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: gastric or gastro-oesophageal junction adenocarcinoma,
PD-L1 expression ≥ 1, HER2+, first-line,
combination with trastuzumab, 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.

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-positive 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-positive 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 August 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 20 March 2024.

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 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 addendum to the benefit assessment prepared by IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods 1 was not used in the benefit assessment of 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:

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

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 trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-positive 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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

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

- trastuzumab in combination with capecitabine and cisplatin

  or

- trastuzumab in combination with 5-fluorouracil and cisplatin

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.

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

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 trastuzumab are approved for the present therapeutic indication.

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

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as 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.

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.

For HER2-positive patients, according to the German S3 guideline and international guidelines, trastuzumab should be added to cisplatin/fluoropyrimidine-based therapy as part of palliative first-line treatment. This recommendation is essentially derived from the results of the ToGA study. The results of this randomised phase III study showed that the addition of trastuzumab to chemotherapy consisting of capecitabine plus cisplatin or 5-fluorouracil plus cisplatin resulted in a significant improvement in median survival time in patients with HER2-positive status compared to chemotherapy alone.

The ToGA study led to the marketing authorisation of trastuzumab in combination with capecitabine or 5-fluorouracil and cisplatin for the treatment of adult patients with HER2-positive metastatic gastric or gastro-oesophageal junction adenocarcinoma who have not previously received cancer therapy for their metastatic disease. The active ingredients capecitabine and 5-fluorouracil are also approved for advanced gastric carcinoma.

According to the written and oral statements of the scientific-medical societies, the first-line systemic therapy for advanced gastric carcinoma is based on a chemotherapy doublet of a fluoropyrimidine (5-fluorouracil or capecitabine) and a platinum analogue (cisplatin or oxaliplatin). In the written statement of the written statement procedure, it was stated that the localisation of the gastro-oesophageal junction or stomach does not play a decisive role in the choice of systemic therapy for adenocarcinomas of the upper gastrointestinal tract. The active ingredients oxaliplatin and cisplatin are to be regarded as at least equivalent in terms of efficacy. Oxaliplatin shows a better safety and side effect profile compared to cisplatin overall. The advantages of oxaliplatin are a lower rate and severity of nausea and vomiting and less pronounced impairment of renal function and hearing, which results in oxaliplatin treatment being preferred.

The platinum and fluoropyrimidine-containing chemotherapies named in the written statement procedure and mentioned in the written statements of the scientific-medical societies on the question of comparator therapy thus include both approved and unapproved medicinal products for the present therapeutic indication - in this case:

oxaliplatin. The active ingredient oxaliplatin is not approved for use in combination therapy with trastuzumab. The present national and international guidelines primarily recommend the approved combination therapy of trastuzumab, cisplatin and 5-fluorouracil or capecitabine, thus focusing on cisplatin as the platinum component in this combination therapy. From the G-BA's perspective, it cannot be concluded on the basis of the available evidence overall that oxaliplatin is generally preferable to cisplatin on the basis of reliable data and corresponding therapy recommendations in the guidelines.

Therefore, it cannot be concluded that the off-label use of medicinal products is generally preferable 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.

In the overall analysis, the G-BA determined trastuzumab in combination with 5-fluorouracil and cisplatin or trastuzumab in combination with capecitabine and cisplatin as the appropriate comparator therapy.

The appropriate comparator therapy determined here includes several therapy options. These therapeutic alternatives are equally appropriate for the comparator therapy.

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.

2.1.3 Extent and probability of the additional benefit

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

<u>Adults with locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma whose tumours express PD-L1 with a CPS ≥ 1; first-line therapy</u>

An additional benefit is not proven.

Justification:

The present benefit assessment is the assessment of pembrolizumab as a combination therapy with trastuzumab as well as fluoropyrimidine and platinum-containing chemotherapy for first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1 following an extension of the therapeutic indication.

For the proof of additional benefit of pembrolizumab, the pharmaceutical company presented the results of the phase III KEYNOTE 811 study.

