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 cancer with MSI-H or dMMR, pretreated)

of 19 January 2023

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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 forms 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 11 November 2021, the pharmaceutical company submitted an application for postponement of the date for the start of the benefit assessment procedure for pembrolizumab, amongst other indications, in the indication "gastric cancer with MSI-H or with dMMR and progression of the disease on or following at least one previous therapy" 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 several therapeutic indications at different times.

In its session on 6 January 2022, 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. All marketing authorisations for the therapeutic indications covered by the application according to Section 35a paragraph 5b SGB V were granted within the 6-month period.

For the present therapeutic indication "gastric cancer with MSI-H or with dMMR and progression of the disease on or following at least one prior therapy", pembrolizumab received the extension of the marketing authorisation as a major type 2 variation as defined according to Annex 2 No. 2a to Regulation (EC) number 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, p. 7) on 25 April 2022. In accordance with the resolution of 6 January 2022, the benefit assessment of the active ingredient pembrolizumab in this new therapeutic indication thus began at the latest within four weeks, i.e., at the latest on 20 July 2022, after the last approval, which took place on 22 June 2022, of pembrolizumab in the therapeutic indications for the treatment of "melanoma in patients aged 12 years and older".

On 18 July 2022, the pharmaceutical company has submitted in due time 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 active ingredient pembrolizumab with the new therapeutic indication "gastric cancer with MSI-H or with dMMR and progression of the disease on or following at least one previous therapy".

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 November 2022 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

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

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

[1] General Methods, version 6.1 from 24.01.2022. 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 as monotherapy is indicated for the treatment of the following MSI-H or dMMR tumours in adults with:

- unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy.

Therapeutic indication of the resolution (resolution of 19.01.2023):

Keytruda as monotherapy is indicated for the treatment of the following MSI-H or dMMR tumours in adults with:

- unresectable or metastatic gastric cancer, who have disease progression on or following at least one prior therapy.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with unresectable or metastatic gastric cancer with microsatellite instability-high (MSI-H) or with mismatch repair deficiency (dMMR) and disease progression on or following one prior therapy

Appropriate comparator therapy for pembrolizumab as monotherapy:

Therapy according to doctor's instructions

b) Adults with unresectable or metastatic gastric cancer with microsatellite instability-high (MSI-H) or with mismatch repair deficiency (dMMR) and disease progression on or following at least two prior therapies

Appropriate comparator therapy for pembrolizumab as monotherapy:

Trifluridine/tipiracil

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, the active ingredients 5-fluorouracil, doxorubicin, epirubicin, mitomycin, carmustine, ramucirumab and the combination of active ingredients trifluridine/tipiracil are approved in the present therapeutic indication.

on 2. It is assumed that curative treatment with definitive radiotherapy is not indicated for patients with unresectable cancer. In the present therapeutic indication, a non-medicinal treatment is therefore not considered.

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

- Trifluridine/tipiracil: Resolution of 2 April 2020
- Ramucirumab: Resolution of 20 October 2016

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a paragraph 7 SGB V.

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 care.

The appropriate comparator therapy is determined against the background that 95% of gastric cancers are adenocarcinomas. Therefore, no separate appropriate comparator therapy is determined for other histologies.

Overall, the evidence is limited for patients with pretreated gastric adenocarcinoma with microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR).

From the available evidence, no indications can be derived that in gastric adenocarcinomas with MSI-H or a dMMR, certain factors are present that clearly argue against treatment with the previous or current standard therapies. Thus, those therapy

options that are independent of the MSI/dMMR status and thus, eligible for the unselected patient population in this respect are considered for the appropriate comparator therapy.

The present therapeutic indication addresses several lines of therapy. For patients who have received prior systemic therapy and for patients who have received two or more prior systemic therapies, the evidence suggests that several treatment options are available. Therefore, in the present therapeutic indication, a distinction is made between a) adults with unresectable or metastatic gastric cancer with disease progression on or following one prior therapy and b) adults with unresectable or metastatic gastric cancer with disease progression on or following at least two prior therapies.

a) Adults with unresectable or metastatic gastric cancer with MSI-H or with dMMR and disease progression on or following one prior therapy

According to the guidelines, systemic therapy is recommended for the present treatment setting. According to the authorisation status, the active ingredient ramucirumab or the combination of active ingredients ramucirumab with paclitaxel can be considered for this. These treatment options are also mentioned in current guidelines as part of the recommendations for systemic therapy.

In the benefit assessment, a hint for a minor additional benefit was identified for ramucirumab in combination with paclitaxel in a resolution of 20 October 2016 compared to therapy according to doctor's instructions. In contrast, with the resolution of 20 October 2016, the G-BA did not determine an additional benefit for ramucirumab as monotherapy compared to best supportive care, against the background that no suitable data were submitted for the benefit assessment. Ramucirumab as monotherapy is therefore not considered as an appropriate comparator therapy.

According to current guidelines, the active ingredients irinotecan, docetaxel and paclitaxel (as monotherapy) are also recommended for the present treatment setting. The active ingredients irinotecan, docetaxel and paclitaxel (as monotherapies) are not approved for the present indication. There is a discrepancy between medicinal products approved in the indication and those used in healthcare/ recommended in guidelines.

In the context of a clinical study, the G-BA considers the following treatment options as suitable comparators for therapy according to doctor's instructions.

- Irinotecan,
- Docetaxel,
- Paclitaxel,
- Ramucirumab in combination with paclitaxel.

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.

b) Adults with unresectable or metastatic gastric cancer with MSI-H or with dMMR and disease progression on or following at least two prior therapies

According to current guidelines and statements of the scientific-medical societies, a treatment with the combination of active ingredients trifluridine/tipiracil is recommended for the present treatment setting after two or more previous systemic therapies. Trifluridine/tipiracil is approved in patients who have already been treated with at least two systemic treatment regimens for advanced disease. In the benefit assessment, the G-BA determined an indication of a minor additional benefit for trifluridine/tipiracil compared to best supportive care in its resolution of 2 April 2020.

In the overall assessment, trifluridine/tipiracil is therefore determined as the appropriate comparator therapy.

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

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:

a) Adults with unresectable or metastatic gastric cancer with microsatellite instability-high (MSI-H) or with mismatch repair deficiency (dMMR) and disease progression on or following one prior therapy

Hint for a non-quantifiable additional benefit

Justification:

The pharmaceutical company submitted the results of the KEYNOTE 061 study to prove the additional benefit of pembrolizumab for the treatment of unresectable or metastatic gastric cancer with MSI-H or dMMR and disease progression on or following one prior therapy.

The KEYNOTE-061 study is a completed, multicentre, open-label RCT comparing pembrolizumab with paclitaxel. The study included adult patients with metastatic or locally advanced, unresectable gastric adenocarcinoma or gastroesophageal junction (GEJ) with progression during or after first-line therapy with a platinum/fluoropyrimidine doublet. At the start of the study, patients could be included regardless of the tumour's programmed cell death ligand (PD-L1) expression. With protocol amendment 7, only patients with PD-L1-expressing tumours were included from 20.03.2016. Overall, 99 (33 %) vs 96 (32 %) patients had no PD-L1 expression of the tumour. Enrolment was limited to patients with Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤ 1. 592 patients were allocated in a 1:1 ratio to either treatment with pembrolizumab (N = 296) or paclitaxel (N = 296). Randomisation was stratified by region (Europe, Israel, North America, Australia vs Asia (including Japan, Korea, Hong Kong, Taiwan, Malaysia, Philippines, Singapore) vs rest of the

world (including South America)), time to disease progression on first-line therapy (< 6 months vs ≥ 6 months) and tumour PD-L1 expression (positive vs negative).

The treatment with pembrolizumab was carried out largely according to the requirements in the product information.

In the KEYNOTE-061 study, paclitaxel was administered IV in a 28-day cycle on days 1, 8 and 15 at a dose of 80 mg/m² body surface area (BSA) with a subsequent pause on day 22. In the KEYNOTE-061 study, treatment was given until confirmed disease progression, unacceptable toxicity, discontinuation of therapy by decision of the doctor or withdrawal of informed consent. An additional discontinuation criterion for pembrolizumab was treatment with a maximum of 35 cycles.

The study was conducted in 140 study sites in Australia, Asia, Europe, North and South America from May 2015 to June 2021.

The co-primary endpoints of the KEYNOTE-061 study were overall survival and progression-free survival, both in patients with PD-L1-expressing tumours. The secondary endpoints were overall survival in all patients regardless of the PD-L1 status of the tumour and endpoints in the categories of morbidity, health-related quality of life and adverse events. All patients in the KEYNOTE-061 study had their tumour microsatellite stability determined. Overall, 15 of 296 (< 1%) patients in the intervention arm and 12 of 296 (< 1%) patients in the comparator arm had tumours with MSI-H (gastric or GEJ tumour).

For the present benefit assessment, the results of the last data cut-off of 10.06.2021, at the end of study, are used. For the patient-reported endpoints, only results from the data cut of 26.10.2017 are available.

Relevant sub-population of the KEYNOTE 061 study

For the benefit assessment, the pharmaceutical company uses a sub-population of the KEYNOTE 061 study. These were patients with gastric cancer and MSI-H (N = 11 intervention arm; N = 10 comparator arm).

However, patients with gastroesophageal junction carcinomas with MSI-H are not included in the relevant sub-population. According to guidelines, gastroesophageal junction carcinomas are partly assigned to gastric cancer (depending on the localisation). For the benefit assessment, no information is available from the pharmaceutical company on the number of gastroesophageal junction carcinomas that are classified as gastric cancers according to guidelines. Thus, it remains unclear whether some of the excluded patients should have been considered for the benefit assessment.

Extent and probability of the additional benefit

Mortality

For the endpoint of overall survival, there is a statistically significant difference to the advantage of pembrolizumab compared to paclitaxel. Taking into account the wide confidence interval [0.08; 0.80] and the small number of patients in the relevant sub-population, there is an associated low precision in the endpoint overall survival. Thus, it is not possible to quantify the extent of the improvement.

Morbidity

Progression-free survival (PFS)

The occurrence of disease progression was assessed using RECIST criteria (version 1.1) in the KEYNOTE 061 study.

There are no signs of statistically differences between the treatment groups.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component "mortality" was already assessed 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 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 extent of the additional benefit remains unaffected.

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

The pharmaceutical company shall submit evaluations for the first deterioration of symptomatology by at least 15 points in the form of time-to-event analyses, collected using the EORTC QLQ-C30 and EORTC QLQ-STO22 questionnaires. In addition, the pharmaceutical company presents results over the course of the study separately for the two treatment arms in descriptive form.

Against the background of a small number of study participants who, after censoring, are included in the evaluation in the already small relevant sub-population, the submitted evaluations of the patient-reported endpoints EORTC QLQ-C30 and EORTC QLQ-STO22 are assessed as not usable.

Health status (assessed by EQ-5D VAS)

The pharmaceutical company shall submit evaluations for the first deterioration of the health status by at least 15 points in the form of time-to-event analyses, collected using the visual analogue scale (VAS) of the EQ-5D questionnaire. In addition, the pharmaceutical company presents results over the course of the study separately for the two treatment arms in descriptive form.

Against the background of a small number of study participants who, after censoring, are included in the evaluation in the already small relevant sub-population, the submitted evaluations of the patient-reported endpoint EQ-5D VAS are assessed as not usable.

Health-related quality of life (assessed using EORTC QLQ-C30)

Health-related quality of life is assessed in the KEYNOTE 061 study using the functional scales of the EORTC QLQ-C30 questionnaire.

In accordance with the explanations on the endpoints of symptomatology and health status, the time-to-event analyses submitted by the pharmaceutical company for health-related quality of life in the dossier are determined as not assessable for the evaluation.

Side effects

Adverse events (AEs) in total

Almost all participants in the KEYNOTE 061 study experienced adverse events. The results for the endpoint "total adverse events" are only presented additionally.

Serious adverse events (SAEs), severe AEs and discontinuation due to AEs

There is no statistically significant difference between the treatment groups for the endpoints SAEs, severe AEs and discontinuation due to AEs.

Specific AEs

Due to the small number of patients in the relevant sub-population, the data regarding specific AEs are not usable.

Overall assessment

For the assessment of the additional benefit of pembrolizumab, results on mortality, morbidity, quality of life and side effects are available from the KEYNOTE 061 study in comparison to paclitaxel.

For the benefit assessment, the pharmaceutical company uses a sub-population of the KEYNOTE 061 study. These were patients with gastric cancer and MSI-H (N = 11 intervention arm; N = 10 comparator arm).

The overall assessment shows a positive effect for the endpoint overall survival.

Against the background of the small number of patients in the relevant sub-population, there is an associated low precision in the endpoint of overall survival. Thus, it is not possible to quantify the extent of the improvement.

No usable data are available for the patient-reported endpoints on morbidity (symptomatology and health status) and health-related quality of life.

The endpoints on side effects show neither advantages nor disadvantages for pembrolizumab.

Against the background of the small number of patients in the relevant sub-population, there is also a low precision associated with the endpoints in the side effects category.

Thus, an non-quantifiable additional benefit is identified for pembrolizumab for the treatment of adults with unresectable or metastatic gastric cancer with MSI-H or with a dMMR and disease progression on or following one prior therapy.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of an multicentre, open-label, randomised controlled study.

The risk of bias across all endpoints is rated as low for the KEYNOTE-061 study.

The risk of bias of the result for the endpoint of overall survival is estimated to be low.

However, there are significant uncertainties due to the small number of patients in the relevant sub-population.

Therefore, in the overall assessment, the reliability of data for the additional benefit determined is classified in the category "hint".

b) Adults with unresectable or metastatic gastric cancer with microsatellite instability-high (MSI-H) or with mismatch repair deficiency (dMMR) and disease progression on or following at least two prior therapies

An additional benefit is not proven.

Justification:

Data basis

For the benefit assessment, the pharmaceutical company submits the results of the pivotal study on pembrolizumab in the present therapeutic indication. This is the KEYNOTE 158 study, which included pretreated patients with advanced (metastatic and / or unresectable) solid tumours.

KEYNOTE 158

The KEYNOTE 158 study is a since February 2016 ongoing multicentre, open-label, single-arm phase II study.

The patients in the study will be treated with pembrolizumab according to the product information. For the benefit assessment, the pharmaceutical company forms a sub-population of patients with gastric cancer and MSI-H and at least 2 previous therapies from cohort K (any advanced tumour (except colorectal cancer) with MSI-H) (N = 23).

In addition to the primary endpoint objective response rate, endpoints of the categories mortality, morbidity, health-related quality of life and side effects were collected.

The study is being conducted in 55 study sites in Asia, Australia, Europe, North and South America.

Comparator data

The KEYNOTE 158 study is an uncontrolled study. Thus, this study does not include a comparator group which allows comparison of the results of treatment with pembrolizumab.

For the benefit assessment, the pharmaceutical company submits a comparison of individual arms of the KEYNOTE 158 and TAGS studies.

TAGS study

The TAGS study is a completed, randomised, double-blind, phase III study comparing trifluridine/tipiracil + best supportive care (BSC) with placebo + BSC. Adult patients with

unresectable, metastatic gastric adenocarcinoma including gastroesophageal junction (GEJ) adenocarcinoma were included. Patients had to have received at least 2 previous treatment regimens for advanced disease. A total of 507 patients were allocated in a 1:1 ratio to treatment with trifluridine/ tipiracil: + BSC (N = 337) or placebo + BSC (N = 170). Information on the MSI-H or dMMR status of the study population is not available.

