + oxaliplatin + capecitabine

  or

- docetaxel + cisplatin + 5-fluorouracil

  or

- Nivolumab in combination with fluoropyrimidine and platinum-containing combination chemotherapy (only for tumours with PD-L1 expression (Combined Positive Score [CPS] ≥ 5))

  or

- 5-fluorouracil + oxaliplatin + epirubicin (only for patients with adenocarcinoma of the oesophagus)

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

<u>Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:</u>

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

Cisplatin is approved as a combination therapy via the active ingredients capecitabine, S-1 (tegafur/ gimeracil/ oteracil) and docetaxel. Oxaliplatin is approved as a combination therapy via the active ingredient capecitabine.

on 2. Radiotherapy is generally considered as a non-medicinal treatment in the present therapeutic indication. Patients for whom radiotherapy with curative objectives is indicated are exceptional cases within the patient group defined by the therapeutic indication and are not considered in the context of the present question. The target population is assumed to be those patients for whom radiotherapy with curative goals is unsuitable. A non-medicinal treatment cannot be considered as an appropriate comparator therapy in this therapeutic indication. This does not affect the use of radiotherapy as a palliative therapy option.

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
- Nivolumab: resolution of 19 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 indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

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.

A joint written statement has been issued by the Working Group for Internal Oncology (AIO) of the German Cancer Society (DKG), the German Society for Haematology and Medical Oncology (DGHO) and the German Society for Gastroenterology and Digestive and Metabolic Diseases (DGVS).

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.

Various fluoropyrimidine and platinum-containing combination chemotherapies are mentioned in the guidelines for the present treatment setting. Accordingly, a fluoropyrimidine and platinum-containing doublet or triplet combination therapy is recommended. With regard to the platinum component, the focus here is specifically on cisplatin and oxaliplatin. With regard to the fluoropyrimidine component, 5-fluorouracil, capecitabine and S-1 (tegafur/ gimeracil/ oteracil) are mentioned. Furthermore, the use of the immune checkpoint inhibitors nivolumab or pembrolizumab together with a fluoropyrimidine and platinum-containing combination is recommended for tumours with an elevated PD-L1 Combined Positive Score (CPS) in accordance with their respective marketing authorisation.

According to current guidelines and the written statement from the scientific-medical societies on the question of comparator therapy, HER2 status is decisive for patients with locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma. Accordingly, the chemotherapy doublet consisting of a fluoropyrimidine (5-fluorouracil or capecitabine) and a platinum analogue (cisplatin or oxaliplatin) is the basis for first-line systemic therapy in HER2-negative patients, whereby the localisation of the gastro-oesophageal junction or stomach does not play

a decisive role. The active ingredients oxaliplatin and cisplatin are to be considered at least equivalent in terms of efficacy, with oxaliplatin being used in the majority of cases due to its better safety and side-effect profile. For PD-L1-positive tumours, the addition of an immune checkpoint inhibitor is the current standard in first-line therapy.

By resolution of 19 May 2022, in the benefit assessment of nivolumab in combination with fluoropyrimidine and platinum-containing combination chemotherapy for the first-line treatment of HER2-negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinomas in adults whose tumours express PD-L1 (Combined Positive Score [CPS] ≥ 5), a hint for a considerable additional benefit of the above combination chemotherapy over FOLFOX (5-fluorouracil + folinic acid + oxaliplatin) or XELOX (capecitabine + oxaliplatin) was identified.

In this extension of the marketing authorisation for pembrolizumab, the indication of HER2-negative gastro-oesophageal junction adenocarcinoma in the product information for pembrolizumab was moved from the therapeutic indication "oesophageal carcinoma" to the therapeutic indication "gastric or GEJ adenocarcinoma" to be assessed[2]. As a result, pembrolizumab in combination with fluoropyrimidine and platinum-containing chemotherapy should not be considered as an approved therapy option in the therapeutic indication of pembrolizumab in combination with fluoropyrimidine and platinum-containing chemotherapy to be assessed, even from a purely formal point of view.

The fluoropyrimidine and platinum-containing doublet or triplet combination therapies mentioned in guidelines and by the scientific-medical societies include both approved and unapproved medicinal products for the therapeutic indication in question. It cannot be derived from the present evidence that the off-label use of medicinal products would generally be preferred to the use of medicinal products approved in the therapeutic indication according to the generally recognised state of medical knowledge. The requirements for exceptionally determining the off-label use of medicinal products as appropriate comparator therapy in accordance with Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) are therefore not met.

