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 (new therapeutic indication: oesophageal or gastroesophageal junction adenocarcinoma, PD-L1 expression ≥ 10 (CPS), first-line, combination with platinum and fluoropyrimidine-based chemotherapy)

of 5 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 pembrolizumab (Keytruda) was listed for the first time on 15 February 2017 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 24 June 2021, Keytruda 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 European 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, 12.12.2008, p. 7).

On 19 March 2021, the pharmaceutical company submitted an application to merge the evaluation procedures of pembrolizumab according to Section 35a, paragraph 5b SGB V. At its session on 6 May 2021, the G-BA approved the request for merger.

On 12 November 2021, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 2 of the Rules of Procedure (VerfO) of the G-BA on the combination of active ingredients pembrolizumab in combination with a platinum and fluoropyrimidine-based chemotherapy.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 15 February 2022, 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 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, and the statements submitted in the written statement and oral hearing procedure, and the addenda 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 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 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 gastroesophageal junction adenocarcinoma, in adults whose tumours express PD-L1 with a CPS ≥ 10.

Therapeutic indication of the resolution (resolution of 5 May 2022):

"see approved therapeutic indication"

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with locally advanced or metastatic squamous cell carcinoma of the oesophagus which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10); first-line therapy

Appropriate comparator therapy for pembrolizumab in combination with cisplatin and 5-fluorouracil:

- Cisplatin in combination with 5-fluorouracil

b1) 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 (Combined Positive Score (CPS) ≥ 10); first-line therapy

Appropriate comparator therapy for pembrolizumab in combination with cisplatin and 5-fluorouracil or capecitabine:

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

- Therapy according to doctor's instructions

b2) Adults with locally advanced or metastatic HER2-positive adenocarcinoma of the oesophagus which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10); first-line therapy

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

- HER2-targeted 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 pembrolizumab, medicinal products with the active ingredients 5-fluorouracil, cisplatin, docetaxel, mitomycin, nivolumab and trastuzumab are approved in the present therapeutic indication.

on 2. A non-medicinal treatment option is not considered for the therapeutic indication in question. This does not affect the use of radiotherapy as a palliative treatment option.

on 3. There are no corresponding resolutions or guidelines of the G-BA for medical products and non-medicinal treatments.

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 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.

For the therapeutic indication, it is assumed that curative treatment with definitive radiotherapy is not an option for patients with unresectable cancer. The treatment decision in the first-line treatment of locally advanced, unresectable or metastatic cancer of the oesophagus is essentially determined by the tumour histology (squamous cell carcinoma, adenocarcinoma) and the HER2 status (HER2-positive, HER2-negative). The therapeutic indication includes the treatment of squamous cell carcinoma of the oesophagus on the one hand, and oesophageal adenocarcinoma and gastroesophageal junction adenocarcinoma on the other. For these treatment settings, different appropriate comparator therapies are determined on the basis of the available therapy recommendations and the authorisation status of the medicinal products under consideration.

a) Adults with locally advanced or metastatic squamous cell carcinoma of the oesophagus which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10); first-line therapy

The available evidence recommends platinum and fluoropyrimidine-containing combination chemotherapy for the treatment of locally advanced, unresectable or metastatic squamous cell carcinoma of the oesophagus. In accordance with the German S3 guideline "Diagnostics and therapy of squamous cell carcinomas and adenocarcinomas of the oesophagus", a combination therapy of cisplatin and a fluoropyrimidine can be used here, whereby infusional 5-fluorouracil and capecitabine are particularly targeted. Capecitabine is not approved in the indication and is therefore not determined as an appropriate comparator therapy. The S3 guideline also points out that a life-prolonging effect of systemic palliative chemotherapy for squamous cell carcinoma of the oesophagus is not certain. For the determination of the appropriate comparator therapy, it is assumed that the patients are eligible for chemotherapy containing cisplatin, as is also intended by the cisplatin therapy in the present therapeutic indication.

In the overall assessment, the G-BA determined cisplatin in combination with 5-fluorouracil as an appropriate comparator therapy for the first-line treatment of adults with locally advanced or metastatic squamous cell carcinoma of the oesophagus which cannot be treated curatively.

b1) 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 (Combined Positive Score (CPS ≥ 10)); first-line therapy

According to the underlying evidence, patients with locally advanced, unresectable or metastatic adenocarcinoma of the oesophagus or of the gastroesophageal junction

and negative HER2 status are treated with doublet or triplet chemotherapy containing platinum and fluoropyrimidine.

The guidelines mention various platinum and fluoropyrimidine-based combination chemotherapies:

- 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).

Overall, with the named treatment options, several treatment options are available for the treatment of patients with advanced HER2-negative adenocarcinoma of the oesophagus or of the gastroesophageal junction. However, only the active ingredients 5-fluorouracil, docetaxel and cisplatin have a marketing authorisation in the present therapeutic indication.

Therefore, there is a discrepancy between the medicinal products approved in the indication and those recommended in the guidelines.

In the context of a clinical study, the above-mentioned treatment options are considered suitable comparators for therapy according to doctor's instructions. These combinations of active ingredients are equally suitable for the implementation of the appropriate comparator therapy.

