Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Pembrolizumab (New Therapeutic Indication: Head And Neck Squamous Cell Carcinoma, First Line, Monotherapy)

of 14 May 2020

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 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 14 November 2019, pembrolizumab received marketing authorisation for a new therapeutic indication:

“KEYTRUDA, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

On 29 November 2019, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient pembrolizumab with the new therapeutic indication in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 2 March 2020, 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. In order to determine the extent of the additional benefit, the G-BA has assessed 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 arrived at the following assessment:

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

2.1.1 Approved therapeutic indication of pembrolizumab (Keytruda®) in accordance with product information

KEYTRUDA, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

Note:

This assessment relates exclusively to the assessment of the additional benefit of pembrolizumab as monotherapy. For the assessment of the additional benefit of pembrolizumab in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, reference is made to the separate benefit assessment procedure for this combination therapy.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) whose tumours express PD-L1 (combined positive score [CPS] ≥ 1); first-line treatment

- Cetuximab + cisplatin or carboplatin + 5-FU

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

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 according to 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 Federal Joint Committee 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 this therapeutic indication, medicinal products with the active ingredients cetuximab, methotrexate, cisplatin, carboplatin, docetaxel, bleomycin, 5-fluorouracil, and mitomycin are approved.

On 2. For the adult patients with recurrent or metastatic squamous cell carcinoma of the head and neck included in this therapeutic indication, it is assumed that an intervention with a curative objective is an exception and therefore not (no longer) indicated. Surgery, radiotherapy, or radiochemotherapy are therefore not considered to be appropriate comparator therapies.

On 3. There are no resolutions on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V.

On 4. The generally state of medical knowledge for the indication was established by means of a systematic search for guidelines and reviews of clinical studies.

Overall, the evidence in this therapeutic indication is limited. In the relevant international guidelines, there is sometimes a comprehensive consideration of squamous cell carcinomas of the head and neck region, but sometimes only certain localisations are addressed.

Despite the aforementioned limitations, current international guidelines agree that for the first-line treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck, therapy with cetuximab in combination with cis- or carboplatin and 5-fluorouracil (5-FU) is recommended.

The guidelines express this recommendation for a treatment situation in which locoregional treatment measures (surgery, radiotherapy) have already been exhausted or are not considered. No differentiation by disease stage is made for this therapeutic option. For the adult patients with recurrent or metastatic squamous cell carcinoma of the head and neck included in this therapeutic indication, the G-BA assumes that an intervention with a curative objective is an exception and therefore does not represent a regular therapy in the therapeutic indication. The combination of cetuximab with cis- or carboplatin and 5-fluorouracil (5-FU) has therefore been determined to be an appropriate comparator therapy.

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

Change of the appropriate comparator therapy

The appropriate comparator therapy was originally determined as follows:

„● Cetuximab + cisplatin or carboplatin + 5-FU

or

● Radiochemotherapy with cisplatin ± 5-FU *(only for patients with locally advanced squamous cell carcinoma of the head and neck region)*

or

● Cisplatin + docetaxel + 5-FU as induction chemotherapy followed by radiotherapy / radiochemotherapy *(only for patients with locally advanced head and neck squamous cell carcinoma)*"

By restricting the appropriate comparator therapy to the combination of cetuximab with cis- or carboplatin and 5-fluorouracil (5-FU), the written statement of clinical experts submitted in this benefit assessment procedure on the uniform clinical consideration of patients with local relapse, which is no longer accessible to locoregional interventions, and patients with metastatic disease are particularly taken into account.

This change in the appropriate comparator therapy has no effect on this benefit assessment nor does it require a repeated implementation of this.

2.1.3 Extent and probability of the additional benefit

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

Hint for a considerable additional benefit.

Justification:

For the benefit assessment, the pharmaceutical company submitted data from the randomised, open-label, actively controlled and currently ongoing Phase III KEYNOTE 048 study.