Overall, the G-BA therefore determined the approved fluoropyrimidine and platinum-containing doublet or triplet combination therapies as well as nivolumab in combination with fluoropyrimidine and platinum-containing combination chemotherapy as the appropriate comparator therapy. In this context, individual therapy options only represent a comparator therapy for the part of the patient population that has the patient and disease characteristics specified in brackets. The therapeutic alternatives are only to be considered equally appropriate in the therapeutic indication, where the patient populations have the same characteristics.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2 https://www.ema.europa.eu/en/documents/variation-report/keytruda-h-c-003820-ii-0117-epar-assessment-report-variation_en.pdf

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of pembrolizumab is assessed as follows:

Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours express PD-L1 with a CPS ≥ 1; first-line therapy

An additional benefit is not proven.

Justification:

To demonstrate the additional benefit, the pharmaceutical company presented the results of the randomised, controlled phase III KEYNOTE 062, KEYNOTE 590 and KEYNOTE 859 studies and additionally prepared these as an IPD meta-analysis due to the similarity of the considered patient population with CPS ≥ 1, intervention and study design.

Description of the KEYNOTE 062 study

KEYNOTE 062 is a completed, multicentre randomised controlled trial (RCT) comparing pembrolizumab as monotherapy versus pembrolizumab in combination with chemotherapy consisting of cisplatin + capecitabine or cisplatin + 5-FU, and versus placebo in combination with this chemotherapy. The two study arms relevant for the benefit assessment were double-blinded; the unblinded study arm, pembrolizumab monotherapy, is not the subject of the present benefit assessment.

The study enrolled adults with locally advanced unresectable or metastatic gastric or gastro-oesophageal junction (GEJ) adenocarcinoma with HER2-negative status, determined according to local standards, whose tumours had to be programmed cell death ligand-1 (PD-L1)-positive with combined positive score (CPS) ≥ 1.

A total of 257 patients were randomised in the intervention arm relevant for the benefit assessment with pembrolizumab in combination with chemotherapy consisting of cisplatin + capecitabine or cisplatin + 5-FU, and 250 in the comparator arm with placebo in combination with this chemotherapy, whereby the intervention arm in the dossier only included 255 patients due to a subsequent exclusion.

For the KEYNOTE 062 study, 5 data cut-offs are available – three pre-specified interim analyses on overall survival, whereby the 3rd pre-specified data cut-off from 26.03.2019 forms the final data cut-off for overall survival, as well as the 4th data cut-off as a non-prespecified long-term follow-up from 19.04.2021 and the 5th data cut-off from 06.06.2022 at the end of study. In the dossier, results on the 4th non-pre-specified data cut-off from 19.04.2021 were presented.

As the 4th data cut-off for the long-term follow-up was non-pre-specified, these results were not used, instead the 3rd data cut-off from 26.03.2019 formed the basis of the benefit assessment.

Of the 505 patients presented in the dossier, assuming that all 191 patients treated with cisplatin + 5-FU had gastric cancer, a potentially relevant 38% (191 of 505 patients) would not have been treated according to the appropriate comparator therapy. Therefore, the subgroup of patients who received cisplatin + 5-FU cannot be used for the present benefit assessment. For the subgroup of patients who received cisplatin + capecitabine, the appropriate comparator therapy has been implemented in the study for gastric as well as GEJ

adenocarcinoma. Therefore, the benefit assessment is based on an approximate sub-population from the subgroup of patients treated with cisplatin + capecitabine with 159 patients in the intervention arm and 155 patients in the comparator arm.

Description of the KEYNOTE 859 study

KEYNOTE 859 is a double-blind, multicentre RCT comparing pembrolizumab in combination with chemotherapy consisting of cisplatin + 5-FU or oxaliplatin + capecitabine versus placebo in combination with this chemotherapy.

The study enrolled adults with locally advanced unresectable or metastatic gastric or gastro-oesophageal junction (GEJ) adenocarcinoma with HER2-negative status, determined according to local standards, in which the PD-L1 expression of the tumours had to be known, whereby positive PD-L1 expression was defined as CPS ≥ 1 in the study protocol.

A total of 790 patients were randomised to the intervention arm with pembrolizumab in combination with chemotherapy consisting of cisplatin + 5-FU or oxaliplatin + capecitabine, and 789 to the comparator arm with placebo in combination with this chemotherapy.

2 data cut-offs were carried out – a pre-specified interim analysis on overall survival from 03.10.2022 as well as a 2nd data cut-off as non-pre-specified long-term follow-up from 22.08.2023. In the dossier, results on the 2nd non-pre-specified data cut-off from 22.08.2023 were presented.

Since the 2nd data cut-off for the long-term follow-up was non-pre-specified, these results were not used, instead the 1st data cut-off from 03.10.2022 formed the basis of the benefit assessment.

The sub-population presented in the dossier is the relevant sub-population for the benefit assessment and comprises patients whose tumours express PD-L1 with a CPS ≥ 1, of whom 618 fall into the intervention arm and 617 into the comparator arm.

Assuming that the sub-population presented in the dossier also includes patients with gastric carcinoma who were treated with cisplatin + 5-FU, this results in a percentage of up to 13% of patients who were not treated according to the appropriate comparator therapy. Since it cannot be assumed that the inclusion of up to 13% of patients with inappropriate implementation of the appropriate comparator therapy has a relevant influence on the results, the sub-population presented in the dossier can be used as an approximation for the benefit assessment.

About the KEYNOTE 590 study

The dossier only contains data on a non-specified data cut-off for this study. Therefore, the data from this study are not used for the present benefit assessment. Since the percentage of the sub-population from this study in the meta-analytically summarised approximated sub-populations of KEYNOTE 062 and KEYNOTE 859 studies is less than 5%, the lack of these study data is negligible for the assessment of the additional benefit.

In summary, the benefit assessment is based on meta-analytically summarised data with approximated sub-populations on pre-specified data cut-offs from the KEYNOTE 062 and KEYNOTE 859 studies on the endpoint category of mortality in comparison with chemotherapy consisting of cisplatin + capecitabine or cisplatin + 5-fluorouracil or oxaliplatin + capecitabine. Only the subgroup of patients treated with cisplatin + capecitabine from the KEYNOTE 062

study is considered and the sub-population from the KEYNOTE 590 study presented in the dossier is not taken into account.

For the submission of non-pre-specified data cut-offs

In order to prove the additional benefit, the pharmaceutical company based its meta-analysis of the KEYNOTE 062, KEYNOTE 590 and KEYNOTE 859 studies exclusively on data from non-pre-specified data cut-offs from long-term follow-ups, arguing that a gain in information can be assumed due to the longer observation period compared to the pre-specified data cut-off. The pharmaceutical company did not prepare the results on pre-specified data cut-offs according to the module templates either in Module 4 of the dossier or subsequently in the written statement procedure - in the knowledge of the corresponding criticism from IQWiG's dossier assessment and corresponding questions in the oral hearing. As a result, data prepared by the pharmaceutical company for the endpoints of the categories of morbidity, health-related quality of life and side effects that are only suitable for sub-populations with regard to the appropriate implementation of the appropriate comparator therapy are missing for the present assessment for the pre-specified data cut-offs. In this respect, suitable data that fulfil the requirements for the evidence of additional benefit are only available for the endpoint "overall survival".

Assessment:

The meta-analytical summary of the KEYNOTE 859 and KEYNOTE 062 studies shows a statistically significant advantage in survival time for the overall survival endpoint for treatment with pembrolizumab + chemotherapy compared to chemotherapy consisting of cisplatin + 5-fluorouracil or cisplatin + capecitabine or oxaliplatin + capecitabine. The results of the KEYNOTE 859 study show a median difference of 1.6 months, while no information on median survival time was available for the KEYNOTE 062 study. Taking into account the effect estimators for the individual studies and that of the meta-analytical summary, a relevant improvement can be determined at endpoint level, for which a benefit beyond one to a minor extent cannot be reliably derived.

Overall, the data presented for the endpoints of the categories of morbidity, health-related quality of life and side effects are incomplete for each of the pre-specified data cut-offs and therefore do not provide a suitable data basis for making a quantitative or qualitative summary: For the approximated sub-population of the KEYNOTE 062 study derived from the subgroup analysis of subjects treated with cisplatin + capecitabine, no data are available for the pre-specified data cut-off for the endpoints of the categories of morbidity, health-related quality of life and side effects overall. Data from the KEYNOTE 859 study are available for the endpoints of the categories of morbidity and health-related quality of life for the approximated sub-population used for the pre-specified data cut-off. However, these are incomplete because results are not presented for all scales of the EORTC instruments used. For the endpoints in the side effects category, no results on a pre-specified data cut-off were available for the approximated sub-population of the KEYNOTE 859 study. The sole use of the results of the KEYNOTE 859 study for the approximated sub-populations of both studies is therefore out of the question.

In conclusion, the data presented on morbidity, health-related quality of life and side effects are considered to be non-assessable, as essential requirements for the evidence of additional benefit are considered unmet and this data basis does not allow an appropriate assessment overall.

Taking into account the only minor benefit in the endpoint overall survival, no consideration can be given to the endpoints in the categories of morbidity, health-related quality of life and side effects. Overall, it is therefore not possible to derive an additional benefit with the necessary certainty.

The G-BA therefore concluded that an additional benefit of pembrolizumab in combination with fluoropyrimidine and platinum-containing chemotherapy in the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours express PD-L1 with CPS ≥ 1 is not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient pembrolizumab. The therapeutic indication assessed here is as follows:

"KEYTRUDA, in combination with fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1."

The G-BA determined various platinum-containing combination chemotherapies as well as the immune checkpoint inhibitor nivolumab in combination with fluoropyrimidine and platinum-containing chemotherapy as the appropriate comparator therapy.

The results of the KEYNOTE 062, KEYNOTE 590 and KEYNOTE 859 studies, also summarised meta-analytically, in which pembrolizumab in combination with fluoropyrimidine and platinum-containing chemotherapy is compared with chemotherapy consisting of cisplatin + 5-fluorouracil or cisplatin + capecitabine or oxaliplatin + capecitabine, are available for the assessment.

In the present assessment, the data for a relevant, approximately suitable sub-population from the meta-analytically summarised KEYNOTE 062 and KEYNOTE 859 studies on pre-specified data cut-offs were considered.

For the overall survival endpoint, there was a statistically significant advantage in survival time for treatment with pembrolizumab + chemotherapy compared to chemotherapy consisting of cisplatin + 5-fluorouracil or cisplatin + capecitabine or oxaliplatin + capecitabine. Taking into account the effect estimators for the individual studies and that of the meta-analytical summary, a relevant improvement can be determined at endpoint level, for which a benefit beyond one to a minor extent cannot be reliably derived.

The data presented on morbidity, health-related quality of life and side effects are considered to be non-assessable, as essential requirements for the evidence of additional benefit are considered unmet and this data basis does not allow an appropriate assessment overall.

This means that, among other things, it is not possible to weigh up the minor benefit in the endpoint of overall survival against the endpoints in the categories of morbidity, health-related quality of life and side effects. Overall, it is therefore not possible to derive an additional benefit with the necessary certainty.

The G-BA therefore concluded that an additional benefit of pembrolizumab in combination with fluoropyrimidine and platinum-containing chemotherapy in the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours express PD-L1 with CPS ≥ 1 is not proven.

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).

In order to ensure consistent determination of the patient numbers in the present therapeutic indication, the G-BA refers to the derivation of the target population on which the resolution on the benefit assessment of nivolumab was based (resolution of 19 May 2022), taking into account the mean values of the percentage ranges for HER2 status, the percentage values of PD-L1-expressing tumours with CPS ≥ 1 of the pharmaceutical company and the current percentage of SHI-insured patients.

For the number of German patients with gastric or gastro-oesophageal junction (GEJ) carcinoma, the predicted incidence of gastric and GEJ carcinomas (diagnosis code C16 according to ICD-10) for 2021 (14,211 patients) is used as the basis for the calculations.

The following calculation steps are used to narrow down this patient group to the target population:

1. The percentage of patients with gastric carcinoma or GEJ with adenocarcinoma is 90% to 95% (12,790 to 13,500 patients).

2a. Of these, 5,453 – 5,756 patients have advanced or metastatic gastric adenocarcinoma.

2b. Of these, 2,302 – 2,430 patients have advanced or metastatic GEJ adenocarcinoma.

3a. The percentage of patients undergoing palliative first-line therapy ranges from 13% to 57.5% (709 to 3,310 patients).

3b. The percentage of patients undergoing palliative first-line therapy ranges from 7.7% to 59.3% (177 to 1,441 patients).

4a. The percentage of patients with HER2-negative status is 82.5% (585 to 2,731 patients).

4b. The percentage of patients with HER2-negative status is 74% (131 to 1,066 patients).

5a. The percentage of PD-L1-expressing tumours with CPS ≥ 1 ranged from 44.9% to 76.2% (263 to 2,081 patients).

5b. The percentage of PD-L1-expressing tumours with CPS ≥ 1 range from 49.4% to 85.9% (65 to 916 patients).

6a. Taking into account the percentage of SHI-insured patients of 87.2%, this results in 229 to 1814 patients. 56 to 799

6b. Taking into account the percentage of SHI-insured patients of 87.2%, this results in 56 to 799 patients.

The sum of sub-steps 6a and 6b results in 285 to 2,613 patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours express PD-L1 with CPS ≥ 1 in first-line therapy.

Due to uncertainties regarding the data basis in the target population in Germany both an overestimation and an underestimation of patient numbers are possible.

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 Keytruda (active ingredient: pembrolizumab) at the following publicly accessible link (last access: 6 May 2024):

https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf

Treatment with pembrolizumab should only be initiated and monitored by specialists in internal medicine, haematology and oncology as well as specialists in internal medicine and gastroenterology and other specialists participating in the Oncology Agreement, all of whom are experienced in the treatment of patients with gastric or gastro-oesophageal junction carcinomas.

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients. The training material contains, in particular, instructions on the management of immune-mediated side effects potentially occurring with pembrolizumab as well as on infusion-related reactions.

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 June 2024).

The costs for the first year of treatment are shown for the cost representation in the resolution.

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 varies from patient to patient 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 the maximum treatment duration, if specified in the product information.

Treatment period:

Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours express PD-L1 with a CPS ≥ 1; first-line therapy

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Pembrolizumab in combination with cisplatin and 5-fluorouracil (5-FU)				
Pembrolizumab	1 x every 21 days	17.4	1	17.4
Cisplatin	Day 1 – 5 of a 21-day cycle	17.4	5	87.0
5-FU	Day 1 – 5 of a 21-day cycle	17.4	5	87.0
Pembrolizumab in combination with oxaliplatin and capecitabine				
Pembrolizumab	21-day cycle	17.4	1	17.4
Oxaliplatin	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
Appropriate comparator therapy				
Cisplatin in combination with capecitabine				
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 in combination with capecitabine				
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
Cisplatin + S-1 (tegafur/ gimeracil/ oteracil)				
Cisplatin	1 x per 28-day cycle for 6 cycles	6.0	1	6.0
S-1 (Tegafur/ gimeracil/ oteracil)	2 x on day 1 - 21 of a 28-day cycle	13.0	21	273.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Cisplatin in combination with 5-fluorouracil (5-FU) (only for patients with adenocarcinoma of the oesophagus)				
Cisplatin	1 x on day 1 of a 21-day cycle	17.4	1	17.4
5-FU	1 x on day 1 - 5 of a 21-day cycle	17.4	5	87.0
Cisplatin in combination with 5-fluorouracil (5-FU) and folinic acid (only for patients with adenocarcinoma of the oesophagus)				
Cisplatin	1 x on day 1 of a 21-day cycle	17.4	1	17.4
5-FU	1 x on day 1 - 5 of a 21-day cycle	17.4	5	87.0
Folinic acid	1 x on day 1 of a 21-day cycle	17.4	1	17.4
Epirubicin in combination with cisplatin and capecitabine				
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[3]
Epirubicin in combination with cisplatin and 5-fluorouracil (5-FU)				
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

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

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
5-FU	1 x daily per 21-day cycle	17.4	21	365[3]
Epirubicin in combination with oxaliplatin and capecitabine				
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[3]
Epirubicin in combination with oxaliplatin and 5-fluorouracil (5-FU) (only for patients with adenocarcinoma of the oesophagus)				
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-FU	1 x daily per 21-day cycle	17.4	21	365[3]
Docetaxel in combination with cisplatin and 5-fluorouracil (5-FU) (only for patients with adenocarcinoma of the oesophagus)				
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-FU	1 x on day 1 – 5 of a 21-day cycle	17.4	5	87.0
Nivolumab in combination with 5-fluorouracil (5-FU) + folinic acid + oxaliplatin (FOLFOX-4) (only for tumours with PD-L1 expression (CPS ≥ 5))				
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-FU	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 (5-FU) + folinic acid + oxaliplatin (mod. FOLFOX-6) (only for tumours with PD-L1 expression (CPS ≥ 5))				
Nivolumab	1 x every 14 days	26.1	1	26.1
5-FU	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 and oxaliplatin (XELOX) (only for tumours with PD-L1 expression (CPS ≥ 5))				
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

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77.7 kg). This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916)[4].