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.

b2) <u>Adults with locally advanced or metastatic HER2-positive adenocarcinoma of the oesophagus which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10); first-line therapy</u>

For patients with HER2-positive adenocarcinoma of the oesophagus, the guidelines recommend a combination therapy of the anti-HER2 antibody trastuzumab with cisplatin and fluoropyrimidines (5-fluorouracil or capecitabine), but this is not (explicitly) approved for the present therapeutic indication.

Only the active ingredients 5-fluorouracil and cisplatin have a marketing authorisation in the present therapeutic indication. There is a discrepancy between the medicinal products approved in the indication and those recommended in the guidelines.

In the context of a clinical study, trastuzumab in combination with cisplatin and capecitabine or trastuzumab in combination with cisplatin and 5-fluorouracil are considered suitable comparators for HER2-targeted therapy according to doctor's instructions. These combinations of active ingredients are equally suitable for the implementation of the appropriate comparator therapy.

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.

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

2.1.3 Extent and probability of the additional benefit

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

a) Adults with locally advanced or metastatic squamous cell carcinoma of the oesophagus which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10); first-line therapy

Indication of a considerable additional benefit.

b1) 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 (Combined Positive Score (CPS) ≥ 10); first-line therapy

An additional benefit is not proven.

Justification:

a) Adults with locally advanced or metastatic squamous cell carcinoma of the oesophagus which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10); first-line therapy

and

b1) 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 (Combined Positive Score (CPS) ≥ 10); first-line therapy

The benefit assessment is based on the pivotal KEYNOTE 590 study for the patient population a) and the meta-analysis of the KEYNOTE 590 and KEYNOTE 062 studies for the patient population b1).

KEYNOTE 590 study

KEYNOTE 590 is an ongoing, double-blind, randomised, multicentre study comparing pembrolizumab in combination with cisplatin and 5-fluorouracil with placebo in combination with cisplatin and 5-fluorouracil.

A total of 749 adults with locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or advanced or metastatic gastroesophageal junction adenocarcinoma were enrolled in the study and randomised in a 1:1 ratio. Randomisation was stratified by histology (adenocarcinoma vs squamous cell carcinoma), region (Asia vs rest of the world) and ECOG-PS (0 vs 1). Patients must not have received treatment for advanced or metastatic disease and must have HER2-negative gastroesophageal junction adenocarcinoma. The HER2 status of the tumours of patients with adenocarcinoma of the oesophagus was not determined in the KEYNOTE 590 study and is therefore unknown.

The percentage of the sub-population of patients with locally advanced unresectable or metastatic squamous cell carcinoma of the oesophagus whose tumours express PD-L1 with a CPS ≥ 10 (patient population a) is 143 patients in each of the intervention and comparator arms. The majority of patients in this sub-population are of Asian descent (69%).

The percentage of patients with locally advanced unresectable or metastatic adenocarcinoma of the oesophagus or advanced or metastatic gastroesophageal junction adenocarcinoma whose tumours express PD-L1 with a CPS ≥ 10 (patient population b1) is 43 patients in the intervention arm and 54 patients in the comparator arm.

Patients were treated in cycles of 3 weeks until disease progression, unacceptable toxicity, medical decision, withdrawal of consent or complete response for a maximum of 35 cycles, with the cisplatin treatment component limited to a maximum of 6 cycles. In both study arms, a total 5-fluorouracil dose of 4,000 mg/m² body surface area/ cycle with a fixed cycle length of 3 weeks was fixed. In contrast, the product information of 5-fluorouracil for the treatment of oesophageal cancer provides for a total dose of 5,000 mg/m² body surface area/ cycle with a cycle length of 3-4 weeks, whereby a dose reduction is only to be carried out if side effects occur.

A changeover of patients from the comparator arm to the treatment of the intervention arm was not planned.

The primary endpoints of the KEYNOTE 590 study are overall survival and progression-free survival. In addition, endpoints of the category's morbidity, health-related quality of life and adverse events are collected in the study.

The results of the data cut-off of 2 July 2020, which is the final analysis, are used for the benefit assessment.

KEYNOTE 062 study

KEYNOTE 062 is a three-arm, partially blinded, randomised, multicentre study that is double-blinded in the arms used for the benefit assessment. In the intervention arm, patients were treated with pembrolizumab in combination with cisplatin and 5-fluorouracil or capecitabine and in the comparator arm with placebo in combination with cisplatin and 5-fluorouracil or capecitabine. The other study arm comprises treatment with a pembrolizumab monotherapy and is not relevant for the present benefit assessment.

The study enrolled adults with locally advanced unresectable or metastatic adenocarcinoma of the stomach or gastroesophageal junction with negative HER2 status who had not yet received treatment for advanced or metastatic disease.

The 763 patients enrolled were assigned to the study arms, randomised in a 1:1:1 ratio. Thereby, 257 patients were assigned to the intervention arm, 250 to the comparator arm and 256 patients to the pembrolizumab monotherapy arm. Randomisation was stratified by geographic region (Europe/ North America vs Asia vs rest of the world), disease stage (locally advanced unresectable vs metastatic) and treatment strategy (5-fluorouracil vs capecitabine).