This three-armed study compares treatment with pembrolizumab in combination with cis- or carboplatin and 5-FU to treatment with cetuximab in combination with cis- or carboplatin and 5-FU as well as with pembrolizumab monotherapy. For this benefit assessment, the study arms for pembrolizumab monotherapy (intervention arm) and for cetuximab in combination with cis- or carboplatin and 5-FU (comparator arm) are relevant. Adult patients with metastatic or unresectable recurrent head and neck squamous cell carcinoma whose disease could no longer be curatively treated by local therapies were included independent of PD-L1 expression. The patients included were not allowed to have received systemic therapy for the recurrent or metastatic disease. A tumour progression after completion of a prior therapy with a curative approach against a locally advanced tumour had to have occurred at the earliest after 6 months, and previous curative systemic therapies against a locally advanced tumour had to have been completed at least 6 months before the start of study. At the start of study, 281 patients were assigned to treatment with pembrolizumab in combination with cis- or carboplatin and 5-FU, 301 patients to treatment with pembrolizumab monotherapy, and 300 patients to treatment with cetuximab in combination with cis- or

carboplatin and 5-FU. The patients were randomised at a ratio of 1:1:1 and stratified by ECOG-PS (0 vs 1), PD-L1 status (Tumour Proportion Score [TPS] < 50% vs TPS ≥ 50%) and human papillomavirus (HPV) status (positive vs negative).

In the KEYNOTE 048 study, patients were treated in accordance with the product information as far as possible. Patients were treated until disease progression, the occurrence of unacceptable side effects, or the decision of the physician or patient. No specifications were made regarding follow-up therapy after discontinuation of the study medication.

The co-primary endpoints of the study are progression-free survival (PFS) and overall survival. Patient-relevant secondary endpoints are symptomatology, health-related quality of life, and adverse events.

The assessment is based on the data cut-off of 25 February 2019, which represents the pre-specified final evaluation of overall survival for the sub-population of patients with PD-L1-expressing tumours (combined positive score [CPS] ≥ 1) in accordance with the approved therapeutic indication.

Extent and probability of the additional benefit

Mortality

In the KEYNOTE 048 study, overall survival is defined as the time from randomisation to death of any cause.

In the relevant sub-population with PD-L1 expression CPS ≥ 1, 197 patients in the intervention arm (76.7%) and 229 in the comparator arm (89.8%) had died by the data cut-off of 25 February 2019. The median survival time is 12.3 months in the intervention arm and 10.3 months in the comparator arm; this corresponds to a median prolongation of 2.0 months. The event time analysis shows a statistically significant difference (hazard ratio (HR): 0.74; [95% confidence interval (CI): 0.61; 0.90]; p value 0.003). The associated Kaplan-Meier curves have an intersecting course. In the first 7 months, the intervention arm shows an initially steeper drop in the Kaplan-Meier curve than the comparator arm. The Kaplan-Meier curves cross after about 8 months; at the end of the observation period, the curve of the intervention arm is above that of the reference arm.

In the sub-group analyses for the overall survival endpoint, there is an effect modification is shown by the characteristic “disease status” (recurrent vs metastatic; p = 0.016) For patients with metastatic carcinoma there is a statistically significant difference to the advantage of pembrolizumab as monotherapy. For patients with recurrent carcinoma there is no difference between the treatment groups.

There is also an effect modification by the characteristic “PD-L1 Status” (CPS < 20 vs CPS ≥ 20; p = 0.022). For patients with PD-L1 expression CPS ≥ 20, there is a statistically significant difference to the benefit of pembrolizumab as monotherapy; for patients with PD-L1 expression CPS < 20, there is no difference.

However, the G-BA considers it justified in this case to make a statement on additional benefit without subdividing according to the characteristic “disease status” or “PD-L1 status”.

The characteristic “disease status” was not a stratification factor during the randomisation. Furthermore, the written statement of the pharmaceutical company specifies that the sub-group of metastatic patients also includes patients who have a recurrent and metastatic disease. Ultimately, even guidelines do not differentiate between recurrent or metastatic patients in their therapy recommendations. For these reasons, there is no separate assessment of additional benefit by “disease status”.

The effect modification on “PD-L1 status” using the CPS is not reflected in the results of the second sub-group analysis on “PD-L1 status” using the TPS (< 50% vs ≥ 50%). The sub-

group analysis for “PD-L1 status” using the TPS shows no statically significant interaction. The importance of PD-L1 expression is controversially discussed in the scientific community. In this therapeutic indication, it is not yet clear whether CPS or TPS is the preferred characteristic and to what extent the respective separation values of these characteristics correlate with each other. For the reasons mentioned above, a separate assessment is not made with regard to “PD-L1 status”.

In the endpoint category mortality, based on the results of the KEYNOTE 048 study, there is thus a prolongation of overall survival; this is assessed as a slight improvement in terms of extent.