KEYNOTE 811 is a double-blind, randomised, multicentre study that has been ongoing since 2018 to compare pembrolizumab in combination with trastuzumab and fluoropyrimidine and

platinum-containing chemotherapy with placebo in combination with trastuzumab and fluoropyrimidine and platinum-containing chemotherapy. 5-fluorouracil + cisplatin (FP) or capecitabine + oxaliplatin (CAPOX) were used as the fluoropyrimidine and platinum-containing chemotherapy regimens in the global cohort of the study. In the Japanese cohort, a combination of S-1 (fixed combination of tegafur, gimeracil and oteracil) and oxaliplatin was administered.

The study is being conducted in 160 study sites in Asia, Australia, Europe and North and South America.

A total of 698 adults with locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma were enrolled in the global cohort of the study relevant for the benefit assessment and randomised in a 1:1 ratio.

The percentage of the sub-population of patients whose tumours express PD-L1 with a CPS ≥ 1 was 298 patients in the intervention arm and 296 patients in the comparator arm. The percentage of patients treated with the treatment regimen trastuzumab in combination with 5-fluorouracil and cisplatin , which is relevant for the benefit assessment, is 47 patients in the intervention arm and 43 patients in the comparator arm.

For the KEYNOTE 811 study, a total of 3 data cut-offs are available:

- 1st data cut-off from 14.07.2020: planned interim analysis after at least 8.5 months of observation period after randomisation of 260 patients
- 2nd data cut-off from 25.05.2022: planned interim analysis after at least 542 events in the PFS endpoint approximately 9 months after randomisation of the last patient
- 3rd data cut-off from 29.03.2023: planned interim analysis after at least 606 events in the PFS endpoint after at least 18 months after randomisation of the last patient

The final analysis of the study is planned after approximately 551 events in the overall survival endpoint and at least 28 months after randomisation of the last patient.

For the benefit assessment, the results of the data cut-off from 29.03.2023 are used.

On the relevant sub-population and the implementation of the appropriate comparator therapy

In the dossier, the pharmaceutical company presented analyses of a sub-population of the KEYNOTE 811 study whose patients have a CPS ≥ 1 and are treated with the FP or CAPOX chemotherapy regimens. The appropriate comparator therapy determined by the G-BA comprises the approved chemotherapies trastuzumab in combination with FP and trastuzumab in combination with capecitabine and cisplatin. The CAPOX chemotherapy regimen used in the study is not included in the appropriate comparator therapy.

In module 4 of the dossier, no specific evaluations are available on the sub-population relevant for the benefit assessment with the FP treatment regimen. The information on the sub-population relevant for the benefit assessment is available in the dossier as part of subgroup analyses, as the selected chemotherapy regimen (FP vs CAPOX) is a pre-specified subgroup feature.

To describe the patient characteristics for the relevant sub-population, the benefit assessment considers approximately all study participants who received the FP chemotherapy regimen, regardless of PD-L-1 status. Almost all patients had metastatic disease (94% in the intervention arm vs 98% in the comparator arm).

Extent and probability of the additional benefit

Mortality

Overall survival

The overall survival is defined in the KEYNOTE 811 study as the time from randomisation to death from any cause.

For the overall survival endpoint, there was no statistically significant difference between pembrolizumab in combination with trastuzumab, 5-fluorouracil and cisplatin compared to trastuzumab in combination with 5-fluorouracil and cisplatin. For overall survival, an additional benefit is therefore not proven.

Morbidity

Symptomatology (EORTC QLQ-C30 and EORTC QLQ-STO22)

Disease symptomatology is assessed in the KEYNOTE 811 study using the symptom scales of the cancer-specific questionnaire EORTC QLQ-C30 and the gastric cancer-specific additional module EORTC QLQ-STO22.

In the present situation, the EORTC QLQ-STO22 questionnaire is considered to be sufficiently valid for both patients with gastric cancer and patients with gastro-oesophageal junction cancer, even though the questionnaire was primarily developed for gastric cancer.

In the dossier, the pharmaceutical company submitted time-to-event analyses on the time to first deterioration by at least 10 points, including the return rates of the questionnaires, only for the patient population it considered with a CPS ≥ 1 regardless of the chemotherapy regimen. The sub-population relevant for the benefit assessment corresponds to approximately 15% of this population, so the available information on the return rates of the questionnaires for the relevant sub-population is not significant and it is not possible to estimate the percentage of missing values. The data are therefore considered unusable.