The sub-population of patients with adenocarcinoma of the oesophagus or gastroesophageal junction whose tumours express PD-L1 with a CPS ≥ 10 (patient population b1) relevant for the benefit assessment consists of 30 patients in the intervention arm and 20 in the control arm.

Patients were treated in cycles of three weeks until disease progression, unacceptable toxicity, medical decision, withdrawal of consent or complete response for a maximum of 35 cycles, with the cisplatin treatment component limited to a maximum of 6 cycles. In both study arms, a total 5-fluorouracil dose of 4,000 mg/m² body surface area/ cycle with a fixed cycle length of 3 weeks was fixed. In contrast, the product information of 5-fluorouracil for the treatment of oesophageal cancer provides for a total dose of 5,000 mg/m² body surface area/ cycle with a cycle length of 3-4 weeks, whereby a dose reduction is only to be carried out if side effects occur.

A changeover of patients from the comparator arm to the treatment of the intervention arm was not planned.

The primary endpoints of the KEYNOTE 062 study were overall survival and progression-free survival. In addition, endpoints of the category's morbidity, health-related quality of life and adverse events are collected in the study.

The results from 26 March 2019, which is the final analysis, are used for the benefit assessment.

<u>Extent and probability of the additional benefit</u>

a) <u>Adults with locally advanced or metastatic squamous cell carcinoma of the oesophagus which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10); first-line therapy</u>

Mortality

Overall survival

The overall survival is defined in the KEYNOTE 590 study as the time from randomisation to death from any cause.

For the endpoint of overall survival, there is a statistically significant difference between the treatment groups to the advantage of pembrolizumab in combination with cisplatin and 5-fluorouracil compared to cisplatin in combination with 5-fluorouracil.

The extent of the prolongation achieved in overall survival is assessed as a significant improvement.

Morbidity

Progression-free survival (PFS)

PFS is operationalised in the KEYNOTE 590 study as the time from randomisation to the first documentation of disease progression or death from any cause, whichever occurs first. The occurrence of disease progression was assessed using RECIST criteria (version 1.1).

There is a statistically significant difference for the PFS endpoint between the treatment groups to the advantage of pembrolizumab in combination with cisplatin and 5-fluorouracil.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component "mortality" is already surveyed in the present study via the endpoint "overall survival" as an independent endpoint. The morbidity component assessment was not done in a symptom-related manner but exclusively by means of imaging (disease progression assessed by radiology according to the RECIST version 1.1 criteria).

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 (EORTC QLQ-C30 and EORTC QLQ-OES18)

Disease symptomatology is assessed in the KEYNOTE 590 study using the symptom scales of the cancer-specific questionnaire EORTC QLQ-C30 and the oesophageal cancer-specific additional module EORTC QLQ-OES18.

The pharmaceutical company submitted responder analyses in the dossier for the time to first deterioration by ≥ 10 points, whereby the information on the operationalisation was partly contradictory. Within the framework of the written statement procedure, clarifying information was provided by the pharmaceutical company in this regard, which means that the evaluations presented are considered adequate.

There were no statistically significant differences between treatment arms for the endpoints of fatigue, nausea and vomiting, insomnia, appetite loss, constipation and diarrhoea assessed with the EORTC QLQ-C30 and for the endpoints of eating, reflux, pain, saliva swallowing, dry mouth, taste, cough, speech and dysphagia assessed with the EORTC QLQ-OES18.

In contrast, for the endpoints pain and dyspnoea (EORTC QLQ-C30) and for the endpoint choking (EORTC QLQ-OES18), there are statistically significant differences to the advantage of pembrolizumab in combination with cisplatin and 5-fluorouracil.

For the pain endpoint (EORTC QLQ-C30), there is an effect modification for the age characteristic. For patients ≥ 65 years of age, there is a statistically significant difference to the advantage of pembrolizumab in combination with cisplatin and 5-fluorouracil compared to cisplatin in combination with 5-fluorouracil. For patients < 65 years of age, there is no statistically significant difference between the treatment arms. The effect modifications for the characteristic age are not shown for any other endpoints, which is why the significance of the subgroup analysis is assessed as too low overall to carry out a separate assessment of the additional benefit according to the age characteristic.

Health status (EQ-5D VAS)

The health status is assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire.

In the dossier, the pharmaceutical company submitted responder analysis, operationalised as time to first deterioration by ≥ 7 points and by ≥ 10 points, respectively.

According to IQWiG's current methodological approach (methods paper 6.1, published on 24 January 2022) and the requirements of the G-BA's module template (last revised: 16 December 2021), a response threshold for responder analyses of at least 15% of the scale range of an instrument (for post hoc analyses of precisely 15% of the scale range) is considered to be necessary for patient-reported endpoints to represent a change noticeable for patients with sufficient certainty.

Against the background that the module template (last revised: 16 December 2021) had not yet entered into force at the start of the present benefit assessment procedure and the G-BA has recognised response thresholds of ≥ 7 and ≥ 10 points for the EQ-5D VAS as a clinically relevant change in previous benefit assessment procedures, the responder analyses with a response threshold of ≥ 7 and ≥ 10 points are used to assess the additional benefit for the present procedure.

There is no statistically significant difference between the study arms for any of the evaluations presented.

In the overall assessment of the results in the endpoint category of morbidity, there are advantages for pembrolizumab in combination with cisplatin and 5-fluorouracil in the symptoms of pain, dyspnoea and choking.

Quality of life

Health-related quality of life is assessed in the KEYNOTE 590 study using the functional scales of the cancer-specific questionnaire EORTC QLQ-C30.

The pharmaceutical company submitted responder analyses in the dossier for the time to first deterioration by ≥ 10 points, whereby the information on the operationalisation was partly contradictory. Within the framework of the written statement procedure, clarifying information was provided by the pharmaceutical company in this regard, which means that the evaluations presented are considered adequate.

Only for emotional functioning was there a statistically significant difference to the advantage of pembrolizumab in combination with cisplatin and 5-fluorouracil. Therefore, in the overall assessment, no difference between the treatment arms relevant for the benefit assessment

is found for pembrolizumab in combination with cisplatin and 5-fluorouracil in the endpoint category of quality of life.

Side effects

Adverse events (AEs) in total

Adverse events occurred in all study participants. The results were only presented additionally.

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

For the endpoints of SAEs and severe AEs, there was no statistically significant difference between the treatment groups.

Therapy discontinuations due to AEs (≥ 1 active ingredient component)

The pharmaceutical company submitted evaluations for the endpoint therapy discontinuations due to AEs in the dossier. However, it was unclear from the data whether these were evaluations of the time to discontinuation of all active ingredient components or evaluations of the time to discontinuation of ≥ 1 active ingredient component.

Within the framework of the written statement procedure, clarifying information in this regard was provided by the pharmaceutical company, whereby the submitted evaluations of the time to discontinuation ≥ 1 active ingredient component are considered adequate.

There is no statistically significant difference between the treatment arms.

Specific AEs

Immune-mediated SAEs

For the endpoint of immune-mediated SAEs (PT collection), there is a statistically significant difference to the disadvantage of pembrolizumab in combination with cisplatin and 5-fluorouracil compared to cisplatin in combination with 5-fluorouracil.

Other specific AEs

For the other specific AEs of musculoskeletal and connective tissue disorders (SOC, AE), general disorders and administration site conditions (SOC, SAE), thrombocytopenia (PT, severe AE) and weight loss (PT, severe AE), there was a statistically significant difference to the advantage of pembrolizumab in combination with cisplatin and 5-fluorouracil.

For immune-mediated severe AEs, there is no statistically significant difference between the treatment arms.

In the overall assessment of the results on side effects, neither an advantage nor a disadvantage can be found for pembrolizumab in combination with cisplatin and 5-fluorouracil compared to cisplatin in combination with 5-fluorouracil. In detail, there is a disadvantage in the immune-mediated SAEs and predominantly advantages in the other specific AEs.

Overall assessment

For the benefit assessment of pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy for the first-line treatment of adults with locally advanced unresectable or metastatic squamous cell carcinoma of the oesophagus whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10), results of the KEYNOTE 590 study on the endpoint categories of mortality, morbidity, quality of life and side effects are available.

In the ongoing study, pembrolizumab in combination with cisplatin and 5-Fluorouracilis being compared with the appropriate comparator therapy cisplatin in combination with 5-fluorouracil.

For overall survival, there is a statistically significant advantage of pembrolizumab in combination with cisplatin and 5-fluorouracil. The prolongation of survival time is assessed as a significant improvement in its extent.

In the endpoint category of morbidity, there are advantages in the symptoms of pain, dyspnoea and choking based on the EORTC QLQ-C30 and the EORTC QLQ-OES18 questionnaires.

For health-related quality of life, there is no difference between the treatment arms that is relevant for the evaluation.

With regard to side effects, neither an advantage nor a disadvantage can be found for pembrolizumab in combination with cisplatin and 5-fluorouracil compared to cisplatin in combination with 5-fluorouracil. In detail, there is a disadvantage in the immune-mediated severe adverse events and predominantly advantages in the other specific adverse events.

In the overall assessment of the present results on the patient-relevant endpoints, the clear advantage in overall survival and further advantages in symptomatology are not offset by any disadvantages.

The G-BA concluded that pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy for the first-line treatment of adults with locally advanced unresectable or metastatic squamous cell carcinoma of the oesophagus whose tumours express PD-L1 (CPS ≥ 10) provides considerable additional benefit compared to the appropriate comparator therapy cisplatin in combination with 5-fluorouracil.

Reliability of data (probability of additional benefit)

This benefit assessment is based on the results of the double-blind, randomised, multicentre, controlled KEYNOTE 590 study.

Overall, the risk of bias at the study level is rated as low.

At the endpoint level, the risk of bias of the endpoint of overall survival is also rated as low.

The results on the patient-reported endpoints are fraught with uncertainties due to the decreasing return rates over the course of the study.

In addition, in the KEYNOTE 590 study, a high percentage of Asian patients (69%) were included in the assessment-relevant sub-population of patients with locally advanced, unresectable or metastatic squamous cell carcinoma of the oesophagus. According to the clinical assessment experts, Asian patients have, among other things, a partly different aetiology of the disease and fewer comorbidities. This leads in particular to uncertainties in the endpoint of overall survival. Overall, the certainty of results for the reality of care in Germany is thus limited.

In the overall assessment, the available data basis is fraught with uncertainties. However, the uncertainties are not rated to be so high as to justify a downgrading of the reliability of data of the overall assessment. In particular, the risk of bias of the endpoint of overall survival is rated as low. Thus, the reliability of data for the additional benefit determined is classified in the category “indication”.

b1) 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 (Combined Positive Score (CPS ≥ 10)); first-line therapy

Mortality

Overall survival

The overall survival was defined in the KEYNOTE 590 and KEYNOTE 062 studies as the time from randomisation to death from any cause.

For the endpoint of overall survival, no statistically significant difference was detected between the treatment arms. An additional benefit of pembrolizumab in combination with cisplatin and 5-fluorouracil or capecitabine is therefore not proven for overall survival.

Morbidity

Progression-free survival (PFS)

PFS was defined in both studies as the period from randomisation to the first documentation of disease progression or death from any cause, whichever occurs first.

In the KEYNOTE 590 study, there is a statistically significant difference in PFS between the treatment groups to the advantage of pembrolizumab in combination with cisplatin and 5-fluorouracil or capecitabine.

In the KEYNOTE 062 study, there is no statistically significant difference between the treatment groups.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component "mortality" is already surveyed in the present study via the endpoint "overall survival" as an independent endpoint. The morbidity component assessment was not done in a symptom-related manner but exclusively by means of imaging (disease progression assessed by radiology according to the RECIST version 1.1 criteria).

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 (EORTC QLQ-C30 and EORTC QLQ-OES18)

Disease symptomatology was assessed in the KEYNOTE 590 and KEYNOTE 062 studies using the symptom scales of the cancer-specific questionnaire EORTC QLQ-C30 and in the KEYNOTE 590 study with the oesophageal cancer-specific additional module EORTC QLQ-OES18.

In the dossier, the pharmaceutical company submitted responder analyses on the time to first deterioration by ≥ 10 points, whereby the information on the operationalisation was partly contradictory with regard to the evaluations of the KEYNOTE 590 study. Within the framework of the written statement procedure, clarifying information was provided by the pharmaceutical company in this regard, which means that the evaluations presented are considered adequate.

There are no statistically significant differences between the treatment arms for the endpoints of fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation and diarrhoea assessed with the EORTC QLQ-C30 questionnaire, and for the endpoints of eating, pain, saliva swallowing, choking, taste, cough, speech and dysphagia assessed with the EORTC QLQ-OES18 questionnaire.

In contrast, for the endpoint reflux (EORTC QLQ-OES18), there is a statistically significant difference to the advantage and for the endpoint of dry mouth (EORTC QLQ-OES18), there is a statistically significant disadvantage of pembrolizumab in combination with cisplatin and 5-fluorouracil or capecitabine compared to the control arm.

For the endpoint of dry mouth (EORTC QLQ-OES18), there was an effect modification for the gender characteristic. For men, there is a statistically significant difference to the disadvantage of pembrolizumab in combination with cisplatin and 5-fluorouracil compared to cisplatin in combination with 5-fluorouracil. For women, there is no statistically significant difference between the treatment arms. The effect modification for the gender characteristic is not shown for any other endpoints, which is why the significance of the subgroup analysis is

assessed as too low overall to carry out a separate assessment of the additional benefit according to the gender characteristic.

Health status (EQ-5D VAS)

Health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire.

In the dossier, the pharmaceutical company submitted responder analysis, operationalised as time to first deterioration by ≥ 7 points and by ≥ 10 points, respectively.

According to IQWiG's current methodological approach (methods paper 6.1, published on 24 January 2022) and the requirements of the G-BA's module template (last revised: 16 December 2021), a response threshold for responder analyses of at least 15% of the scale range of an instrument (for post hoc analyses of precisely 15% of the scale range) is considered to be necessary for patient-reported endpoints to represent a change noticeable for patients with sufficient certainty.

Against the background that the module template (last revised: 16 December 2021) had not yet entered into force at the start of the present benefit assessment procedure and the G-BA has recognised response thresholds of ≥ 7 and ≥ 10 points for the EQ-5D VAS as a clinically relevant change in previous benefit assessment procedures, the responder analyses with a response threshold of ≥ 7 and ≥ 10 points are used to assess the additional benefit for the present procedure.

There is no statistically significant difference between the study arms for any of the evaluations presented.

Overall, for pembrolizumab in combination with cisplatin and 5-fluorouracil, there is an advantage in the reflux symptom and a disadvantage in the dry mouth symptom in the endpoint category of morbidity, so that in the overall assessment, no relevant difference for the benefit assessment is found between the treatment arms.

Quality of life

Health-related quality of life was assessed using the functional scales of the cancer-specific questionnaire EORTC QLQ-C30.

In the dossier, the pharmaceutical company submitted responder analyses on the time to first deterioration by ≥ 10 points, whereby the information on the operationalisation was partly contradictory with regard to the evaluations of the KEYNOTE 590 study. Within the framework of the written statement procedure, clarifying information was provided by the pharmaceutical company in this regard, which means that the evaluations presented are considered adequate.

There is no statistically significant difference between the treatment arms, which means that neither an advantage nor a disadvantage of pembrolizumab in combination with cisplatin and 5-fluorouracil or capecitabine can be determined for the quality of life.

Side effects

Adverse events

Adverse events occurred in almost all study participants. The results were only presented additionally.

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

For the endpoints of SAEs and severe AEs, there was no statistically significant difference between the treatment groups.

Therapy discontinuations due to AEs (≥ 1 active ingredient component)

The pharmaceutical company submitted evaluations for the endpoint therapy discontinuations due to AEs in the dossier. However, it was unclear from the data whether these were evaluations of the time to discontinuation of all active ingredient components or evaluations of the time to discontinuation of ≥ 1 active ingredient component.

Within the framework of the written statement procedure, clarifying information in this regard was provided by the pharmaceutical company, whereby the submitted evaluations of the time to discontinuation ≥ 1 active ingredient component are considered adequate.

There is a statistically significant difference between the treatment arms to the disadvantage of pembrolizumab in combination with cisplatin and 5-fluorouracil or capecitabine.

Specific AEs

Immune-mediated SAEs, immune-mediated severe AEs

For immune-mediated SAEs and immune-mediated severe AEs (PT collection), there is no statistically significant difference between the treatment arms in each case.

Other specific AEs

For endocrine disorders (SOC, AE), there is a statistically significant difference to the disadvantage of pembrolizumab in combination with cisplatin and 5-fluorouracil or capecitabine.

Overall, the results on side effects for pembrolizumab in combination with cisplatin and 5-fluorouracil or capecitabine compared to cisplatin in combination with 5-fluorouracil or capecitabine show a moderate disadvantage for the endpoint of treatment discontinuations due to AEs and in detail, a disadvantage for a specific AE.

Overall assessment

For the benefit assessment of pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative adenocarcinoma of the oesophagus or of the gastroesophageal junction whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10), the meta-analytic results of the KEYNOTE 590 and KEYNOTE 062 studies are available for the endpoint categories of mortality, morbidity, quality of life and side effects.

The studies compare pembrolizumab in combination with cisplatin and 5-fluorouracil or capecitabine with cisplatin in combination with 5-fluorouracil or capecitabine.

For the endpoint of overall survival, no statistically significant difference was detected between the treatment arms. With regard to overall survival, an additional benefit of pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy is therefore not proven.

In the endpoint categories of morbidity and health-related quality of life, there are no differences between the treatment arms that are relevant for the benefit assessment.

With regard to side effects, pembrolizumab in combination with cisplatin and 5-fluorouracil or capecitabine shows a disadvantage for the endpoint of treatment discontinuations due to adverse events and in detail, a disadvantage for a specific adverse event.

In the overall assessment of the available results on the patient-relevant endpoints, there is a moderate disadvantage of pembrolizumab in combination with cisplatin and 5-fluorouracil or capecitabine in terms of side effects for the endpoint of treatment discontinuations due to adverse events. However, the disadvantage does not reach a level that would justify a lower benefit.

As a result, the G-BA concluded that an additional benefit is not proven for pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative adenocarcinoma of the oesophagus or of the gastroesophageal junction whose tumours express PD-L1 (CPS ≥ 10) compared to the appropriate comparator therapy.

b2) Adults with locally advanced or metastatic HER2-positive adenocarcinoma of the oesophagus which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10); first-line therapy

An additional benefit is not proven.

Justification:

No data for an assessment of the additional benefit of pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy compared to the appropriate comparator therapy were submitted with the dossier by the pharmaceutical company.

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 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 gastroesophageal junction adenocarcinoma, in adults whose tumours express PD-L1 with a CPS ≥ 10. “

In the therapeutic indication to be considered, three patient groups were distinguished:

a) Adults with locally advanced or metastatic squamous cell carcinoma of the oesophagus which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10); first-line therapy

b1) 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 (Combined Positive Score (CPS) ≥ 10); first-line therapy

b2) Adults with locally advanced or metastatic HER2-positive adenocarcinoma of the oesophagus which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10); first-line therapy

Patient group a)

Results on overall survival, morbidity, quality of life and side effects are available for this patient group.

The assessment is based on the KEYNOTE 590 study comparing pembrolizumab in combination with cisplatin and 5-fluorouracil with cisplatin in combination with 5-fluorouracil. The comparator therapy in the study corresponds to the appropriate comparator therapy for the present patient group.

For overall survival, there is an advantage of pembrolizumab in combination with cisplatin and 5-fluorouracil. The prolongation in survival time is assessed as a significant improvement.

In the endpoint category of morbidity, there are advantages of pembrolizumab in combination with cisplatin and 5-fluorouracil in terms of disease symptomatology.

For health-related quality of life and side effects, there is no relevant difference for the assessment between the treatment arms.

Uncertainties remain due to the decreasing return rates for the patient-reported endpoints over the course of the study and the high percentage of Asian patients (69%) in patient group a). However, the uncertainties are not rated to be so high as to justify a downgrading of the reliability of data of the overall assessment.