Morbidity

Progression-free survival (PFS)

The PFS is a co-primary endpoint of the KEYNOTE 048 study and is operationalised as the time between randomisation and the time of first disease progression after RECIST or death by any cause. In the event time analyses, there was no statistically significant difference between the treatment arms.

Symptomatology and health status (EQ-5D visual analogue scale)

In study KEYNOTE 048, the symptomatology or the health status of the patients is assessed by the symptom scales of the EORTC QLQ-C30 and EORTC QLQ-H&N35 questionnaires or the visual analogue scale of the EQ-5D.

However, the analyses regarding the time until the first confirmed clinically relevant deterioration by at least 10 points or 7 and 10 points submitted for this purpose by the pharmaceutical company cannot be used in the present situation.

In order to record a confirmed deterioration after the start of study, at least two additional surveys were required: one to first record a deterioration and another to confirm it. At the same time, there are already high progression rates in the early course of the study, especially in the intervention arm. However, the questionnaires were collected only once per cycle for the first four 3-week cycles and then only every second cycle. Because of the discontinuation of the questionnaire survey following progression, it is increasingly unlikely, particularly in the intervention arm, that a confirmed deterioration will be observed as the study progresses. The results in the present case are therefore not considered usable.

In the endpoint category morbidity, an additional benefit of pembrolizumab as monotherapy is thus not proven.

Quality of life

In the KEYNOTE 048 study, health-related quality of life is reported by patients and is assessed using the functional scales of the EORTC QLQ-C30 and EORTC QLQ-H&N35 questionnaires.

The same limitations described above apply to the responder analyses presented. The results are therefore also considered unusable.

Accordingly, an additional benefit of pembrolizumab as monotherapy in the quality of life category is not proven.

Side effects

Adverse events (AE) in total
Nearly all patients in the relevant study arms of the KEYNOTE 048 study experienced an adverse event. The results for the endpoint “total adverse events” are only presented on a supplementary basis.

Serious AE
In the KEYNOTE 048 study, approx. 41% of patients in the intervention arm and approx. 49% of patients in the comparator arm experienced a serious adverse event (SAE). In the event time analyses, there was no statistically significant difference between the treatment arms.

Severe AE (CTCAE grade ≥ 3)
A severe adverse event (CTCAE grade ≥ 3) was experienced by approx. 55% of patients in the intervention arm and approx. 83% of patients in the comparator arm. In the intervention arm, a severe AE (CTCAE grade ≥ 3) occurred 4.6 months (median) later than in the comparator arm. The event-time analysis shows a statistically significant difference to the benefit of pembrolizumab as monotherapy.

Therapy discontinuation because of AE
Approx. 12% of patients in the intervention and 27% in the comparator arm discontinued treatment because of adverse events. The event-time analysis shows a statistically significant difference to the benefit of pembrolizumab as monotherapy.

Specific AE
For the specific AEs at the PT level, only data on incidence are available; the assessment is therefore based on relative risks.

For the specific adverse events, there are statistically significant differences to the advantage of pembrolizumab as monotherapy with respect to paronychia (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs [CTCAE grade ≥ 3]), ear and labyrinth disorders (SOC, AEs), asthenia (PT, AEs), dizziness (PT, AEs), blood and lymphatic system disorders (SOC, AEs [CTCAE grade ≥ 3]), anaemia (PT, AEs [CTCAE grade ≥ 3]), gastrointestinal disorders (SOC AEs [CTCAE grade ≥ 3]), mucosa inflammation (PT, AEs [CTCAE grade ≥ 3]), investigations (SOC AEs [CTCAE grade ≥ 3]), and hypomagnesaemia (SOC AEs [CTCAE grade ≥ 3]). In contrast, there is a disadvantage in respiratory, thoracic, and mediastinal disorders (SOC, AEs [CTCAE grade ≥ 3]).

Long-term data on the immune-mediated AE of pembrolizumab are not available in this therapeutic indication.

In the overall consideration of the endpoint category side effects, there are clear advantages for pembrolizumab as monotherapy. In summary, there is a considerable additional benefit of pembrolizumab as monotherapy in the endpoint category side effects.

<u>Overall assessment</u>

For the benefit assessment of pembrolizumab as monotherapy for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1, results of the KEYNOTE 048 study on overall survival, morbidity, health-related quality of life, and side effects are available.