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 time-to-event analyses on first-time deterioration by at least 15 points, including the return rates of the questionnaires, only for the patient population it considered with a CPS ≥ 1 regardless of the chemotherapy regimen. The sub-population relevant for the benefit assessment corresponds to approximately 15% of this population, so the available information on the return rates of the questionnaires for the relevant sub-population is not significant and it is not possible to estimate the percentage of missing values. The data are therefore considered unusable.

Quality of life

Health-related quality of life is assessed in the KEYNOTE 811 study using the functional scales of the cancer-specific questionnaire EORTC QLQ-C30.

In the dossier, the pharmaceutical company submitted time-to-event analyses on the time to first deterioration by at least 10 points, including the return rates of the questionnaires, only for the patient population it considered with a CPS ≥ 1 regardless of the chemotherapy regimen. The sub-population relevant for the benefit assessment corresponds to approximately 15% of this population, so the available information on the return rates of the

questionnaires for the relevant sub-population is not significant and it is not possible to estimate the percentage of missing values. The data are therefore considered unusable.

Side effects

Adverse events (AEs) in total

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

In the dossier, the pharmaceutical company presented evaluations for the relevant sub-population in the form of subgroup analyses for the endpoint of therapy discontinuations due to AEs. However, it is 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. Evaluations of the time to discontinuation of at least one active ingredient component is considered necessary for the benefit assessment. The data are therefore considered unusable.

Specific AEs

Cardiac disorders (severe AE), immune-mediated SAE, immune-mediated severe AE

No evaluations are available for the relevant sub-population for the endpoints of cardiac disorders (severe AEs), immune-mediated SAEs and immune-mediated severe AEs. This results from the fact that the evaluations of the relevant sub-population were taken from the subgroup analyses of the pharmaceutical company.

Against the background that immune-mediated AEs are to be expected with the use of PD-1 inhibitors, potentially negative effects on endpoints of immune-mediated AEs are therefore not identified.

Other specific AEs

It was not possible to select any other specific AEs, as the data on time-to-event analyses according to PT and SOC are incomplete for the relevant sub-population. This results from the fact that the evaluations of the relevant sub-population were taken from the subgroup analyses of the pharmaceutical company.

In the overall assessment of the results on side effects, neither an advantage nor a disadvantage was found for pembrolizumab in combination with trastuzumab, 5-fluorouracil and cisplatin compared to trastuzumab, 5-fluorouracil and cisplatin with regard to SAEs and severe AEs (CTCAE grade ≥ 3). However, no usable results or none at all were available for evaluations of therapy discontinuations due to AEs, cardiac disorders (severe AEs), immune-mediated SAEs, immune-mediated severe AEs and other specific AEs for the relevant sub-population.

Overall assessment

For the benefit assessment of pembrolizumab in combination with trastuzumab as well as fluoropyrimidine and platinum-containing chemotherapy for first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1, results from the KEYNOTE 811 study are available for the endpoint categories of mortality, morbidity, quality of life and side effects.

For the benefit assessment, a sub-population of the ongoing study is used, in which pembrolizumab in combination with trastuzumab, 5-fluorouracil and cisplatin is compared with the appropriate comparator therapy trastuzumab in combination with 5-fluorouracil and cisplatin.

There is no statistically significant difference for the overall survival.

Disease symptomatology was assessed in the study using the cancer-specific questionnaire EORTC QLQ-C30 and the gastric cancer-specific additional module EORTC QLQ-STO22. In addition, the health status was recorded using the EQ-5D VAS. However, the respective evaluations are unusable due to unknown return rates in relation to the relevant sub-population.

Health-related quality of life was assessed in the study using the EORTC QLQ-C30 questionnaire. However, the relevant evaluations are also unusable due to unknown return rates in relation to the relevant sub-population.

With regard to side effects, neither an advantage nor a disadvantage was found for pembrolizumab in combination with trastuzumab, 5-fluorouracil and cisplatin compared to trastuzumab, 5-fluorouracil and cisplatin with regard to SAEs and severe AEs (CTCAE grade ≥ 3). However, no usable results were available for therapy discontinuations due to AEs, cardiac disorders (severe AEs), immune-mediated SAEs, immune-mediated severe AEs and other specific AEs for the relevant sub-population.

In the overall analysis of the present results on the patient-relevant endpoints, there was no statistically significant difference between the treatment groups for overall survival. There are no assessable data for the evaluation of morbidity (disease symptomatology, health status) and quality of life. For the side effects, neither an advantage nor a disadvantage can be derived for the overall rates of the endpoints SAEs and severe AEs (CTCAE grade ≥ 3). For other endpoints in the category of side effects, no usable data are available.

The G-BA thus concluded that an additional benefit of pembrolizumab in combination with trastuzumab, 5-fluorouracil and cisplatin for first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a 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 trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1."

As the appropriate comparator therapy, the G-BA determined two combination therapies as alternative comparator therapies: trastuzumab in combination with 5-fluorouracil and cisplatin or trastuzumab in combination with capecitabine and cisplatin.

The assessment is based on the KEYNOTE 811 study, in which the therapy regimen pembrolizumab in combination with trastuzumab, 5-fluorouracil and cisplatin is compared with trastuzumab in combination with 5-fluorouracil and cisplatin in the sub-population relevant for the benefit assessment. Results are available on overall survival, morbidity, quality of life and side effects.

For the overall survival endpoint, there was no statistically significant difference between pembrolizumab in combination with trastuzumab, 5-fluorouracil and cisplatin compared to trastuzumab in combination with 5-fluorouracil and cisplatin.

In the endpoint categories of morbidity and health-related quality of life, there are no usable data for the benefit assessment. The relevant evaluations are unusable due to unknown return rates in relation to the relevant sub-population.

With regard to side effects, neither an advantage nor a disadvantage was found for pembrolizumab in combination with trastuzumab, 5-fluorouracil and cisplatin compared to trastuzumab, 5-fluorouracil and cisplatin with regard to SAEs and severe AEs (CTCAE grade ≥ 3). However, no usable results were available for therapy discontinuations due to AEs, cardiac disorders (severe AEs), immune-mediated SAEs, immune-mediated severe AEs and other specific AEs for the relevant sub-population.

As a result, the G-BA states that 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).

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-positive status is 17.5% (124 to 579 patients).

4b. The percentage of patients with HER2-positive status is 26% (46 to 375 patients).

5a. The percentage of PD-L1-expressing tumours with CPS ≥ 1 range from 44.9% to 85.4% (56 to 495 patients).

5b. The percentage of PD-L1-expressing tumours with CPS ≥ 1 range from 49.4% to 84.5% (23 to 317 patients).

6a. Taking into account the percentage of SHI-insured patients of 87.2%, this results in 49 to 431 patients. 56 to 799

6b. Taking into account the percentage of SHI-insured patients of 87.2%, this results in 20 to 276 patients.

The sum of sub-steps 6a and 6b results in 68 to 707 patients with locally advanced unresectable or metastatic HER2-positive 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: 12 June 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).

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

Treatment period:

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 for the maximum treatment duration, if specified in the product information.

The annual treatment costs shown refer to the first year of treatment.

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 trastuzumab, 5-fluorouracil and cisplatin				
Pembrolizumab	1 x per 21-day cycle	17.4	1	17.4
	or			
	1 x per 42-day cycle	8.7	1	8.7
Trastuzumab	1 x per 21-day cycle	17.4	1	17.4
5-fluorouracil	1 x on day 1-5 of a 21-day cycle	17.4	5	87
Cisplatin	1 x per 21-day cycle	17.4	1	17.4
Appropriate comparator therapy				
Trastuzumab in combination with capecitabine and cisplatin				
Trastuzumab	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
Cisplatin	1 x per 21-day cycle	17.4	1	17.4
Trastuzumab in combination with 5-fluorouracil and cisplatin				
Trastuzumab	1 x per 21-day cycle	17.4	1	17.4
5-fluorouracil	1 x on day 1-5 of a 21-day cycle	17.4	5	87

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Cisplatin	1 x per 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)[2].

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.