As a result, the G-BA finds an indication of a considerable additional benefit compared to the appropriate comparator therapy of cisplatin in combination with 5-fluorouracil.

Patient group b1)

Results on overall survival, morbidity, quality of life and side effects are available for this patient group.

The assessment is based on the KEYNOTE 590 and KEYNOTE 062 studies comparing pembrolizumab in combination with cisplatin and 5-fluorouracil or capecitabine with cisplatin in combination with 5-fluorouracil or capecitabine. The comparator therapy in the study represents an adequate implementation of the appropriate comparator therapy for the present patient group.

However, there were no statistically significant differences between the treatment arms for the overall survival.

In the endpoint categories of morbidity and health-related quality of life, there are no relevant differences for the benefit assessment between the treatment arms.

With regard to side effects, a moderate disadvantage in therapy discontinuations due to adverse events can be observed for pembrolizumab in combination with cisplatin and 5-fluorouracil or capecitabine. However, this does not reach a level that would justify a lower benefit.

As a result, the G-BA states that an additional benefit is not proven.

Patient group b2)

For this patient group, no data are available for the assessment of the additional benefit.

An additional benefit 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).

The patient numbers derived by the pharmaceutical company in the dossier are an underestimate.

This is due in particular to the exclusion of patients with locally advanced unresectable carcinoma, the exclusion of patients who have already received therapy at an earlier stage and who suffer a progression, and an underestimation of the incidence of oesophageal cancer.

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: 16 February 2022):

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 oesophageal cancer.

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: 15 April 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.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements were applied (average 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).

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				
Patient population a), b1) and b2)				
Pembrolizumab + cisplatin + 5-fluorouracil				
Pembrolizumab	1 x per 21-day cycle	17.4	1	17.4
	or			
	1 x per 42-day cycle	8.7	1	8.7
Cisplatin	1 x per 21-day cycle	17.4	1	17.4
5-fluorouracil	1 x on day 1-5 of a 21-day cycle cycle	17.4	5	87
Patient population b1)				
Pembrolizumab + cisplatin + capecitabine				
Pembrolizumab	1 x per 21-day cycle	17.4	1	17.4
	or			
	1 x per 42-day cycle	8.7	1	8.7
Cisplatin	1 x per 21-day cycle	17.4	1	17.4
Capecitabine	2 x daily on day 1-14 of a 21-day cycle	17.4	14	243.6
Appropriate comparator therapy				
cisplatin + 5-fluorouracil				
Cisplatin	1 x per 21-day cycle	17.4	1	17.4

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 1-5 of a 21-day cycle cycle	17.4	5	87
Patient population b1)				
Therapy according to doctor's instructions[2] - cisplatin + 5-fluorouracil				
Cisplatin	1 x per 21-day cycle	17.4	1	17.4
5-fluorouracil	1 x on day 1-5 of a 21-day cycle cycle	17.4	5	87
Therapy according to doctor's instructions - Cisplatin + docetaxel + 5-fluorouracil[2]				
Cisplatin	1 x per 21-day cycle	17.4	1	17.4
Docetaxel	1 x per 21-day cycle	17.4	1	17.4
5-fluorouracil	1 x on day 1-5 of a 21-day cycle cycle	17.4	5	87
Patient population b2)				
HER2-targeted therapy according to doctor's instructions[3]				

[2] Costs are only shown for the active ingredients cisplatin, 5-fluorouracil and docetaxel. In addition to these, the following medicinal product combinations S-1 (tegafur/ gimeracil/ oteracil) + cisplatin, capecitabine + cisplatin, 5-fluorouracil + oxaliplatin + folinic acid [FLO and FOLFOX], capecitabine + oxaliplatin, infusional 5-fluorouracil + folinic acid + cisplatin [PLF], epirubicin + cisplatin + capecitabine [ECX], epirubicin + oxaliplatin + capecitabine [EOX], epirubicin + cisplatin + infusional 5-fluorouracil [ECF], 5-fluorouracil + oxaliplatin + epirubicin, infusional 5-fluorouracil + folinic acid + oxaliplatin + docetaxel [FLOT regimen] are also suitable comparators for the present benefit assessment in the context of a therapy according to doctor's instructions. These medicinal product combinations contain active ingredients that are not approved in the present therapeutic indication, and therefore, no costs are presented for these medicinal products.

[3] The medicinal product combinations trastuzumab + cisplatin + capecitabine and trastuzumab + cisplatin + 5-fluorouracil are suitable comparators for the present benefit assessment in the context of HER2-targeted therapy according to doctor's instructions. All medicinal therapies that represent a suitable comparator for the present benefit assessment in the context of HER2-targeted therapy according to a doctor's instructions are not approved in the present therapeutic indication, which is why no costs are presented for these medicinal products.

Consumption:

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					
Patient population a), b1) and b2)					
Pembrolizumab + cisplatin + 5-fluorouracil					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	8.7	34.8 x 100 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
5-fluorouracil	800 mg/m^2 = 1,520 mg	1520 mg	2 x 1,000 mg	87	174 x 1,000 mg
Patient population b1)					
Pembrolizumab + cisplatin + capecitabine					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 mg x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	8.7	34.8 mg x 100 mg
Cisplatin	80 mg/m^2	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
Appropriate comparator therapy					
Patient population a)					
cisplatin + 5-fluorouracil					
Cisplatin	80 mg/m^2 = 152 mg	152 mg	1 x 100 mg + 1 x 50 mg	17.4	17.4 x 100 mg + 17.4 x 50 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
			+ 1 x 10 mg		+ 17.4 x 10 mg
5-fluorouracil	800 mg/m² = 1,520 mg	1,520 mg	2 x 1,000 mg	87	174 x 1,000 mg
Patient population b1)					
Therapy according to doctor's instructions[2] - cisplatin + 5-fluorouracil					
Cisplatin	80 mg/m² = 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/m² = 1,520 mg	1,520 mg	2 x 1,000 mg	87	174 x 1,000 mg
Therapy according to doctor's instructions - Cisplatin + docetaxel + 5-fluorouracil[2]					
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
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	1 x 140 mg + 1 x 20 mg	17.4	17.4 x 140 mg + 17.4 x 20 mg
5-fluorouracil	750 mg/m² = 1,425 mg	1,425 mg	1 x 1,000 mg + 1 x 500 mg	87	87 x 1,000 mg + 87 x 500 mg
Patient population b2)					
HER2-targeted therapy according to doctor's instructions[3]					

Costs:

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					

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
Patient population a), b1) and b2)					
Pembrolizumab 100 mg	1 CIS	€ 3,037.30	€ 1.77	€ 170.17	€ 2,865.36
Cisplatin 10 mg	10 ml CIS	€ 17.49	€ 1.77	€ 0.30	€ 15.42
Cisplatin 50 mg	50 ml CIS	€ 47.67	€ 1.77	€ 1.73	€ 44.17
Cisplatin 100 mg	100 ml CIS	€ 76.55	€ 1.77	€ 3.10	€ 71.68
5-fluorouracil 1,000 mg[4]	20 ml SFI	€ 16.64	€ 1.77	€ 0.42	€ 14.45
Patient population b1)					
Pembrolizumab 100 mg	1 CIS	€ 3,037.30	€ 1.77	€ 170.17	€ 2,865.36
Cisplatin 10 mg	10 ml CIS	€ 17.49	€ 1.77	€ 0.30	€ 15.42
Cisplatin 50 mg	50 ml CIS	€ 47.67	€ 1.77	€ 1.73	€ 44.17
Cisplatin 100 mg	100 ml CIS	€ 76.55	€ 1.77	€ 3.10	€ 71.68
Capecitabine 150 mg[4]	120 FCT	€ 54.11	€ 1.77	€ 3.39	€ 48.94
Capecitabine 500 mg[4]	120 FCT	€ 151.81	€ 1.77	€ 11.11	€ 138.93
Appropriate comparator therapy					
Cisplatin 10 mg	10 ml CIS	€ 17.49	€ 1.77	€ 0.30	€ 15.42
Cisplatin 50 mg	50 ml CIS	€ 47.67	€ 1.77	€ 1.73	€ 44.17
Cisplatin 100 mg	100 ml CIS	€ 76.55	€ 1.77	€ 3.10	€ 71.68
Docetaxel 20 mg	1 ml CIS	€ 112.43	€ 1.77	€ 4.80	€ 105.86
Docetaxel 140 mg	7 ml CIS	€ 719.30	€ 1.77	€ 33.60	€ 683.93
5-fluorouracil 500 mg	10 ml IIS	€ 14.13	€ 1.77	€ 0.23	€ 12.13
5-fluorouracil 1,000 mg	20 ml IIS	€ 16.64	€ 1.77	€ 0.62	€ 14.45
Abbreviations: FCT = film-coated tablets, CIS = concentrate for the preparation of an infusion solution, IIS = injection/infusion solution, SFI = solution for injection					

LAUER-TAXE® last revised: 15 April 2022

[4] 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.

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							
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.							
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 - 4.4 l/day	10 x 1000 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		

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 25 August 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

The appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 22 June 2021.

On 12 November 2021, 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 2, number 5 VerfO.

By letter dated 16 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 pembrolizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 February 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 15 February 2022. The deadline for submitting written statements was 9 March 2022.

The oral hearing was held on 28 March 2022.

By letter dated 29 March 2022, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 14 April 2022. On 25 April 2022, the IQWiG submitted a new version of IQWiG's addendum to the G-BA. This version 1.1 dated 25 April 2022 replaces version 1.0 of the addendum dated 14 April 2022.

On 1 April 2022, the IQWiG submitted a new version of IQWiG's dossier assessment to the G-BA. This version 1.1 dated 01 April 2022 replaces version 1.0 of the dossier assessment dated 11 February 2022. The assessment result was not affected by the changes in version 1.1 compared to version 1.0.

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 26 April 2022, and the proposed resolution was approved.

At its session on 5 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
Subcommittee Medicinal products	22 June 2021	New determination of the appropriate comparator therapy
Working group Section 35a	23 March 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	28 March 2022	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	6 April 2022 21 April 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	26 April 2022	Concluding discussion of the draft resolution
Plenum	5 May 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 5 May 2022

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

Prof. Hecken