In the endpoint category mortality, there is a statistically significant difference to the advantage of pembrolizumab as monotherapy compared with treatment with cetuximab in combination with cis- or carboplatin and 5-FU. In the sub-group analyses, there is an effect modification by the characteristic “disease status”; this results in a statistically significant difference in favour of pembrolizumab as monotherapy for patients with metastatic disease. Thus, there is no statistically significant difference for patients with recurrent disease. There is also an effect modification by the feature “PD-L1 status”. For patients with PD-L1 expression CPS ≥ 20, there is a statistically significant difference to the benefit of

pembrolizumab as monotherapy; for patients with PD-L1 expression CPS < 20, there is no difference.

In its assessment of the available sub-group analyses on the characteristic “disease status” and “PD-L1 status”, the G-BA comes to the conclusion that the interpretation of these effect modifications is subject to relevant uncertainties. A separate assessment of the additional benefit according to illness status and PD-L1 status is not carried out.

Compared with cetuximab in combination with cis- or carboplatin and 5-FU, pembrolizumab as monotherapy leads to a prolongation of overall survival; this is assessed as a small improvement.

With regard to morbidity and health-related quality of life measured by the EORTC QLQ-C30, EORTC QLQ-H&N35 and EQ 5D-VAS, there are no usable data. Because of the early onset progression events in the KEYNOTE 048 study, particularly in the intervention arm, and the discontinuation of the questionnaire survey following progression, the results on the responder analyses for the time until the first confirmed clinically relevant deterioration do not allow for valid conclusions.

In the endpoint category side effects, there are clear advantages for pembrolizumab as monotherapy through a decrease in severe AE (CTCAE grade ≥ 3) and therapy discontinuation because of AE. In detail, there are mainly advantages also in the area of the specific AE. Overall, pembrolizumab as monotherapy leads to a significant reduction of side effects.

As a result, the G-BA found a considerable additional benefit for pembrolizumab as monotherapy for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1 compared with cetuximab in combination with cis- or carboplatin and 5-FU.

Reliability of data (probability of additional benefit)

This assessment is based on the results of the open-label, randomised, actively controlled Phase III KEYNOTE 048 study. The risk of bias at the study level is classified as low.

The overall survival endpoint shows effect modifications in the characteristics disease status and PD-L1 status (CPS). The Kaplan-Meier curves for overall survival intersect after about 8 months; only then does the benefit for patients treated with pembrolizumab become apparent. Based on the available data, it remains unclear whether the hazard ratio presented adequately reflects the effect over the entire observation period.

For patient-reported endpoints on morbidity and quality of life, there are no usable data. Statements on morbidity and quality of life are particularly important in the present palliative therapy situation.

Because of the open study design, the results for the endpoint therapy discontinuation because of AE are also considered highly biased.

Based on the evidence available, the reliability of data is thus classified in the “hint” category.

2.1.4 Summary of the assessment

This assessment concerns the benefit assessment of a new therapeutic indication for the active ingredient pembrolizumab:

“KEYTRUDA, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.”

This assessment refers to the assessment of pembrolizumab as monotherapy.

Cetuximab + cisplatin or carboplatin + 5-FU was determined as the appropriate comparator therapy.

For the benefit assessment, the pharmaceutical company presents the results of the randomised, open-label, actively controlled KEYNOTE 048 study in which pembrolizumab as monotherapy is compared with cetuximab in combination with cis- or carboplatin and 5-FU.

In the endpoint category mortality, there is a statistically significant difference for the endpoint overall survival in the event time analysis to the advantage of pembrolizumab as monotherapy. In the sub-group analyses, there is an effect modification by the characteristic "disease status"; this results in a statistically significant difference in favour of pembrolizumab as monotherapy for patients with metastatic disease. Thus, there is no statistically significant difference for patients with recurrent disease. There is also an effect modification by the feature "PD-L1 status". For patients with PD-L1 expression CPS ≥ 20, there is a statistically significant difference to the benefit of pembrolizumab as monotherapy; for patients with PD-L1 expression CPS < 20, there is no difference.

In its assessment of the available sub-group analyses on the characteristic "disease status" and "PD-L1 status", the G-BA comes to the conclusion that the interpretation of these effect modifications is subject to relevant uncertainties. A separate assessment of the additional benefit according to illness status and PD-L1 status is not carried out.