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 trastuzumab, 5-fluorouracil and cisplatin					
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
Trastuzumab	Cycle 1: 8 mg kg/BW = 621.6 mg	621.6 mg	1 x 420 mg + 1 x 150 mg + 1 x 60 mg	1	1 x 420 mg + 1 x 150 mg + 1 x 60 mg
	From cycle 2 onwards: 6 mg kg/BW = 466.2 mg	466.2 mg	1 x 420 mg + 1 x 60 mg	16.4	16.4 x 420 mg + 16.4 x 60 mg
5-fluorouracil	800 mg/m² = 1,528 mg	1,528 mg	1 x 2,500 mg	87	87 x 2,500 mg

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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
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
Appropriate comparator therapy					
Trastuzumab in combination with capecitabine and cisplatin					
Trastuzumab	Cycle 1: 8 mg kg/BW = 621.6 mg	621.6 mg	1 x 420 mg + 1 x 150 mg + 1 x 60 mg	1	1 x 420 mg + 1 x 150 mg + 1 x 60 mg
	From cycle 2 onwards: 6 mg kg/BW = 466.2 mg	466.2 mg	1 x 420 mg + 1 x 60 mg	16.4	16.4 x 420 mg + 16.4 x 60 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
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
Trastuzumab in combination with 5-fluorouracil and cisplatin					
Trastuzumab	Cycle 1: 8 mg kg/BW = 621.6 mg	621.6 mg	1 x 420 mg + 1 x 150 mg + 1 x 60 mg	1	1 x 420 mg + 1 x 150 mg + 1 x 60 mg
	From cycle 2 onwards: 6 mg kg/BW = 466.2 mg	466.2 mg	1 x 420 mg + 1 x 60 mg	16.4	16.4 x 420 mg + 16.4 x 60 mg
5-fluorouracil	800 mg/m² = 1,528 mg	1,528 mg	1 x 2,500 mg	87	87 x 2,500 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
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

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:

Adults with locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma whose tumours express PD-L1 with a CPS ≥ 1; first-line 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
Medicinal product to be assessed					
Pembrolizumab	1 CIS	€ 2,974.82	€ 2.00	€ 166.60	€ 2,806.22
Trastuzumab 60 mg	1 PIC	€ 325.56	€ 2.00	€ 17.40	€ 306.16
Trastuzumab 150 mg	1 PIC	€ 798.23	€ 2.00	€ 43.57	€ 752.66
Trastuzumab 420 mg	1 PIC	€ 2,216.22	€ 2.00	€ 123.28	€ 2,090.94
5-fluorouracil 2,500 mg[3]	1 SII	€ 23.60	€ 2.00	€ 0.97	€ 20.63
Cisplatin 10 mg	1 CIS	€ 17.53	€ 2.00	€ 0.30	€ 15.23
Cisplatin 50 mg	1 CIS	€ 47.71	€ 2.00	€ 1.73	€ 43.98
Cisplatin 100 mg	1 CIS	€ 76.59	€ 2.00	€ 3.10	€ 71.49
Appropriate comparator therapy					
Trastuzumab 60 mg	1 PIC	€ 325.56	€ 2.00	€ 17.40	€ 306.16

3 Fixed reimbursement rate

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
Trastuzumab 150 mg	1 CIS	€ 798.23	€ 2.00	€ 43.57	€ 752.66
Trastuzumab 420 mg	1 CIS	€ 2,216.22	€ 2.00	€ 123.28	€ 2,090.94
5-fluorouracil 2,500 mg[3]	1 SFI	€ 23.60	€ 2.00	€ 0.97	€ 20.63
Capecitabine 150 mg[3]	120 FCT	€ 54.15	€ 2.00	€ 3.39	€ 48.76
Capecitabine 500 mg[3]	120 FCT	€ 151.84	€ 2.00	€ 11.11	€ 138.73
Cisplatin 10 mg	1 CIS	€ 17.53	€ 2.00	€ 0.30	€ 15.23
Cisplatin 50 mg	1 CIS	€ 47.71	€ 2.00	€ 1.73	€ 43.98
Cisplatin 100 mg	1 CIS	€ 76.59	€ 2.00	€ 3.10	€ 71.49
Abbreviations: FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution; SII = solution for injection / infusion; SFI = solution for injection; PIC = powder for the preparation of an infusion solution concentrate					

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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.

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

3 Fixed reimbursement rate

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:

Adults with locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction 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 8 November 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 10 October 2023.

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 2 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 26 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.

By letter dated 8 May 2024, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 31 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	08 November 2022	Implementation of the appropriate comparator therapy
Subcommittee Medicinal products	10 October 2023	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, Commissioning of the IQWiG with the supplementary assessment of documents
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