The pharmaceutical company primarily uses the results of the total population of the trifluridine/tipiracil arm (gastric adenocarcinoma including GEJ adenocarcinoma) for the comparison of individual arms. For the endpoint overall survival, the pharmaceutical company presents supplementary results of the sub-population excluding patients with GEJ adenocarcinoma (N = 239).

The study was conducted in 110 study sites in Europe, Asia and the United States from February 2016 to January 2018.

In addition to the primary endpoint overall survival, endpoints of the categories morbidity, health-related quality of life and side effects were collected.

Assessment:

The results from the KEYNOTE 158 study alone are not suitable for assessing the additional benefit of pembrolizumab as they do not allow a comparison with the appropriate comparator therapy.

MSI-H/dMMR tumour status

Pembrolizumab is approved for adults for the treatment of unresectable or metastatic gastric cancer with MSI-H or dMMR and disease progression on or following at least one prior therapy.

Accordingly, the pharmaceutical company only considers cohort K from the KEYNOTE 158 study, which included patients with dMMR/MSI-H.

In the context of the study on the appropriate comparator therapy, the pharmaceutical company does not submit any information on the existence of the MSI-H/dMMR status.

The significance of the MSI-H/dMMR tumour status cannot be conclusively assessed according to the present state of medical knowledge.

Methodology of the comparison of individual arms of different studies

The pharmaceutical company presents results comparing individual arms between pembrolizumab (KEYNOTE-158 study) and trifluridine/tipiracil (TAGS study). For the trifluridine/tipiracil arm of the TAGS study, they use the total population for the endpoints overall survival, SAE and severe AE. In addition, the pharmaceutical company presents an evaluation of the endpoint overall survival with the sub-population with gastric adenocarcinoma of the TAGS study.

The comparisons of individual arms submitted by the pharmaceutical company are comparisons without a bridge comparator. These comparisons have inherent uncertainty due to the lack of randomisation and are not an adequate method of indirect comparison. Moreover, there are no effects for which it can be safely excluded in the present situation of

a comparison of individual arms that they do not result solely from a systematic bias due to confounding variables.

Conclusion:

Overall, the data presented are not suitable to demonstrate an additional benefit compared to the appropriate comparator therapy, which is why an additional benefit of pembrolizumab as monotherapy in adult patients with unresectable or metastatic gastric cancer with MSI-H or dMMR and disease progression on or following at least two previous therapies 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 is approved as monotherapy for the treatment of unresectable or metastatic gastric cancer with MSI-H or dMMR and disease progression on or following at least one prior therapy.

The G-BA distinguishes between two patient groups, taking into account the number of previous therapies.

a) Adults with unresectable or metastatic gastric cancer with microsatellite instability-high (MSI-H) or with mismatch repair deficiency (dMMR) and disease progression on or following one prior therapy

The appropriate comparator therapy was determined by G-BA to be a therapy according to doctor's instructions.

For the benefit assessment, the pharmaceutical company submitted the results of the completed, multicentre, open-label RCT KEYNOTE 061 comparing pembrolizumab with paclitaxel.

For the benefit assessment, the pharmaceutical company uses a sub-population of the KEYNOTE 061 study. These were patients with gastric cancer and MSI-H (N = 11 intervention arm; N = 10 comparator arm).

For the endpoint of overall survival, there is a statistically significant difference to the advantage of pembrolizumab compared to paclitaxel.

Against the background of the small number of patients in the relevant sub-population, there is an associated low precision in the endpoint of overall survival. Thus, it is not possible to quantify the extent of the improvement.

No usable data are available for the patient-reported endpoints on morbidity (symptomatology and health status) and health-related quality of life.

The endpoints on side effects show neither advantages nor disadvantages for pembrolizumab.

Against the background of the small number of patients in the relevant sub-population, there is also a low precision associated with the endpoints in the side effects category.

Thus, for pembrolizumab as monotherapy, an indication of non-quantifiable additional benefit is identified.

b) Adults with unresectable or metastatic gastric cancer with microsatellite instability-high (MSI-H) or with mismatch repair deficiency (dMMR) and disease progression on or following at least two prior therapies

The G-BA determined the combination of active ingredients trifluridine/tipiracil as an appropriate comparator therapy.

For the benefit assessment, the pharmaceutical company submitted the results from the KEYNOTE 158 study for the treatment with pembrolizumab. This is an uncontrolled study and therefore, does not include a comparator group.

For the assessment of the additional benefit, the pharmaceutical company submits a comparison of individual arms of the KEYNOTE 158 and TAGS studies.

These comparisons have inherent uncertainty due to the lack of randomisation and are not an adequate method of indirect comparison. Moreover, there are no effects for which it can be safely ruled out that they do not result solely from systematic bias.

Overall, the data presented are not suitable to demonstrate an additional benefit compared to the appropriate comparator therapy, which is why an additional benefit of pembrolizumab as monotherapy 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).

a) Adults with unresectable or metastatic gastric cancer with microsatellite instability-high (MSI-H) or with mismatch repair deficiency (dMMR) and disease progression on or following one prior therapy

+

b) Adults with unresectable or metastatic gastric cancer with microsatellite instability-high (MSI-H) or with mismatch repair deficiency (dMMR) and disease progression on or following at least two prior therapies

The resolution is based on the information from the dossier of the pharmaceutical company regarding the number of patients.

The pharmaceutical company's data on the number of patients in the SHI target population are considered underestimated. The main reasons for this are the exclusion of patients who are diagnosed in previous years and have metastasised disease in the year under review and the exclusion of patients who do not have remote metastases but whose tumour is inoperable. In addition, for patient population a and b, only those patients were recorded who actually received second- or third-line therapy. For the upper limit, however, the patients with a progression are relevant (patients who are in principle eligible for therapy).

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: 3 January 2023):

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 cancer.

Before initiation of therapy with pembrolizumab, the presence of microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR) should be confirmed by a validated test in a tumour sample.

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 January 2023).

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.

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	continuously, 1 x every 21 days	17.4	1	17.4
	or			
	continuously, 1 x every 42 days	8.7	1	8.7
Appropriate comparator therapy				
a) Adults with unresectable or metastatic gastric cancer with microsatellite instability-high (MSI-H) or with mismatch repair deficiency (dMMR) and disease progression on or following one prior therapy				
Therapy according to doctor's instructions[2]				
Ramucirumab - combination with paclitaxel				
Ramucirumab	continuously, on day 1 and 15 of a 28-day cycle	13.0	2	26.0
Paclitaxel	continuously, on day 1, 8 and 15 of a 28-day cycle	13.0	3	39.0
Ramucirumab - monotherapy				
Ramucirumab	continuously, every 14 days	26.1	1	26.1
b) Adults with unresectable or metastatic gastric cancer with microsatellite instability-high (MSI-H) or with mismatch repair deficiency (dMMR) and disease progression on or following at least two prior therapies				
Trifluridine/tipiracil	continuously, 2 x day on days 1-5 and 8-12 of a 28-day cycle	13.0	10	130.0

Consumption:

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

[2] In the context of a clinical study, the all following treatment options are considered suitable comparators for therapy according to doctor's instructions: Irinotecan, docetaxel, paclitaxel, ramucirumab in combination with paclitaxel. Irinotecan, docetaxel and paclitaxel (monotherapy) are not approved in the present therapeutic indication, which is why these costs are not shown.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body height: 1,72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916).[3]

As it is not always possible to achieve the exact calculated dose per day with the commercially available dose potencies, in these cases rounding up or down to the next higher or lower available dose that can be achieved with the commercially available dose potencies as well as the scalability of the respective dosage form.

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	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
Appropriate comparator therapy					
a) Adults with unresectable or metastatic gastric cancer with microsatellite instability-high (MSI-H) or with mismatch repair deficiency (dMMR) and disease progression on or following one prior therapy					
Therapy according to doctor's instructions[2]					
Ramucirumab - combination with paclitaxel					
Ramucirumab	8 mg /kg = 616 mg	616 mg	1 x 500 mg + 2 x 100 mg	26.0	26.0 x 500 mg + 52.0 x 100 mg
Paclitaxel	80 mg / m² = 152 mg	152 mg	1 x 100 mg + 2 x 30 mg	39.0	39.0 x 100 mg + 78.0 x 30 mg
Ramucirumab - monotherapy					
Ramucirumab	8 mg /kg = 616 mg	616 mg	1 x 500 mg + 2 x 100 mg	26.1	26.1 x 500 mg + 52.2 x 100 mg

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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
b) Adults with unresectable or metastatic gastric cancer with microsatellite instability-high (MSI-H) or with mismatch repair deficiency (dMMR) and disease progression on or following at least two prior therapies					
Trifluridine/ tipiracil	65 mg	130 mg	2 x 20 mg + 6 x 15 mg	130.0	260.0 x 20 mg + 780.0 x 15 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.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Pembrolizumab 100 mg	1 CIS	€ 2,974.79	€ 1.77	€ 285.60	€ 2,687.42
Appropriate comparator therapy					
Paclitaxel 30 mg	1 CIS	€ 102.13	€ 1.77	€ 4.31	€ 96.05
Paclitaxel 100 mg	1 CIS	€ 289.43	€ 1.77	€ 13.20	€ 274.46
Ramucirumab 100 mg	1 CIS	€ 441.14	€ 1.77	€ 40.80	€ 398.57
Ramucirumab 500 mg	1 CIS	€ 2,141.31	€ 1.77	€ 204.00	€ 1,935.54
Trifluridine/ tipiracil 15 mg/6.14 mg	60 FCT	€ 2,348.73	€ 1.77	€ 93.46	€ 2,253.50
Trifluridine/ tipiracil 20 mg/8.19 mg	60 FCT	€ 3,112.42	€ 1.77	€ 124.62	€ 2,986.03
Abbreviations: FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution					

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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.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Medicinal product to be assessed							
Paclitaxel							
Dexamethasone[4] 20 mg	50 TAB	€ 118.85	€ 1.77	€ 0.00	€ 117.08	39.0	€ 91.32
Dimetindene IV 1 mg/10 kg	5 x 4 mg SFI	€ 23.67	€ 1.77	€ 5.81	€ 16.09	39.0	€ 251.00
Cimetidine IV 300 mg	10 AMP each 200 mg	€ 19.77	€ 1.77	€ 0.40	€ 17.60	39.0	€ 137.28
Abbreviations: SFI = solution for injection; TAB = tablets; AMP = ampoules							

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 € 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 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

[4] Fixed-price medicinal products and solitary

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 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 Pembrolizumab

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall designate 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.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

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 23 February 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 18 July 2022, 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, number 2 VerfO.

By letter dated 25 July 2022 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 28 October 2022, and the written statement procedure was initiated with publication on the G-BA website on 1 November 2022. The deadline for submitting written statements was 22 November 2022.

The oral hearing was held on 5 December 2022.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 10 January 2023, and the proposed resolution was approved.

At its session on 19 January 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	23 February 2021	Determination of the appropriate comparator therapy
Working group Section 35a	29 November 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	5 December 2022	Conduct of the oral hearing
Working group Section 35a	13 December 2022 3 January 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	10 January 2023	Concluding discussion of the draft resolution
Plenum	19 January 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 19 January 2023

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

Prof. Hecken