4 Federal health reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

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

Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours express PD-L1 with a CPS ≥ 1; first-line therapy

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					
Pembrolizumab in combination with cisplatin and 5-fluorouracil (5-FU)					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
Cisplatin	80 mg/m² = 152.8 mg	152.8 mg	1 x 100 mg + 1 x 50 mg + 1 x 10 mg	87.0	87.0 x 100 mg + 87.0 x 50 mg + 87.0 x 10 mg
5-FU	800 mg/m² = 1,528 mg	1,528 mg	1 x 2,500 mg	87.0	87.0 x 2,500 mg
Pembrolizumab in combination with oxaliplatin and capecitabine					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
Oxaliplatin	130 mg/m² = 248.3 mg	248.3 mg	1 x 200 mg + 1 x 50 mg	17.4	17.4 x 200 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
Appropriate comparator therapy					
Cisplatin in combination with capecitabine					
Cisplatin	80 mg/m² = 152.8 mg	152.8 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/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
Oxaliplatin in combination with capecitabine					
Oxaliplatin	130 mg/m² = 248.3 mg	248.3 mg	1 x 200 mg + 1 x 50 mg	17.4	17.4 x 200 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 +

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
					974.4 x 150 mg
Cisplatin + S-1 (tegafur/ gimeracil/ oteracil)					
Cisplatin	75 mg/m² = 143.3 mg	143.3 mg	1 x 100 mg + 1 x 50 mg	6.0	6.0 x 100 mg + 6.0 x 50 mg
S-1 (Tegafur/ gimeracil/ oteracil)	25 mg/m² = 50 mg	2 x 50 mg = 100 mg	4 x 15 mg + 2 x 20 mg	273.0	1,092 x 15 mg + 546 x 20 mg
Cisplatin in combination with 5-fluorouracil (5-FU) (only for patients with adenocarcinoma of the oesophagus)					
Cisplatin	80 mg/m² = 152.8 mg	152.8 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-FU	800 mg/m² = 1,528.0 mg	1,528.0 mg	1 x 2,500 mg	87.0	87.0 x 2,500 mg
Cisplatin in combination with 5-fluorouracil (5-FU) and folinic acid (only for patients with adenocarcinoma of the oesophagus)					
Cisplatin	80 mg/m² = 152.8 mg	152.8 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-FU	800 mg/m² = 1,528.0 mg	1,528.0 mg	1 x 2,500 mg	87.0	87.0 x 2,500 mg
Folinic acid	400 mg/m² = 764.0 mg	764.0 mg	1 x 800 mg	17.4	17.4 x 800 mg
Epirubicin in combination with cisplatin and capecitabine					
Epirubicin	50 mg/m² = 95.5 mg	95.5 mg	1 x 100 mg	17.4	17.4 x 100 mg
Cisplatin	60 mg/m² = 114.6 mg	114.6 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 = 1,193.8 mg	2,387.5 mg	4 x 500 mg + 4 x 150 mg	365	1,460 x 500 mg + 1,460 x 150 mg
Epirubicin in combination with cisplatin and 5-fluorouracil (5-FU)					
Epirubicin	50 mg/m² = 95.5 mg	95.5 mg	1 x 100 mg	17.4	17.4 x 100 mg
Cisplatin	60 mg/m² = 114.6 mg	114.6 mg	1 x 100 mg + 2 x 10 mg	17.4	17.4 x 100 mg + 34.8 x 10 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
5-FU	200 mg/m² = 382.0 mg	382.0 mg	1 x 500 mg	365	365 x 500 mg
Epirubicin in combination with oxaliplatin and capecitabine					
Epirubicin	50 mg/m² = 95.5 mg	95.5 mg	1 x 100 mg	17.4	17.4 x 100 mg
Oxaliplatin	130 mg/m² = 248.3 mg	248.3 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 = 1,193.8 mg	2,387.5 mg	4 x 500 mg + 4 x 150 mg	365	1,460 x 500 mg + 1,460 x 150 mg
Epirubicin in combination with oxaliplatin and 5-fluorouracil (5-FU) (only for patients with adenocarcinoma of the oesophagus)					
Epirubicin	50 mg/m² = 95.5 mg	95.5 mg	1 x 100 mg	17.4	17.4 x 100 mg
Oxaliplatin	130 mg/m² = 248.3 mg	248.3 mg	1 x 200 mg + 1 x 50 mg	17.4	17.4 x 200 mg + 17.4 x 50 mg
5-FU	200 mg/m² = 382.0 mg	382.0 mg	1 x 500 mg	365	365 x 500 mg
Docetaxel in combination with cisplatin and 5-fluorouracil (5-FU) (only for patients with adenocarcinoma of the oesophagus)					
Docetaxel	75 mg/m² = 143.3 mg	143.3 mg	1 x 160 mg	17.4	17.4 x 160 mg
Cisplatin	75 mg/m² = 143.3 mg	143.3 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-FU	750 mg/m² = 1,432.5 mg	1,432.5 mg	1 x 2,500 mg	87.0	87.0 x 2,500 mg
Nivolumab in combination with 5-fluorouracil (5-FU) + folinic acid + oxaliplatin (FOLFOX-4) (only for tumours with PD-L1 expression (CPS ≥ 5))					
Nivolumab	240 mg	240 mg	2 x 120 mg	26.1	52.2 x 120 mg
5-FU	400 mg/m² = 764.0 mg	764.0 mg	1 x 1,000 mg	52.2	52.2 x 1,000 mg
	600 mg/m² = 1,146.0 mg	1,146.0 mg	1 x 2,500 mg		52.2 x 2,500 mg
Folinic acid	200 mg/m² = 382.0 mg	382.0 mg	1 x 400 mg	52.2	52.2 x 400 mg
Oxaliplatin	85 mg/m²	162.4 mg	1 x 200 mg	26.1	26.1 x 200 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	= 162.4 mg				
Nivolumab in combination with 5-fluorouracil (5-FU) + folinic acid + oxaliplatin (mod. FOLFOX-6) (only for tumours with PD-L1 expression (CPS ≥ 5))					
Nivolumab	240 mg	240 mg	2 x 120 mg	26.1	52.2 x 120 mg
5-FU	400 mg/m² = 764.0 mg	764.0 mg	1 x 1,000 mg	26.1	26.1 x 1,000 mg
	2,400 mg/m² = 4,584.0 mg	4,584.0 mg	1 x 5,000 mg		26.1 x 2,500 mg
Folinic acid	400 mg/m² = 764.0 mg	764.0 mg	1 x 800 mg	26.1	26.1 x 800 mg
Oxaliplatin	85 mg/m² = 162.4 mg	162.4 mg	1 x 200 mg	26.1	26.1 x 200 mg
Nivolumab in combination with capecitabine and oxaliplatin (XELOX) (only for tumours with PD-L1 expression (CPS ≥ 5))					
Nivolumab	360 mg	360 mg	3 x 120 mg	17.4	52.2 x 120 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
Oxaliplatin	130 mg/m² = 248.3 mg	248.3 mg	1 x 200 mg + 1 x 50 mg	17.4	17.4 x 200 mg + 17.4 x 50 mg

Costs:

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. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

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					
Pembrolizumab 200 mg	4 CIS	€ 2,974.82	€ 2.00	€ 166.60	€ 2,806.22
Capecitabine [5] 500 mg	120 FCT	€ 151.84	€ 2.00	€ 11.11	€ 138.73
Capecitabine [5] 150 mg	120 FCT	€ 54.15	€ 2.00	€ 3.39	€ 48.76
Cisplatin 100 mg	1 CIS	€ 76.59	€ 2.00	€ 3.10	€ 71.49
Cisplatin 50 mg	1 CIS	€ 47.71	€ 2.00	€ 1.73	€ 43.98
Cisplatin 10 mg	1 CIS	€ 17.53	€ 2.00	€ 0.30	€ 15.23
5-fluorouracil [5] 2,500 mg	1 SFI	€ 23.60	€ 2.00	€ 0.97	€ 20.63
Oxaliplatin 200 mg	1 CIS	€ 396.85	€ 2.00	€ 18.30	€ 376.55
Oxaliplatin 50 mg	1 CIS	€ 107.06	€ 2.00	€ 4.54	€ 100.52
Appropriate comparator therapy					
Calcium folinate 400 mg	1 SFI	€ 165.51	€ 2.00	€ 12.20	€ 151.31
Calcium folinate 800 mg	1 SFI	€ 304.65	€ 2.00	€ 23.20	€ 279.45
Capecitabine [5] 500 mg	120 FCT	€ 151.84	€ 2.00	€ 11.11	€ 138.73
Capecitabine [5] 150 mg	120 FCT	€ 54.15	€ 2.00	€ 3.39	€ 48.76
Cisplatin 100 mg	1 CIS	€ 76.59	€ 2.00	€ 3.10	€ 71.49
Cisplatin 50 mg	1 CIS	€ 47.71	€ 2.00	€ 1.73	€ 43.98
Cisplatin 10 mg	1 CIS	€ 17.53	€ 2.00	€ 0.30	€ 15.23
Docetaxel 160 mg	1 CIS	€ 515.78	€ 2.00	€ 23.94	€ 489.84
Epirubicin 100 mg	1 CIS	€ 300.84	€ 2.00	€ 13.74	€ 285.10
5-fluorouracil [5] 5,000 mg	1 SFI	€ 34.02	€ 2.00	€ 1.80	€ 30.22
5-fluorouracil [5] 2,500 mg	1 SFI	€ 23.60	€ 2.00	€ 0.97	€ 20.63
5-fluorouracil [5] 1000 mg	1 SII	€ 16.67	€ 2.00	€ 0.42	€ 14.25
5-fluorouracil [5] 500 mg	1 SII	€ 14.16	€ 2.00	€ 0.22	€ 11.94
Nivolumab 120 mg	1 CIS	€ 1,546.96	€ 2.00	€ 85.05	€ 1,459.91
Oxaliplatin 200 mg	1 CIS	€ 396.85	€ 2.00	€ 18.30	€ 376.55
Oxaliplatin 50 mg	1 CIS	€ 107.06	€ 2.00	€ 4.54	€ 100.52
S-1 (tegafur/ gimeracil/ oteracil) 15 mg	84 HC	€ 344.15	€ 2.00	€ 18.43	€ 323.72
S-1 (tegafur/ gimeracil/ oteracil) 20 mg	84 HC	€ 455.09	€ 2.00	€ 24.57	€ 428.52
Abbreviations: FCT = film-coated tablets; HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; SII = solution for injection/infusion; SFI = solution for injection					

LAUER-TAXE® last revised: 1 June 2024

5 Fixed reimbursement rate

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 of 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 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

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							
Pembrolizumab + cisplatin + 5-FU							
Antiemetic treatment: In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin. The product information for cisplatin does not provide any specific information on this, which is why the necessary costs cannot be quantified.							
Hydration and forced diuresis							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	87.0	€ 792.57
Sodium chloride 0.9% inf. sol., 3 l - 4.4 l/day	10 x 1,000 ml INF	€ 35.47	€ 1.77	€ 1.12	€ 32.58	87.0	€ 850.34 - € 1315.52
	10 x 500 ml INF	€ 22.72	€ 1.14	€ 0.69	€ 20.89		
Appropriate comparator therapy							

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
Antiemetic treatment: In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin. The product information for cisplatin does not provide any specific information on this, which is why the necessary costs cannot be quantified.							
Cisplatin + S-1 (tegafur/ gimeracil/ oteracil)							
Hydration and forced diuresis							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	6.0	€ 91.10
Sodium chloride 0.9% inf. sol., 3 - 4.4 l/day	10 x 1,000 ml INF	€ 35.47	€ 1.77	€ 1.12	€ 32.58	6.0	€ 65.16 - € 118.63
	10 x 500 ml INF	€ 22.72	€ 1.14	€ 0.69	€ 20.89		
Cisplatin + capecitabine **Cisplatin + 5-FU** **Cisplatin + 5-FU + folinic acid** **Epirubicin + cisplatin + capecitabine** **Epirubicin + cisplatin + 5-FU** **Docetaxel + cisplatin + 5-FU**							
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% inf. sol., 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		
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 1.10.2009 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 agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (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.

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of

designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible

concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

a) Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours express PD-L1 with a CPS ≥ 1; first-line therapy

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for pembrolizumab (Keytruda); Keytruda 25 mg/ml concentrate for the preparation of an infusion solution; last revised: March 2024

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 21 February 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 09 January 2024.

On 29 December 2023, the pharmaceutical company submitted a dossier for the benefit assessment of pembrolizumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2, sentence 1 VerfO.

By letter dated 3 January 2024 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 pembrolizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 March 2024, and the written statement procedure was initiated with publication on the G-BA website on 2 April 2024. The deadline for submitting statements was 23 April 2024.

The oral hearing was held on 6 May 2024.

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 11 June 2024, and the proposed resolution was approved.

At its session on 20 June 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	21 February 2023	Implementation of the appropriate comparator therapy
Subcommittee Medicinal products	9 January 2024	New implementation of the appropriate comparator therapy
Working group Section 35a	30 April 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	6 May 2024	Conduct of the oral hearing
Working group Section 35a	15 May 2024 5 June 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	11 June 2024	Concluding discussion of the draft resolution
Plenum	20 June 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 20 June 2024

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

Prof. Hecken