Pembrolizumab as monotherapy leads to a prolongation of overall survival, which is assessed as a minor improvement.

For the patient-reported endpoints on morbidity and quality of life, there are no usable data.

In the endpoint category side effects, there are clear advantages for pembrolizumab as monotherapy through a decrease in severe AE (CTCAE grade ≥ 3) and therapy discontinuation because of AE. In detail, there are mainly advantages also in the area of the specific AE. Overall, pembrolizumab as monotherapy leads to a significant reduction of side effects.

As a result, the G-BA found a considerable additional benefit for pembrolizumab as monotherapy compared with cetuximab in combination with cis- or carboplatin and 5-FU.

Because of the open study design, the existing uncertainties in the overall survival endpoint with regard to the effect modifications, and the intersecting Kaplan-Meier curves, and taking into account the lack of usable data for patient-reported endpoints on morbidity and quality of life, only a hint for an additional benefit can be derived with regard to the reliability of data.

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

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

The G-BA bases its resolution on the information from the dossier of the pharmaceutical company. The calculation used to derive patient numbers is comprehensible, and the magnitude of the figures arrived at are largely plausible. Uncertainties arise mainly from the fact that the pharmaceutical company was unable to identify data on the resectability of a relapse and thus take them into account when deriving patient numbers. In addition, the source on the proportion of patients with first-line treatment for the metastatic or unresectable recurrent stage is subject to uncertainty regarding its transferability to the German health care context.

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: 8 April 2020):

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

Treatment with pembrolizumab may only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in otorhinolaryngology, and other specialists participating in the Oncology Agreement who are experienced in the treatment of patients with head and neck tumours. According to the requirements for risk minimisation activities in the EPAR (European Public Assessment Report), the pharmaceutical company must provide the following information material on pembrolizumab:

− Training and information material for doctors/medical professionals

− Training and information material for the patient

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 April 2020).

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

For dosages depending on body weight (BW) or body surface, the average body measurements were used as a basis (average body size: 1.72 m, average body weight: 77 kg).[2] From this, a body surface area of 1.90 m² is calculated (calculation according to Du Bois 1916).

Treatment duration:

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	1 × per 21-day cycle	17.4	1	17.4
	or			
	1 × per 42-day cycle	8.7	1	8.7
Appropriate comparator therapy				
Cisplatin + 5-fluorouracil + cetuximab				
Cisplatin	1 × per 21-day cycle	17.4	1	17.4

[2] German Federal Office For Statistics, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
+ 5-fluorouracil	4 × per 21-day cycle	17.4	4	69.6
+ cetuximab	1 × per 7-day cycle	52.1	1	52.1
Carboplatin + 5-fluorouracil + cetuximab				
Carboplatin	1 × per 21-day cycle	17.4	1	17.4
+ 5-fluorouracil	4 × per 21-day cycle	17.4	4	69.6
+ cetuximab	1 × per 7-day cycle	52.1	1	52.1

Usage and consumption:

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Pembrolizumab	200 mg	200 mg	2 × 100 mg	17.4	34.8 × 100 mg
	or				
	400 mg	400 mg	4 × 100 mg	8.7	34.8 × 100 mg
Appropriate comparator therapy					
Cisplatin + 5-fluorouracil + cetuximab					
Cisplatin	100 mg/m² BSA	190 mg	2 × 100 mg	17.4	34.8 × 100 mg
+ 5-fluorouracil	1,000 mg/m² BSA	1900 mg	2 × 1,000 mg	69.6	139.2 × 1,000 mg
+ cetuximab	*Initial dose in Week 1*				

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	400 mg/m² BSA	760 mg	3 × 100 mg	1	3 × 100 mg
			1 × 500 mg		1 × 500 mg
	Dosage from Week 2:				
	250 mg/m² BSA	475 mg	1 × 500 mg	51.1	51.1 × 500 mg
Carboplatin + 5-fluorouracil + cetuximab					
Carboplatin	400 mg/m² BSA	756 mg	1 × 50 mg	17.4	17.4 × 50 mg
			1 × 150 mg		17.4 × 150 mg
			1 × 600 mg		17.4 × 600 mg
+ 5-fluorouracil	1,000 mg/m² BSA	1900 mg	2 × 1,000 mg	69.6	139.2 × 1,000 mg
+ cetuximab	*Initial dose in Week 1*				
	400 mg/m² BSA	760 mg	3 × 100 mg	1	3 × 100 mg
			1 × 500 mg		1 × 500 mg
	Dosage from Week 2:				
	250 mg/m² BSA	475 mg	1 × 500 mg	51.1	51.1 × 500 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 Sections 130 and 130 a 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 product:

Designation of the therapy	Package 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	€ 3,083.93	€ 1.77	€ 172.85	€ 2,909.31
Appropriate comparator therapy					
Carboplatin 50 mg	1 CIS	€ 34.38	€ 1.77	€ 1.11	€ 31.50
Carboplatin 150 mg	1 CIS	€ 82.79	€ 1.77	€ 3.40	€ 77.62
Carboplatin 600 mg	1 CIS	€ 300.57	€ 1.77	€ 13.74	€ 285.06
Cetuximab 100 mg	1 IS	€ 303.15	€ 1.77	€ 16.17	€ 285.21
Cetuximab 500 mg	1 IS	€ 1,471.55	€ 1.77	€ 80.86	€ 1,388.92
Cisplatin 100 mg	1 CIS	€ 76.31	€ 1.77	€ 3.10	€ 71.44
Fluorouracil 1000 mg[3]	5 SFI	€ 37.18	€ 1.77	€ 2.07	€ 33.34
Abbreviations: CIS = concentrate for the preparation of an infusion solution; IS = solution for infusion; SFI = solution for injection					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 April 2020

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 assessed 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 standard expenditure in the course of the treatment are not shown.

Non-prescription medicinal products that are reimbursable by the statutory health insurance in accordance with Annex I of the Pharmaceuticals Directive (OTC exemption list) are not subject to the current medicinal product price regulation. Instead, in accordance with Section 129, paragraph 5a SGB V, when a non-prescription medicinal product is sold and invoiced in accordance with Section 300, for the insured person, a pharmaceutical selling price in the amount of the selling price of the pharmaceutical company – plus the surcharges according to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the 31 December 2003 version – shall apply.

[3] Fixed reimbursement rate

Designation of the therapy	Package 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
Appropriate comparator therapy							
Cisplatin							
Anti-emetic treatment							
In clinical practice, appropriate anti-emetic treatment is established before and/or after cisplatin administration. The product information of cisplatin does not contain any concrete information on this, which is why the necessary costs cannot be quantified.							
Mannitol 10% infusion solution, 37.5 g/day	10 × 500 ml	€ 106.22	€ 5.31	€ 9.81	€ 91.10	17.4	€ 158.51
Sodium chloride 0.9% infusion solution, 3–4.4 l/day	10 × 1,000 ml 10 × 500 ml	€ 35.47 € 22.72	€ 1.77 € 1.14	€ 1.12 € 0.69	€ 32.58 € 20.89	17.4	€ 170.07 – € 263.11
Cetuximab							
Pre-medication							
According to the product information of cetuximab (Erbitux®), patients must be pretreated with an antihistamine and a corticosteroid at least 1 h before the first infusion of cetuximab. This premedication is also recommended before all further infusions. The product information does not provide any further details in this respect; the costs necessary for premedication can therefore not be quantified.							

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) 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 special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: 11. Supplementary Agreement of 1 March 2020 to the contract on price formation for substances and preparations of substances), surcharges for the preparation of parenteral preparations containing cytostatics of a maximum of € 81 per ready-to-use preparation and for the preparation of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall apply. These additional costs are not added to the pharmacy sales price but rather follow the rules for calculating 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 ingredients, the invoicing of discards, and the

calculation of application containers and carrier solutions according to the regulations of Annex 3 of the Hilfstaxe.

3. Bureaucratic costs

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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 27 November 2018.

On 29 November 2019, 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 VerfO.

By letter dated 29 November 2019 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient pembrolizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 February 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 2 March 2020. The deadline for submitting written statements was 23 March 2020.

The oral hearing was held on 6 April 2020.

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 were discussed at the session of the subcommittee on 5 May 2020, and the proposed resolution was approved.

At its session on 14 May 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	27 November 2018	Determination of the appropriate comparator therapy
Working group Section 35a	1 April 2020	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	6 April 2020	Conduct of the oral hearing

Working group Section 35a	16 April 2020 29 April 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal Products	5 May 2020	Concluding discussion of the draft resolution
Plenum	14 May 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 14 May 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken