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: non-small cell lung carcinoma, non-squamous, first line, combination with pemetrexed and platinum chemotherapy)

of 19 September 2019

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 shall pass a resolution 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 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 4 September 2018, pembrolizumab received the marketing authorisation for a new therapeutic indication classified as a major variation of type 2 according to Annex 2, number 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 December 2008, p. 7).

On 24 July 2018, the pharmaceutical company filed an application to consolidate the evaluation procedures for pembrolizumab according to Section 35a, paragraph 5b of the German Social Code, Book V (SGB V). At its session on 20 September 2018, the G-BA approved the application for consolidation in accordance with Section 35a, paragraph 5b of the German Social Code (SGB V).

On 28 March 2019, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient pembrolizumab with the new therapeutic indication

“Keytruda, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations.”

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 July 2019 on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

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

In the light of the above and taking into account the comments 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, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations.

2.1.2 Appropriate comparator therapy

For pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy for the first-line treatment of metastatic squamous NSCLC in adults without EGFR or ALK positive tumour mutations, the appropriate comparator therapy is:

a) Adult patients with first-line treatment of metastatic squamous NSCLC without EGFR or ALK positive tumour mutations whose tumours express PD-L1 with a < 50% tumour proportion score (TPS[2]):
   - Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)

     or
   - Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed; *cf* Annex VI to Section K of the Pharmaceuticals Directive)

     or
   - Carboplatin in combination with nab-paclitaxel

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.

2 TPS: Tumour Proportion Score

b) Adult patients with first-line treatment of metastatic squamous NSCLC without EGFR or ALK positive tumour mutations whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS):

- Pembrolizumab as monotherapy

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 accordance with authorisation status, first-line treatment of metastatic non-squamous NSCLC without EGFR- or ALK-positive mutation includes medicinal products with the active ingredients cisplatin, docetaxel, etoposide, gemcitabine, ifosfamide, mitomycin, paclitaxel, nab-paclitaxel, pemetrexed, vindesin, vinorelbine, the protein kinase inhibitors crizotinib (ROS1-positive NSCLC), dabrafenib (NSCLC with BRAF V600 mutation) and trametinib (NSCLC with BRAF V600 mutation), and the antibodies pembrolizumab and bevacizumab. Carboplatin in combination with nab-paclitaxel is approved for the present therapeutic indication and can also be prescribed off-label.

On 2. Non-medicinal treatments were not taken into consideration. The implementation of radiotherapy or surgery as a palliative therapy option remains unaffected.

On 3. The following resolutions and guidelines of the G-BA have been issued for medicinal therapies in the present therapeutic indication:

- Pembrolizumab (NSCLC with PD-L1 expression ≥ 50% TPS): Resolution of 3 August 2017 on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V
- Dabrafenib (NSCLC with BRAF-V600 mutation): Resolution of 19 October 2017 on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V
- Trametinib (NSCLC with BRAF-V600 mutation): Resolution of 19 October 2017 on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V
- Crizotinib (ROS-1-positives NSCLC): Resolution of 16 March 2017 on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V

– Carboplatin: Resolution of 18 October 2018 on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex VI – Off-label use Part A Item III: Carboplatin for advanced non-small cell lung carcinoma (NSCLC) – combination therapy

On 4. The general state of medical knowledge was illustrated by systematic research for guidelines and reviews of clinical studies in the present indication.

Against the background of the evidence available, the G-BA differentiates the patients in the present therapeutic indication into two sub-populations according to PD-L1 expression with a separation value of 50% (TPS).

a) Adult patients with first-line treatment of metastatic squamous NSCLC without EGFR or ALK positive tumour mutations whose tumours express PD-L1 with a < 50% tumour proportion score (TPS):
In patients with PD-L1 expression < 50%, guidelines recommend the current therapy standard in the form of platinum-based combination chemotherapy with a third-generation cytostatic agent consisting of cisplatin or carboplatin and a third-generation cytostatic agent (vinorelbine, gemcitabine, docetaxel, paclitaxel or pemetrexed). From the evidence, it is not possible to deduce whether a combination is inferior or superior with respect to therapeutic benefit. Carboplatin, unlike cisplatin, is not approved for the treatment of NSCLC. However, it may be prescribed as "off-label use" for patients (see Annex VI to Section K of the Pharmaceuticals Directive); the selection of the platinum component should be based on the different toxicity profiles and existing patient comorbidities. The guidelines also recommend nab-paclitaxel in combination with carboplatin in this therapeutic indication. This is authorised in combination with carboplatin for first-line treatment of NSCLC. It is considered by the G-BA to be another equally appropriate therapeutic option in the therapeutic indication.

Because pembrolizumab is used in combination with pemetrexed and cisplatin/carboplatin in this therapeutic indication, it can be assumed that the patients are generally suitable for combination chemotherapy and that mono-chemotherapies cannot be considered as an appropriate comparator therapy.

b) Adult patients with first-line treatment of metastatic squamous NSCLC without EGFR or ALK positive tumour mutations whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS):
Current guidelines recommend pembrolizumab monotherapy for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score. The corresponding benefit assessment of pembrolizumab based on the Keynote-024 study showed an indication of a considerable additional benefit compared with platinum-based chemotherapy (resolution of 3 August 2017). Pembrolizumab led to a significant improvement in overall survival, delayed the occurrence of significant disease symptoms and adverse events (CTCAE grade ≥ 3), and showed beneficial effects on health-related quality of life. The G-BA therefore defines pembrolizumab as the only appropriate comparator therapy for the first-line treatment of patients with PD-L1 expression ≥ 50% (TPS).

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

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of pembrolizumab in combination with pemetrexed and platinum chemotherapy is assessed as follows:

a) Adult patients with first-line treatment of metastatic squamous NSCLC without EGFR or ALK positive tumour mutations whose tumours express PD-L1 with a < 50% tumour proportion score (TPS):

For adult patients with first-line treatment of metastatic squamous NSCLC without EGFR or ALK positive tumour mutations whose tumours express PD-L1 with a < 50% (TPS[2]) there is a non-quantifiable additional benefit for pembrolizumab in combination with pemetrexed and platinum chemotherapy compared with pemetrexed in combination with platinum chemotherapy.

Justification:

The benefit assessment is based on the data from the KEYNOTE 021G and KEYNOTE 189 RCTs submitted in the dossier of the pharmaceutical company.
Both RCTs are currently ongoing randomized, controlled parallel group studies with similar study designs. Then differ mainly in the treatment option in the context of platinum-based chemotherapy.
KEYNOTE 021G (cohort G of the KEYNOTE 021 study) is an open-label study comparing pembrolizumab in combination with pemetrexed and carboplatin versus pemetrexed and carboplatin. KEYNOTE 189 is a blinded study comparing pembrolizumab in combination with pemetrexed and cisplatin/carboplatin versus pemetrexed and cisplatin/carboplatin.
Both studies included adults with histologically or cytologically confirmed non-squamous NSCLC in Stage IV without EGFR mutation or ALK translocation and without prior systemic therapy with Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤ 1. The KEYNOTE 021G study additionally included Stage IIIB patients. In both studies, PD-L1 expression was measured immunohistochemically and expressed as TPS[2]. In the KEYNOTE 021G study, 123 patients stratified by PD-L1 expression (separation value 1%) were randomly assigned at a ratio of 1:1 either to treatment with pembrolizumab in combination with carboplatin and pemetrexed (N = 60) or to treatment with carboplatin and pemetrexed (N = 63). In the KEYNOTE 189 study, 616 patients stratified by platinum component, PD-L1 expression (separation value 1%), and smoker status were randomly assigned at a ratio of 2:1 to treatment with pembrolizumab in combination with pemetrexed and cisplatin/carboplatin (N = 410) or pemetrexed and cisplatin/carboplatin (N = 206). The primary endpoints were objective response rate in KEYNOTE 021G and overall survival in KEYNOTE 189 PFS.
The benefit assessment for the KEYNOTE 021G study is based on the 2nd data cut-off of 31 May 2017 which was created *post hoc* at the request of the EMA. For the KEYNOTE 189 study, the cut-off of 8 November 2017 coincided with the *a priori* planned interim analysis after approx. 373 PFS events.

With regard to the implementation of the off-label use of carboplatin in accordance with the Pharmaceuticals Directive prior to the last amendment, which entered into force on 4 January 2019 (Annex VI to Section K of the AM-RL Part A Item III), no consideration of the criteria of the AM-RL was reported for treatment with carboplatin-based chemotherapy. The pharmaceutical company therefore formed a TPC (Treatment of Physician's Choice) sub-population based on a retrospective survey in which the investigator was to justify the decision for a carboplatin-based combination chemotherapy on a patient-individual basis; this included all patients treated according to the criteria of the AM-RL. These TPC sub-populations were used as the basis for the present benefit assessment for the respective sub-populations A and B, which were formed with regard to PD-L1 expression (via TPS). They comprise 20 patients

per study arm in the KEYNOTE 021G study and 162 and 88 patients in the intervention and control arm, respectively of the KEYNOTE 189 study.

In the KEYNOTE 189 study, the platinum component was determined on a patient-individual basis by the investigator prior to randomisation. In the KEYNOTE 021G study, only carboplatin was available as a treatment option.

In both studies, patients were treated until disease progression, the occurrence of unacceptable side effects or treatment discontinuation at the discretion of the investigator or patient. In both studies, patients were able to switch from the comparator arm to monotherapy with pembrolizumab after disease progression, if appropriate.

In KEYNOTE 189, the proportions of patients with antineoplastic follow-up therapy administered outside the study protocol were 30.5% and 20.9% in the intervention arm and comparator arm, respectfully, at the time of the data cut-off in the entire study population. In the KEYNOTE 021G study, the proportions of patients with anti-neoplastic follow-up therapy other than pembrolizumab monotherapy were 47.5% and 45.9% in the intervention arm and comparator arm, respectively, at the time of the data cut-off in the entire study population. In accordance with the study protocol, 32.5% and 39.7% of patients in KEYNOTE 189 and KEYNOTE 021G studies, respectively had switched from the comparator arm to pembrolizumab monotherapy, whereby the censoring occurred at the time of the respective data cut-off.

By resolution of 18 October 2018 (entered into force on 4 January 2019), Annex VI to Section K of the AM-RL Part A Item III – Carboplatin for advanced non-small cell lung carcinoma (NSCLC) – combination therapy was amended to provide for patients eligible for platinum-based combination therapy with a third-generation cytostatic agent such as paclitaxel, docetaxel, or gemcitabine; the selection of the platinum component (carboplatin or cisplatin) in each case should be based on the different toxicity profile of the two substances and the existing comorbidities.

Extent and probability of the additional benefit

Mortality

In the KEYNOTE 021G and KEYNOTE 189 studies, overall survival was defined as the period from randomization to death of any cause.

In the KEYNOTE 021G study, the median survival time at the time of the 2nd data cut-off of 31 May 2017 for the evaluation-relevant TPC sub-population with PD-L1 expression < 50% (TPS) was 14.9 months in the comparator arm; in the intervention arm, the median was not yet reached (HR: 0.41; [95% confidence interval (CI): 0.15; 1.09]; p value = 0.073).

In the KEYNOTE 189 study, the median survival time at the time of the data cut-off of 8 November 2017 for the evaluation-relevant TPC sub-population with PD-L1 expression < was 50% (TPS) was 12.1 months in the comparator arm; in the intervention arm, the median was not yet reached (HR: 0.58; [95% CI: 0.39; 0.86]; p value 0.008).

In the meta-analysis of the KEYNOTE 021G and KEYNOTE 189 studies, overall survival was statistically significantly prolonged by the administration of pembrolizumab in combination with pemetrexed and platinum chemotherapy for the evaluation-relevant TPC sub-population with PD-L1 expression < 50% (TPS) (HR: 0.55; [95% CI: 0.38; 0.77]; p value 0.001).

The sub-group analysis for the endpoint overall survival showed proof of an effect modification by the characteristic “sex”. According to the study, women had better results than men.

The hazard ratio was HR = 0.17 (95% CI [0.02; 1.40]; p = 0.100) for the sub-group of female patients in study 021G and HR = 0.37 (95% CI [0.19; 0.74]; p = 0.005) for the sub-group of female patients in study 189, whereby a statistically significant difference for pembrolizumab

in combination with pemetrexed and platinum chemotherapy compared with platinum-based chemotherapy was found in the meta-analysis of the two studies (HR: 0.31 (95% CI [0.17; 0.59]; p < 0.001). The median survival in the comparator arm was 20.9 months for study 021G and 10.6 months for study 189; the median was not yet reached in the intervention arm.

In the sub-group of male patients, the hazard ratio was HR = 0.48 (95% CI [0.14; 1.66]; p = 0.244) in study 021G and HR = 0.78 (95% CI [0.46; 1.32]; p = 0.345) in study 189. The meta-analysis of the two studies did not show any statistically significant difference between the treatment arms (HR: 0.73 (95% CI [0.45; 1.18]; p = 0.200). The median survival in the comparator arm was 10.6 months for study 021G and 12.9 months for study 189; the median was not yet reached in the intervention arm.

However, as explained below, the G-BA considers it justified to make a statement on the additional benefit without subdividing it by sex.

These are subgroup analyses of subpopulations from the respective studies. The criteria for subpopulation formation (PD-L1 expression <, ≥ 50% (TPS)) and also the characteristic gender were no stratification factors in randomization. In addition, it must be taken into account that there was no separate list of patient characteristics by gender for the subpopulation under consideration, which could have been taken into account to estimate the potential imbalances in known, for the response to therapy and the prognosis of the factors relevant for patients.

For these reasons, there is no separate assessment of additional benefit by sex. Nevertheless, these are relevant findings from the present assessment that need to be considered when interpreting the results for the whole sub-population for the “overall survival” endpoint. As a result, the endpoint of overall survival is identified as having a non-quantifiable additional benefit.

Morbidity

Symptomology

In the KEYNOTE 189 study, the symptom scales of the EORTC QLQ-C30 and EORTC QLC-LC13 questionnaires were used to record the symptomology. In both cases, the time until the first clinically relevant deterioration is defined as an increase in score of at least 10 points from baseline. In the KEYNOTE 021G study, the endpoint category symptomology was not surveyed.

In the KEYNOTE 189 study, for the constipation endpoint collected by the EORTC QLQ-C30, there was a statistically significant benefit in favour of pembrolizumab in combination with platinum-based chemotherapy compared with platinum-based chemotherapy (HR: 0.59; 95% CI [0.38; 0.90]; p = 0.013).

The endpoint-specific bias potential for the endpoints of symptomatology in KEYNOTE 189 is high, since in the relevant subpopulation a high proportion of patients was not included in the evaluation due to a lack of baseline values and the response rates decreased significantly during the course of the study.

Health status

In the KEYNOTE 189 study, health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire.

For the benefit assessment, the pharmaceutical company presented responder analyses for the period up to the first clinically relevant deterioration in which a change on the VAS of a patient of at least 7 or 10 points compared with baseline was defined as a response.

These responder analyses were not used in the IQWiG dossier evaluation because the study underlying the derivation of the minimal important difference (MID) (Pickard *et al.*, 2007) was classified as unsuitable to validate the MID. This is justified on one hand by the fact that the work mentioned does not contain a longitudinal study to determine the MID, which is assumed in the current scientific discussion on deriving a valid MID. In addition, the anchors ECOG-PS and FACT-G used in the study are not considered suitable for deriving the MID. Given the fact that the validation study in question has already been used in earlier evaluations, in the present evaluation, the G-BA nevertheless uses the responder analyses to assess the effects on the symptomology.

The responder analyses show no significant difference between both treatment arms, neither on the basis of an MID of 7 nor of 10 points.

Quality of life

In the KEYNOTE 189 study, the global health status and functional scales of the EORTC QLQ-C30 were used to measure health-related quality of life. The time until the first clinically relevant deterioration is considered; this is defined as a decrease in score by at least 10 points from baseline, whereby there was no statistically significant difference between the treatment arms for this endpoint.

In the KEYNOTE 021G study, this endpoint category was not collected.

The endpoint-specific bias potential for the endpoints of the health-related quality of life in KEYNOTE 189 is high, since in the relevant subpopulation a high proportion of patients was not included in the evaluation due to a lack of baseline values and the response rates decreased significantly during the course of the study.

Side effects

Adverse events (AE)

Adverse events (AE) occurred at least once in almost every patient in both treatment arms. The results for the endpoint "Adverse events (total)" are therefore presented only on a supplementary basis.

In the KEYNOTE 189 and KEYNOTE 021G studies, an elicitation of AE was planned up to 30 days after the end of treatment or the start of a new antineoplastic therapy (depending on which event occurred first).

Serious adverse events (SAE)

The survey of SAE and immune-mediated SAE was planned in the KEYNOTE study 189 to 90 days after the end of treatment or 30 days after the end of treatment when a new antineoplastic therapy was started (whichever occurred first). Similarly, KEYNOTE 021G included SAE and immune-mediated SUE (as well as immune-mediated UAE and immune-mediated severe AE (CTCAE grade ≥ 3)) until 90 days after the end of treatment or the start of a new antineoplastic therapy (depending on which event occurred first).

With regard to this operationalization, it should be noted that a relevant proportion of therapy changers from the control arm to pembrolizumab monotherapy as follow-up therapy at 35 % and 28 %, respectively, occurred in KEYNOTE 021G and KEYNOTE 189.
For these patients, only events up to the time of therapy change, i.e. up to 21 days after therapy discontinuation, were included in the analysis. Thus, the follow-up periods between patients with change of therapy and patients without change of therapy differ significantly, as the follow-up in patients without change of therapy was 90 days as planned. For the SAE and the immune-mediated SAE (studies KEYNOTE 021G and KEYNOTE 189) as well as the immune-

mediated AE and immune-mediated severe AE (CTCAE grade ≥ 3; KEYNOTE 021G) no usable data are available.

From the point of view of the G-BA, the chosen operationalisation is problematic for the evaluation and the present result of this operationalisation could have been avoided by defining a uniform duration of the follow-up.

Severe AE *(CTCAE grade 3 or 4)*

In the KEYNOTE 021G and KEYNOTE 189 meta-analyses, the endpoint severe AEs (CTCAE grade ≥ 3) showed a statistically significant advantage for pembrolizumab in combination with platinum-based chemotherapy over platinum-based chemotherapy (HR: 0.74; 95%-KI [0.55; 0.9957]; p = 0.047).

The endpoint specific bias potential for the endpoints severe AE (CTCAE grade ≥ 3) (in both studies) and immune-mediated AE as well as immune-mediated severe AE (CTCAE grade ≥ 3) (only in KEYNOTE 189) is assessed as high, as no data are available on the observation period and on the temporal distribution of therapy discontinuations. At the time of the relevant data cuts of both studies, relevant proportions of patients had discontinued therapy, in particular due to progression. This was to a greater extent the case in the control arm in relation to the total population of the studies.
If dependencies exist between the occurrence of progressions and AE events, this may change the observation of AE events. This is also possible to a much greater extent in the control arm.
For the relevant subpopulation, information on the exact number of therapy discontinuations per arm and a complete listing of termination reasons are not available.
Whether a relevant number of incomplete observations occur due to potentially informative reasons, cannot be estimated.

Discontinuation because of AE

For the endpoint "Discontinuation because of AE" no statistically significant difference between the treatment arms was found.

In the KEYNOTE 021G study, this endpoint has a high distortion potential due to the open study design.

Overall assessment

For the assessment of the additional benefit of pembolizumab in combination with pemetrexed and platinum chemotherapy compared with pemetrexed and platinum chemotherapy, the results of the KEYNOTE 021G and KEYNOTE 189 studies on mortality (overall survival), morbidity (symptomology and health status) (KEYNOTE 189 only), quality of life (KEYNOTE 189 only), and side effects are available.

In the endpoint category mortality, the meta-analysis of the two studies shows a statistically significant benefit of pembrolizumab in combination with pemetrexed and platinum chemotherapy for the endpoint overall survival.

Within the framework of sub-group analyses, there is proof for an effect modification by the characteristic “sex”, which for women shows a statistically significant difference in favour of pembrolizumab in combination with pemetrexed and platinum chemotherapy. There is therefore no statistically significant difference for men.

In its assessment of the sub-group analyses available, the G-BA comes to the conclusion that the interpretation of the characteristic “sex” is subject to relevant uncertainties. There is no separate assessment of the additional benefit according to gender. Nevertheless, these are relevant findings from the present assessment that need to be considered when interpreting

the results for the whole sub-population for the “overall survival” endpoint. As a result, the endpoint of overall survival is identified as having a non-quantifiable additional benefit.

In the endpoint category morbidity (symptomology) in the KEYNOTE 189 study, there was a statistically significant benefit for the endpoint constipation from treatment with pembrolizumab in combination with pemetrexed and platinum chemotherapy.

The results on health-related quality of life show no statistically significant differences between treatment arms.

With respect to side effects, the meta-analysis of the KEYNOTE 021G and KEYNOTE 189 studies for the endpoint AEs (CTCAE grade ≥ 3) showed a statistically significant difference in favour of pembrolizumab in combination with pemetrexed and platinum chemotherapy.

For the endpoint “therapy discontinuation because of adverse events”, no statistically significant difference between the treatment arms was found.
For the endpoints “serious adverse events (SAE)” and “immune-mediated SAE” (from the KEYNOTE 021G and KEYNOTE 189 studies) as well as the endpoints “immune-mediated AEs” and “immune-mediated AEs (CTCAE grade ≥ 3)” (from the KEYNOTE 021G study) no usable evaluations are available.

Assuming that it is not possible to quantify the extent of the identified additional benefit in the overall survival endpoint for the whole sub-population, the G-BA concludes that there is a non-quantifiable additional benefit for pembrolizumab in combination with pemetrexed and platinum chemotherapy for the first-line treatment of metastatic non-squamous NSCLC in patients with a PD-L1 expression of < 50% (TPS) compared with pemetrexed in combination with platinum chemotherapy.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of two RCTs with the appropriate comparative therapy platinum-based chemotherapy – an open, randomised, controlled comparison (KEYNOTE 021G) on one hand and a double-blind, randomised, controlled comparison (KEYNOTE 189) on the other hand. The cross-endpoint risk of bias is considered low for both studies.

In the context of the meta-analysis, the KEYNOTE 021G study, in addition to the KEYNOTE 189 study, makes only a comparatively small contribution in terms of the number of patients.

The endpoint specific risk of bias for the overall survival endpoint is considered low.

For the endpoint categories morbidity and health-related quality of life, only data from the KEYNOTE 189 study are available; these were not collected in the KEYNOTE 021G study. No data are available on the observation periods for morbidity and health-related quality of life in the KEYNOTE189 study. The endpoint specific risk of bias for the endpoints symptomology and health-related quality of life in KEYNOTE 189 is high.

The endpoint specific bias potential for the endpoints severe AE (CTCAE grade ≥ 3) (KEYNOTE 021G and KEYNOTE 189 studies) and immune-mediated AE as well as immune-mediated severe AE (CTCAE grade ≥ 3) (only in KEYNOTE 189) is assessed as high, as no data are available on the observation period and on the temporal distribution of therapy discontinuations.

Whether a relevant number of incomplete observations occur due to potentially informative reasons, cannot be estimated.

Since for the endpoints SAE and immune-mediated SAE (studies KEYNOTE 021G and KEYNOTE 189) as well as immune-mediated AE and immune-mediated severe AE (CTCAE ≥ 3) (only KEYNOTE 021G) there are no usable evaluations available, a full evaluation of side effects is more difficult.

In the KEYNOTE 021G study, there is also a high risk of bias for the endpoint discontinuation because of AE because of the open study design.

In a balancing decision, the G-BA classifies the reliability of data in the “hint” category based on the evidence available.

b) Adult patients with first-line treatment of metastatic squamous NSCLC without EGFR or ALK positive tumour mutations whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS):

For adult patients with first-line treatment of metastatic squamous NSCLC without EGFR or ALK positive tumour mutations whose tumours express PD-L1 with a ≥ 50% (TPS[2]) there is a non-quantifiable additional benefit for pembrolizumab in combination with pemetrexed and platinum chemotherapy compared with pembrolizumab.

Justification:

The benefit assessment is based on the adjusted indirect comparison presented in the dossier of the pharmaceutical company. On the intervention side (pembrolizumab in combination with platinum-based chemotherapy) the KEYNOTE 021G and KEYNOTE 189 studies are compared with the bridge comparator platinum-based chemotherapy. On the appropriate comparator therapy side (pembrolizumab monotherapy) the KEYNOTE 024 and KEYNOTE 042 studies are compared with the bridge comparator platinum-based chemotherapy.

The studies on the intervention side (KEYNOTE 021G and KEYNOTE 189) have already been described for sub-population A.

The studies on the side of appropriate comparator therapy (KEYNOTE 024 and KEYNOTE 042) are randomised, open, controlled studies. KEYNOTE 024 has already been completed (September 2014 to May 2016), and KEYNOTE 042 is currently ongoing (started in November 2014).

The KEYNOTE 024 study included adult patients with histologically or cytologically confirmed metastatic NSCLC without systematic pretreatment and without EGFR mutation or ALK translocation with PD-L1 tumour expression ≥ 50%. 305 patients stratified by histology, geographical region, and ECOG-PS were randomised to the treatment arms at a ratio of 1:1 – 154 patients in the pembrolizumab arm and 151 patients in the control arm (platinum-based combination chemotherapy). In the control arm, 47 patients (31%) were treated with cisplatin and 103 patients (68%) with carboplatin. The suitability for the respective treatment before randomisation was decided by the investigator on a patient-individual basis. The underlying data cut-off is 9 May 2016. The study was terminated at that time because of the superiority of pembrolizumab over platinum-based chemotherapy in terms of overall survival.

The KEYNOTE 042 study included adult patients with histologically or cytologically confirmed locally advanced or metastatic NSCLC without systematic pretreatment with PD-L1 tumour expression ≥ 1%. 1274 patients stratified by histology, geographical region, and PD-L1 expression were randomised to the treatment arms at a ratio of 1:1 – 637 patients in the pembrolizumab arm and 637 patients in the control arm (carboplatin-based combination chemotherapy with paclitaxel or pemetrexed),whereby the suitability for the respective

treatment was decided by the investigator on a patient-individual basis before randomisation. The underlying data cut-off is 26 February 2018.

In both studies the patients were treated until disease progression, until unacceptable side effects occurred, or until the study was discontinued at the discretion of the investigator or the patient (in the KEYNOTE 042 study, also until complete response). In both treatment arms, the patients could be treated with follow-up therapies after discontinuation of the study medication. In the KEYNOTE 024 study, a change from the comparison group to the intervention group was permitted for disease progression and suitability, whereas in the KEYNOTE 042 study, a change from the comparison group to the intervention group was not explicitly part of the study design.

For the indirect comparison, the study populations of the KEYNOTE 024 and KEYNOTE 042 studies were restricted to patients with non-squamous NSCLC in the metastatic stage for whom a therapy with carboplatin/cisplatin in combination with pemetrexed (KEYNOTE 024) or carboplatin in combination with pemetrexed (KEYNOTE 042) was defined as the platinum-based chemotherapy prior to randomisation.

With regard to the implementation of the off-label use of carboplatin in accordance with the Pharmaceuticals Directive prior to the last amendment, which entered into force on 4 January 2019 (Annex VI to Section K of the AM-RL Part A Item III), no consideration of the criteria of the AM-RL was reported for treatment with carboplatin-based chemotherapy.
The pharmaceutical company therefore formed a TPC (Treatment of Physician's Choice) sub-population based on a retrospective survey in which the investigator was to justify the decision for a carboplatin-based combination chemotherapy on a patient-individual basis; this included all patients treated according to the criteria of the AM-RL. This TPC sub-population comprises a total of 470 patients from the four aforementioned KEYNOTE studies: 95 with pembrolizumab in combination with platinum-based chemotherapy (pemetrexed in combination with cisplatin/carboplatin), 165 with pembrolizumab monotherapy, and 210 with the bridge comparator platinum-based chemotherapy (pemetrexed in combination with cisplatin/carboplatin) were used for the assessment.

The data from the study report now available for the Chinese KEYNOTE 042 extension study are not used for the present benefit assessment. The reason for this is that, on one hand, the overall population was not evaluated separately according to PD-L1 status and, on the other hand, no *post-hoc* survey was carried out by the Chinese investigators to decide on the justification for the patient-individual carboplatin-based combination chemotherapy, whereby the retrospective formation of the TPC sub-populations relevant for the present benefit assessment was not possible.

By resolution of 18 October 2018 (entered into force on 4 January 2019), Annex VI to Section K of the AM-RL Part A Item III – carboplatin for advanced non-small cell lung carcinoma (NSCLC) – combination therapy was amended to provide for patients eligible for platinum-based combination therapy with a third-generation cytostatic agent such as paclitaxel, docetaxel, or gemcitabine; the selection of the platinum component (carboplatin or cisplatin) in each case should be based on the different toxicity profile of the two substances and the existing comorbidities.

Similarity of studies in indirect comparison

Between the studies used for the present indirect comparison are sufficiently comparable with regard to the characteristics of the relevant sub-populations. However, there are differences

between the studies regarding the different treatment options of platinum-based chemotherapy. While in the KEYNOTE 189 and KEYNOTE 024 studies, the patients of the relevant sub-populations in the comparator arm received either carboplatin or cisplatin in combination with pemetrexed, in the KEYNOTE 021G and KEYNOTE042 studies, all patients of the relevant sub-populations in the comparator arm received only carboplatin with pemetrexed. Furthermore, there is a difference between the studies with respect to the characteristic region; in the KEYNOTE 042 study, the proportion of patients from non-EU countries is significantly higher than in the KEYNOTE 189 and 024 studies (no data on the KEYNOTE 021G study). Furthermore, the observation periods for the endpoint overall survival showed clear differences between the studies (approx. 9 months to approx. 20 months). However, the observation period for overall survival was balanced between the arms in the individual studies.

There are also further uncertainties regarding the comparability of the studies used for the indirect comparison on the basis of the results observed for the efficacy endpoints. In particular, the studies included showed clear differences in the survival times of the patients examined.

Furthermore, between the studies and also between the study arms within individual studies, there was in part a different distribution of men and women in the respective sub-populations relevant for the assessment.

The described differences between the studies KEYNOTE 021G and KEYNOTE 189 as well as KEYNOTE 024 and KEYNOTE 042 do not, however, lead to the assumption of similarity being rejected for the indirect comparison. The studies used are therefore sufficiently comparable with regard to the characteristics of the relevant subpopulations.

Extent and probability of the additional benefit

Mortality

For the studies on the intervention (KEYNOTE 021G and KEYNOTE 189) and the appropriate comparator therapy (KEYNOTE 024 and KEYNOTE 042), overall survival was defined as the time from randomisation to death of any cause.

For the indirect comparison according to Bucher, the KEYNOTE 021G and KEYNOTE 189 studies formed the intervention side (pembrolizumab in combination with platinum-based chemotherapy) compared with the bridge comparator platinum-based chemotherapy. In the KEYNOTE 021G study, the median survival time at the time of the 2nd data cut-off of 31 May 2017 for the evaluation-relevant TPC sub-population with PD-L1 expression ≥ was 50% (TPS) was 19.0 months in the comparator arm; in the intervention arm, the median was not yet reached (HR: 0.30; [95% CI: 0.06; 1.48]; p value 0.140). In the KEYNOTE 189 study, the median survival time at the time of the data cut-off of 8 November 2017 for the evaluation-relevant TPC sub-population with PD-L1 expression ≥ was 50% (TPS) was 10.0 months in the comparator arm; in the intervention arm, the median was not yet reached (HR: 0.33; [95% CI: 0.17; 0.62]; p value < 0001).

For the indirect comparison according to Bucher, the KEYNOTE 024 and KEYNOTE 042 studies formed the appropriate comparator therapy side (pembrolizumab monotherapy chemotherapy) compared with the bridge comparator platinum-based chemotherapy. In the KEYNOTE 024 study, the median survival time at the time of the data cut-off of 9 May 2016 for the evaluation-relevant TPC sub-population with PD-L1 expression ≥ was 50% (TPS) was 12.6 months in the comparator arm; in the intervention arm, the median was not yet reached (HR: 0.66; [95% CI: 0.38; 1.16]; p value 0.149). In the KEYNOTE 042 study, the median survival time at the time of the data cut-off of 26 February 2018 for the evaluation-relevant TPC sub-population with PD-L1 expression ≥ was 50% (TPS) was 16.7 and 16.4 in the intervention and comparator arm, respectively (AD: +0.3 months; HR: 0.88; [95% CI: 0.60; 1.30]; p value 0.524).

In the indirect comparison according to Bucher, this results in a statistically significantly longer overall survival for the assessment-relevant TPC sub-population with PD-L1 expression ≥ 50% (TPS) through the administration of pembrolizumab in combination with platinum-based chemotherapy (HR: 0.40; [95% CI: 0.20; 0.79]; p value 0.008).

The sub-group analysis for the endpoint overall survival showed an effect modification based on the adjusted indirect comparison by the characteristic “sex”.

For the intervention based on the indirect comparison according to Bucher, the hazard ratio for the subgroup of female patients in study 189 was HR = 0.08 (95% CI [0.02; 0.34]; p < 0.001); a hazard ratio of 0.12 was calculated for both studies 189 and 021G combined (95% CI [0.04; 0.37]; p value: no data available). For Study 189, the median survival time in this sub-group was 8.0 months in the comparator arm; the median was not yet reached in the intervention arm. In the sub-group of female patients, no separate data could be calculated for study 021G.

For the intervention based on the indirect comparison according to Bucher, the hazard ratio for the subgroup of male patients in study 189 was HR = 0.73 (95% CI [0.29; 1.79]; p < 0.490); a hazard ratio of 0.68 was calculated for both studies 189 and 021G combined (95% CI [0.30; 1.56]; p value: no data available). The median survival time in this subgroup has not yet been achieved for studies 189 and 021G. In the sub-group of male patients, no separate data can be calculated for study 021G.

Based on the indirect comparison according to Bucher, for the sub-group of female patients, this results in a statistically significantly longer overall survival for the assessment-relevant TPC sub-population with PD-L1 expression ≥ 50% (TPS) through the administration of pembrolizumab in combination with platinum-based chemotherapy compared with pembrolizumab monotherapy (HR: 0.09; [95% CI: 0.03; 0.32]; p value < 0.001).

For the appropriate comparator therapy based on the indirect comparison according to Bucher, the hazard ratio for the sub-group of female patients in study 024 was HR = 1.33 (95% CI [0.45.]); 3.92]; p = 0.607) and in study 042, HR=1.33 (95% CI [0.79; 2.24]; p = 0.292); a hazard ratio of 1.27 was calculated for both studies together (95% CI [0.77; 2.11]; p value: no data available). In study 042, the median survival time in this subgroup was 7.7 vs 8.0 months in intervention vs comparator arm. In study 042, the median was not yet reached in both arms.

For the appropriate comparator therapy based on the indirect comparison according to Bucher, the hazard ratio for the sub-group of male patients in study 024 was HR = 0.48 (95% CI [0.23.]); 0.96]; p = 0.038) and in study 042, HR = 0.60 (95% CI [0.38; 0.96]; p = 0.032); a hazard ratio of 0.58 was calculated for both studies together (95% CI [0.39; 0.88]; p value: no data available). The median survival time in study 024 was 12.6 months in this sub-group in the comparator arm; this was not yet achieved in the intervention arm. In study 042, the median survival time in this sub-group was 11.7 vs 6.6 months in intervention vs comparator arm.

Based on the indirect comparison according to Bucher, for the sub-group of male patients, there is no statistically significant difference in overall survival for the assessment-relevant TPC sub-population with PD-L1 expression ≥ 50% (TPS) through the administration of pembrolizumab in combination with platinum-based chemotherapy compared with pembrolizumab monotherapy (HR: 1.16; [95% CI: 0.46; 2.94]; p value 0.754).

However, as explained below, the G-BA considers it justified to make a statement on the additional benefit without subdividing it by sex.

These are subgroup analyses of subpopulations from the respective studies. The criteria for subpopulation formation (PD-L1 expression <, ≥ 50% (TPS)) and also the characteristic gender were no stratification factors in randomization. In addition, it must be taken into account that there was no separate list of patient characteristics by gender for the subpopulation under consideration, which could have been taken into account to estimate the potential imbalances in known, for the response to therapy and the prognosis of the factors relevant for patients.

For these reasons, there is no separate assessment of additional benefit by sex. Nevertheless, these are relevant findings from the present assessment that need to be considered when interpreting the results for the whole sub-population for the “overall survival” endpoint. As a result, the endpoint of overall survival is identified as having a non-quantifiable additional benefit.

Morbidity

Symptomology

In order to record the symptomology the symptom scales of the questionnaires EORTC QLQ-C30 and EORTC QLQ- LC13 were used for each study per arm of the indirect comparison. This was the case for the intervention in the KEYNOTE 189 study and for the comparator in the KEYNOTE 024 study. In both cases, the time until the first clinically relevant deterioration is defined as an increase in score of at least 10 points from baseline. In the KEYNOTE 021G and KEYNOTE 042 studies, the endpoint category symptomology was not surveyed. Thus, on each side of the indirect comparison, there is only one study with high risk of bias for this endpoint. For the KEYNOTE 189 study, this is due to the high proportion of patients who were not included in the evaluation because of a lack of baseline values and the significantly lower return rates during the course of the study. For the KEYNOTE 024 study, the high risk of bias results from the fact that the study was unblinded and that it is a subjectively collected endpoint. Statements on the additional benefit are therefore not possible based on the results from the indirect comparison.

Health status

In the KEYNOTE 189 and KEYNOTE 024 studies, health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire.

For the benefit assessment, the pharmaceutical company presented responder analyses for the period up to the first clinically relevant deterioration in which a change on the VAS of a patient of at least 7 or 10 points compared with baseline was defined as a response.
In the KEYNOTE 021G and KEYNOTE 042 studies, the endpoint category health status was not surveyed. Thus, on each side of the indirect comparison, there is only one study with high risk of bias for this endpoint. Statements on the additional benefit are therefore not possible based on the results from the indirect comparison.

Quality of life

In the KEYNOTE 189 and KEYNOTE 024 studies, the global health status and functional scales of the EORTC QLQ-C30 were used to measure health-related quality of life. The time until the first clinically relevant deterioration is considered; this is defined as a decrease in score by at least 10 points from baseline.

In the KEYNOTE 021G and KEYNOTE 042 studies, this endpoint category was not surveyed. Thus, on each side of the indirect comparison, there is only one study with high risk of bias for this endpoint. Statements on the additional benefit are therefore not possible based on the results from the indirect comparison.

Side effects

Adverse events (AE)

On the indirect comparison intervention side, in both the KEYNOTE 021G and KEYNOTE 189 studies, an adverse event occurred in all patients in both study arms. On the side of the

appropriate comparator therapy, in the KEYNOTE 024 study, 94.7% of patients in the intervention arm and 94.5% in the comparator arm experienced an adverse event. In the KEYNOTE 042 study, this was true for 98.9% of patients in the intervention arm and for all patients in the comparator arm.

Serious adverse events (SAE)

In the KEYNOTE 189 and KEYNOTE 024 studies, the elicitation of SAE and immune-mediated SAE (as well as immune-mediated AE and immune-mediated severe AE (CTCAE grade ≥ 3) in KEYNOTE 024) until 90 days after the end of treatment or until 30 days after the end of treatment when a new antineoplastic therapy was initiated (whichever occurred first). Similarly, in KEYNOTE 021G and KEYNOTE 042, the elicitation of SAE and immune-mediated SAE (as well as immune-mediated AE and immune-mediated severe AE (CTCAE grade ≥ 3)) were planned to be assessed until 90 days after the end of treatment or the start of a new antineoplastic therapy (depending on which event occurred first).

As explained in the corresponding remarks under subpopulation a), the follow-up periods between patients with change of therapy and patients without change of therapy deviate significantly from each other due to the available operationalization. For the SAE and immune-mediated SAE (all four studies) as well as the immune-mediated AE and immune-mediated severe AE (CTCAE grade ≥ 3; KEYNOTE 021G, KEYNOTE 024 and KEYNOTE 042) there are therefore no usable data available.

From the point of view of the G-BA, the selected operationalization is problematic for the evaluation and the present result of this operationalization could have been avoided, by establishing a uniform duration for the follow-up.

Adverse Events (CTCAE grade 3 or 4)

In the context of the indirect comparison according to Bucher, there is no difference with respect to AE with CTCAE grade 3 or 4 for the assessment-relevant TPC sub-population with PD-L1 expression ≥ 50% (TPS) through the administration of pembrolizumab in combination with platinum-based chemotherapy.

The subgroup analysis for the endpoint severe AE showed an effect modification by the characteristic “sex” based on the adjusted indirect comparison.

For the intervention based on the indirect comparison, the hazard ratio for the subgroup of female patients in KEYNOTE study 189 was HR = 0.84 (95% CI [0.40; 1.77]; p = 0.654); a hazard ratio of 0.75 was calculated for both studies 189 and 021G combined (95% CI [0.37; 1.50]; p value: no data available). In this sub-group for the KEYNOTE 189 study, the median time to event was 4.9 months in the intervention arm and 4.0 months in the comparator arm. In the sub-group of female patients, no separate data could be calculated for the KEYNOTE 021G study.

For the appropriate comparator therapy based on the indirect comparison according to Bucher, the hazard ratio for the sub-group of female patients in study 024 was HR = 1.03 (95% CI [0.46.]); 2.31]; p = 0.285) and in study 042, HR = 1.14 (95% CI [0.62; 2.10]; p = 0.662); a hazard ratio of 1.10 was calculated for both studies together (95% CI [0.68; 1.79]; p value: no data available). In study 042, the median time until event in this subgroup was 5.5 vs 6.2 months in intervention vs comparator arm. In study 042, the median was not yet reached in both arms.

Based on the indirect comparison according to Bucher, for the sub-group of female patients, there is no significant difference in adverse events for the assessment-relevant TPC sub-population with PD-L1 expression ≥ 50% (TPS) through the administration of pembrolizumab in combination with platinum-based chemotherapy compared with pembrolizumab monotherapy (HR: 0.68; [95% CI: 0.29; 1.58]; p value 0.373).

For the intervention based on the indirect comparison, the hazard ratio for the subgroup of male patients in KEYNOTE study 189 was HR = 1.90 (95% CI [0.92; 3.89]; p = 0.081); a hazard ratio of 1.55 was calculated for both studies 189 and 021G combined (95% CI [0.83; 2.90]; p value: no data available). In this sub-group for the KEYNOTE 189 study, the median time to event was 3.0 months in the intervention arm and 16.6 months in the comparator arm. In the sub-group of male patients, no separate data can be calculated for the KEYNOTE 021G study.

For the appropriate comparator therapy based on the indirect comparison according to Bucher, the hazard ratio for the sub-group of male patients in study 024 was HR = 0.51 (95% CI [0.30.; 0.87]; p = 0.013) and in study 042, HR = 0.75 (95% CI [0.44; 1.28]; p = 0.940); a hazard ratio of 0.61 was calculated for both studies together (95% CI [0.42; 0.89]; p value: no data available). In study 024, the median time to event in this subgroup was 6.2 vs 1.3 months in intervention vs comparator arm. In study 042, the median survival time in this sub-group was 11.6 vs 3.9 months in intervention vs comparator arm.

Based on the indirect comparison according to Bucher, for the sub-group of male patients for the assessment-relevant TPC sub-population with PD-L1 expression ≥ 50% (TPS), there is a significantly significant difference in favour of pembrolizumab in combination with platinum-based chemotherapy compared with pembrolizumab monotherapy (HR: 2.53; [95% CI: 1.22; 5.23]; p value 0.012).

As explained in the comments on the overall survival endpoint, the G-BA believes there are relevant uncertainties in the interpretation of the sub-group analyses available for the “sex” characteristic. Therefore, it is considered justified to make a statement on additional benefit without subdividing it by sex. Nevertheless, these are relevant findings from the present assessment that need to be considered when interpreting the results for the whole sub-population for the “severe AE” endpoint.

Based on the indirect comparison, there is also an effect modification for the characteristic brain metastases at the start of study. In patients with brain metastases, a statistically significant advantage of pembrolizumab in combination with pemetrexed and platinum chemotherapy was demonstrated at the start of study. In patients without brain metastases at the start of study, there was no difference between the treatment groups. Considering that this effect modification is only shown for this one endpoint and not also for other patient-relevant endpoints, the characteristic brain metastases at the start of study is not further considered for the present assessment.

The endpoint specific bias potential for the endpoints severe AE (CTCAE grade ≥ 3) (all 4 studies) and immune-mediated AE as well as immune-mediated severe AE (CTCAE grade ≥ 3) (only in KEYNOTE 189) is assessed as high, since no data are available on the duration of observation and on the temporal distribution of therapy discontinuations. At the time of the relevant data cuts of both studies, relevant proportions of patients had discontinued therapy, in particular due to progression. This was to a greater extent the case in the control arm in relation to the total population of the studies.
If dependencies exist between the occurrence of progressions and AE events, this may change the observation of AE events. This is also possible to a much greater extent in the control arm.
For the relevant subpopulation, information on the exact number of therapy discontinuations per arm and a complete listing of termination reasons are not available.
Whether a relevant number of incomplete observations occur due to potentially informative reasons, cannot be estimated.

Discontinuation because of AE

For the endpoint “Discontinuation because of AE”, there was no statistically significant difference between the treatment arms.

In the KEYNOTE 021G, KEYNOTE 024 and KEYNOTE 042 studies, there is also a high distortion potential for the endpoint discontinuation because of AE due to their open study design.

Overall assessment

For the assessment of the additional benefit of pembrolizumab in combination with pemetrexed and platinum chemotherapy compared to monotherapy with pembrolizumab, an adjusted indirect comparison from the KEYNOTE 021G and KEYNOTE 189 studies (intervention side) and the KEYNOTE 024 and KEYNOTE 042 studies (appropriate comparator therapy studies) is available. Results on mortality (overall survival) and side effects are available.

In the endpoint category mortality, the indirect comparison for the endpoint overall survival shows a statistically significant advantage of pembrolizumab in combination with pemetrexed and platinum chemotherapy.

Within the framework of sub-group analyses, there is proof for an effect modification by the characteristic “sex”, which for women shows a statistically significant difference in favour of pembrolizumab in combination with pemetrexed and platinum chemotherapy. There is therefore no statistically significant difference for men.

In its assessment of the available subgroup analyses on the characteristic "gender", the G-BA comes to the conclusion that the interpretation of this effect modification is subject to relevant uncertainties. There is no separate assessment of the additional benefit according to gender. Nevertheless, these are relevant findings from the present assessment that need to be considered when interpreting the results for the whole sub-population for the “overall survival” endpoint. As a result, the endpoint of overall survival is identified as having a non-quantifiable additional benefit.

In the endpoint categories morbidity and health-related quality of life, no conclusions can be derived from the indirect comparison.

The indirect comparison for the endpoint AEs (CTCAE grade ≥ 3) shows no statistically significant difference between the treatment groups in terms of side effects.

Within the framework of sub-group analyses, there is proof for an effect modification by the characteristic “sex”, which for men shows a statistically significant difference to the detriment of pembrolizumab in combination with pemetrexed and platinum chemotherapy. There is therefore no statistically significant difference for women.
As explained in the comments on the overall survival endpoint, there is no separate assessment of additional benefit by sex.

For the endpoint “Discontinuation because of AE”, there was no statistically significant difference between the treatment arms.

For the endpoints “serious adverse events (SAE)” and “immune-mediated SAE” (from all four studies) as well as the endpoints “immune-mediated AEs” and “immune-mediated AEs (CTCAE grade ≥ 3)” (from the KEYNOTE 021G, KEYNOTE 024, and KEYNOTE 042 studies) no usable evaluations are available.

Assuming that the extent of the identified added benefit cannot be quantified in the endpoint overall survival for the whole subpopulation and that beyond 21, an assessment of symptoms and health-related quality of life is not possible, the G-BA comes to the conclusion that pembrolizumab in combination with pemetrexed and platinum chemotherapy for the first-line treatment of metastatic non-plate epithelial NSCLC in patients with a PD-L1 expression of ≥ 50%. (TPS) versus pemetrexed in combination with platinum chemotherapy has an additional benefit, of which the extent is not quantifiable.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of an adjusted indirect comparison of the RCTs KEYNOTE 189 (double-blind) and KEYNOTE 021G (open) on the intervention side and

the RCTs KEYNOTE 024 (open) and KEYNOTE 042 (open) on the appropriate comparator therapy side. The cross-endpoint risk of bias is considered low for all studies.

With regard to the reliability of data of the evidence submitted, it should be noted that results based on adjusted, indirect comparisons per se show a low degree of certainty of results. When assessing the indirect comparison presented, it should also be borne in mind that there are uncertainties with regard to the sufficient similarity of the studies included. These concern in particular clear differences between the studies with regard to the survival times of the patients examined as well as with regard to the distribution of men and women in the respective sub-populations relevant for evaluation.

The endpoint specific risk of bias for the overall survival endpoint is considered low.

In the endpoint categories morbidity and health-related quality of life there are no usable evaluations because these have a high potential for distortion for the respective endpoint and on each side of the indirect comparison, data for only one study data were available.

The endpoint specific bias potential for the endpoints severe AE (CTCAE grade ≥ 3) (all 4 studies) and immune-mediated AE as well as immune-mediated severe AE (CTCAEGrad ≥ 3) (only in KEYNOTE 189) is assessed as high, since no data are available on the duration of observation and on the temporal distribution of therapy discontinuations. Whether there is a relevant number of incomplete observations for potentially informative reasons cannot be estimated.

Since for the endpoints SAE and immune-mediated SAE (all four studies) as well as immune-mediated AE and immune-mediated severe AE (CTCAE grade ≥ 3) (KEYNOTE 021G, KEYNOTE 024 and KEYNOTE 042) are not available, a full evaluation of the side effects is difficult.

In the KEYNOTE 021G, KEYNOTE 024 and KEYNOTE 042 studies, there is also a high risk of bias for the endpoint discontinuation because of AE because of the open study design.

In a balancing decision, the G-BA classifies the reliability of data in the “hint” category based on the evidence available.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of a new therapeutic indication for pembrolizumab.

The therapeutic indication assessed here is as follows: “Keytruda, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations”.

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

a) Adult patients with first-line treatment of metastatic squamous NSCLC without EGFR or ALK positive tumour mutations whose tumours express PD-L1 with a < 50% tumour proportion score (TPS):

and

b) Adult patients with first-line treatment of metastatic squamous NSCLC without EGFR or ALK positive tumour mutations whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS).

About patient group a)

The appropriate comparator therapy was determined by the G-BA as follows:

- Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)

  or

- Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed; *cf* Annex VI to Section K of the Pharmaceuticals Directive)

  or

- Carboplatin in combination with nab-paclitaxel

For this patient group, the pharmaceutical company presents the results of the randomised controlled studies KEYNOTE 189 (double-blind; pembrolizumab in combination with pemetrexed and cisplatin/carboplatin vs pemetrexed and cisplatin/carboplatin) and KEYNOTE 021G (open; pembrolizumab in combination with pemetrexed and carboplatin vs pemetrexed plus carboplatin). The benefit assessment is based on all patients who were treated according to the criteria of the AM-RL.

In the endpoint category mortality, pembrolizumab in combination with pemetrexed and platinum chemotherapy showed a statistically significant benefit for the endpoint overall survival.

Sub-group analyses revealed proof of an effect modification by the characteristic “sex”. However, because the interpretation of these subgroup analyses was subject to relevant uncertainties, a separate assessment of the additional benefit by sex was dispensed with. For the endpoint of overall survival, a non-quantifiable additional benefit was identified.

In the endpoint category morbidity in the KEYNOTE 189 study, there was a statistically significant benefit for the endpoint constipation from treatment with pembrolizumab in combination with pemetrexed and platinum chemotherapy.

In the health-related quality of life category, the results showed no statistically significant differences between treatment arms.

In the side effects category, the endpoint of adverse events (CTCAE grade ≥ 3) showed a statistically significant difference in favour of pembrolizumab in combination with pemetrexed and platinum chemotherapy.

For the endpoint “therapy discontinuation because of adverse events”, no statistically significant difference between the treatment arms was found.

Remaining uncertainties in the category side effects concern the endpoints “serious adverse events (SAE)”, “immune-mediated SAE”, “immune-mediated AEs”, and “immune-mediated AEs (CTCAE grade ≥ 3)” because no usable statements were available for these endpoints.

In the overall view, because it is not possible to quantify the extent of the additional benefit identified in the endpoint overall survival for the whole sub-population and taking into account that a full assessment of adverse reactions is difficult, the G-BA identifies a non-quantifiable additional benefit.

Especially against the background that the KEYNOTE 021G study contributed only a comparatively small part in terms of number of patients and taking into account the fact that a full evaluation of the side effects is difficult and that a high risk of bias must be considered for a number of endpoints, only a hint for an additional benefit can be derived with regard to the reliability of data.

About patient group b)

Pembrolizumab as monotherapy was determined as an appropriate comparator therapy by the G-BA:

For this patient group, the pharmaceutical company presents an adjusted indirect comparison to demonstrate an additional benefit. The RCTs KEYNOTE 189 (double-blind; pembrolizumab in combination with pemetrexed and cisplatin/carboplatin vs pemetrexed in combination with

cisplatin/carboplatin) and KEYNOTE 021G (open; pembrolizumab in combination with pemetrexed and carboplatin vs pemetrexed in combination with carboplatin) were used on the intervention side. The randomised, open, controlled studies KEYNOTE 024 (pembrolizumab vs platinum-based combination chemotherapy) and KEYNOTE 042 (pembrolizumab vs carboplatin-based combination chemotherapy) were consulted on the appropriate comparator therapy side. The benefit assessment is based on all patients who were treated according to the criteria of the AM-RL.

In the endpoint category mortality, the indirect comparison for the endpoint overall survival showed a statistically significant advantage of pembrolizumab in combination with pemetrexed and platinum chemotherapy.

Sub-group analyses revealed proof of an effect modification by the characteristic “sex”. However, because the interpretation of these subgroup analyses was subject to relevant uncertainties, a separate assessment of the additional benefit by sex was dispensed with. For the endpoint of overall survival, a non-quantifiable additional benefit was identified.

No usable evaluations were available in the endpoint categories morbidity and health-related quality of life.

In the side effects category, there was no statistically significant difference between treatment groups for the endpoint AEs (CTCAE grade ≥ 3). Sub-group analyses revealed proof of an effect modification by the characteristic “sex”, which, as in overall survival, did not lead to a separate assessment of the additional benefit by sex.

For the endpoint “Discontinuation because of AE”, there was no statistically significant difference between the treatment arms.

On one hand, remaining uncertainties in the category side effects concern the endpoints “serious adverse events (SAE)”, “immune-mediated SAE”, “immune-mediated AEs”, and “immune-mediated AEs (CTCAE grade ≥ 3)” because no usable statements were available for these endpoints.

In the overall view, because it is not possible to quantify the extent of the additional benefit identified in the endpoint overall survival for the whole sub-population and taking into account that a full assessment of adverse reactions is difficult and an assessment of symptomology and health-related quality of life is not possible, the G-BA identifies a non-quantifiable additional benefit.

Particularly in view of the per se low certainty of results in adjusted, indirect comparisons and remaining uncertainties with regard to the sufficient similarity of the studies included and taking into account that a full assessment of adverse reactions is difficult and that for a number of endpoints a high distortion potential must be taken into account, only a hint of an additional benefit can be derived with regard to the reliability of the data.

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

The G-BA uses the following derivation of patient numbers in order to enable a consistent examination of patient numbers, taking into account the most recent resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the present therapeutic indication (osimertinib: 17 January 2019; alectinib: 21 June 2018; ceritinib: 1 February 2018):

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

For the number of German patients with lung cancer, the incidence for 2019 (56 979 patients) from the dossier of the pharmaceutical company is used as the basis for the calculations.

This patient group is limited to the target population via nine calculation steps:

1. The proportion of lung cancer patients with NSCLC is approx. 80.3–82%.[3]

2. Of these, 49.2% are Stage IV patients.[4]

3. The proportion of activating EGFR mutations is approx. 4.9–10.3%.[3,5]

4. The proportion with ALK translocations is approx. 2–3.9%. [6,7]

5. Non-squamous histology is present in 63.1% of Stage IIIB/IV NSCLC patients. [7]

6. First-line therapy is performed in 76.9 to 78.5% of cases.[4]

7. The sum of the driver mutations from sub-steps 3 to 4 is subtracted from sub-step 2.

8a. The proportion of patients with Stage IV NSCLC with PD-L1 expressing tumours (TPS < 50%) is 71.1%. [4]

8b. The proportion of patients with Stage IV NSCLC with PD-L1 expressing tumours (TPS ≥ 50%) is 28.9%. [4]

9. Number of SHI patients: 85.9%. [8]

For

a) adult patients with first-line treatment of metastatic squamous NSCLC without EGFR or ALK positive tumour mutations whose tumours express PD-L1 with a < 50% tumour proportion score (TPS):

   this results in approx. 5,700 to 6,480 patients

b) adult patients with first-line treatment of metastatic squamous NSCLC without EGFR or ALK positive tumour mutations whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS):

   this results in approx. 2,320 to 2,640 patients

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: 10 July 2019):

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

Treatment with pembrolizumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in internal medicine and pneumology, specialists in pulmonary medicine, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with non-small cell lung carcinoma.

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3 Resolution on osimertinib of 17 January 2019
4 Resolution on pembrolizumab of 3 August 2017
5 Data are based on the data obtained from histology (squamous vs non-squamous) independent proportional values
6 Resolution on crizotinib of 16 June 2016
7 Resolution on nivolumab of 20 October 2016
8 Dossier of the pharmaceutical company

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

In patients with NSCLC whose tumours show a high PD-L1 expression, the risk of side effects of a combination therapy compared with a monotherapy with pembrolizumab should be considered and the benefit-risk ratio of a combination therapy individually evaluated.

For women, the results show better therapeutic effects of pembrolizumab in combination with pemetrexed and platinum chemotherapy than men, especially for overall survival. This is evident from the sub-group evaluations by sex in the relevant sub-populations of the present benefit assessment. The better therapeutic effects for women are shown both compared with pemetrexed plus platinum chemotherapy (PD L1 expression < 50%, TPS) and to pembrolizumab as monotherapy (PD L1 expression ≥ 50%, TPS). This should be considered in the individual therapy decision.

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 September 2019).

The recommended dosage for pembrolizumab in monotherapy is 200 mg every 3 weeks or 400 mg every 6 weeks. The three-week therapy scheme is used to calculate the costs.

According to the product information (Cisplatin Accord (last updated: April/2015)), the dosage of cisplatin varies depending on the combination partner. According to the product information of the combination partners, the single dose of cisplatin in combination with vinorelbine or gemcitabine is 75–100 mg/m^2, in combination with docetaxel or pemetrexed, 75 mg/m^2, and in combination with paclitaxel, 80 mg/m^2.

Carboplatin is based on a cycle duration of 3 weeks. For the use of carboplatin in the off-label indication “combination therapy for advanced NSCLC”, the dosage specified in Annex VI of the Pharmaceuticals Directive is up to 500 mg/m² or AUC 6.0 (Area Under the Curve). For the use of carboplatin in combination with nab-paclitaxel, the dosage of AUC 6.0 is also used according to the product information.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year, even if the actual treatment duration is patient-individual and/or is shorter on average.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Pembrolizumab	1 x per 21-day cycle	17 cycles	1	17
+ pemetrexed	1 x per 21-day cycle	17 cycles	1	17
+ carboplatin	1 x per 21-day cycle	17 cycles	1	17
	or			
+ cisplatin	1 x per 21-day cycle	17 cycles	1	17
Appropriate comparator therapy				
Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
a) Adult patients with first-line treatment of metastatic squamous NSCLC without EGFR or ALK positive tumour mutations whose tumours express PD-L1 with a < 50% tumour proportion score (TPS)				
Cisplatin or carboplatin in combination with a third generation cytostatic agent				
Cisplatin	1 x per 21-day cycle	17 cycles	1	17
Carboplatin	1 x per 21-day cycle	17 cycles	1	17
+ vinorelbine	2 x per 21-day cycle	17 cycles	2	34
+ gemcitabine	2 x per 21-day cycle	17 cycles	2	34
+ docetaxel	1 x per 21-day cycle	17 cycles	1	17
+ paclitaxel	1 x per 21-day cycle	17 cycles	1	17
+ pemetrexed	1 x per 21-day cycle	17 cycles	1	17

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Carboplatin in combination with nab-paclitaxel				
Carboplatin	1 x per 21-day cycle	17 cycles	1	17
+ nab-paclitaxel	3 x per 21-day cycle	17 cycles	3	51
b) Adult patients with first-line treatment of metastatic squamous NSCLC without EGFR or ALK positive tumour mutations whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS)				
Pembrolizumab	1 x per 21-day cycle	17 cycles	1	17

Usage and consumption:

The body surface calculated using the Du Bois formula using an average body weight of 77.0 kg and an average body height of 1.72 m (according to the 2017 microcensus) = 1.90 m² (calculated to 2 decimal places). Differences between women and men were not to be considered because of the therapeutic indication. [9]

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual mean consumption according to potency
Medicinal product to be assessed					
Pembrolizumab	200 mg	200 mg	2 × 100 mg -	17	34 × 100 mg
Pemetrexed	500 mg/m² = 950 mg	950 mg	2 × 500 mg	17	34 × 500 mg
+ carboplatin	500 mg/m² = 950 mg	950 mg	1 × 600 mg + 1 × 450 mg	17	17 × 600 mg + 17 × 450 mg
	or				

[9] https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual mean consumption according to potency
+ cisplatin	75 mg/m² = 142.5 mg	142.5 mg	1 × 100 mg + 1 × 50 mg	17	17 × 100 mg + 17 × 50 mg
Appropriate comparator therapy					
a) Adult patients with first-line treatment of metastatic squamous NSCLC without EGFR or ALK positive tumour mutations whose tumours express PD-L1 with a < 50% tumour proportion score (TPS)					
Cisplatin or carboplatin in combination with a third generation cytostatic agent					
Cisplatin	75 mg/m² = 142.5 mg	142.5 mg	1 × 100 mg + 1 × 50 mg	17	17 × 100 mg + 17 × 50 mg
	80 mg/m² = 152 mg	152 mg	1 × 100 mg + 1 × 50 mg + 1 × 10 mg	17	17 × 100 mg + 17 × 50 mg + 17 × 10 mg
	100 mg/m² = 190 mg	190 mg	2 × 100 mg	17	34 × 100 mg
Carboplatin	500 mg/m² = 950 mg	950 mg	1 × 600 mg + 1 × 450 mg	17	17 × 600 mg + 17 × 450 mg
+ vinorelbine	25 mg/m² = 47.5 mg	47.5 mg	1 × 50 mg	34	34 × 50 mg
	30 mg/m² = 57 mg	57 mg	1 × 50 mg + 1 × 10 mg	34	34 × 50 mg + 34 × 10 mg
+ gemcitabine	1,250 mg/m² = 2,375 mg	2,375 mg	1 x 2,000 mg + 2 x 200 mg	34	34 × 2,000 mg +

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual mean consumption according to potency
					68 × 200 mg
+ docetaxel	75 mg/m² = 142.5 mg	142.5 mg	1 × 160 mg	17	17 × 160 mg
+ paclitaxel	175 mg/m² = 332.5 mg	332.5 mg	2 × 100 mg + 1 × 150 mg	17	34 × 100 mg + 17 × 150 mg
+ pemetrexed	500 mg/m² = 950 mg	950 mg	2 × 500 mg	17	34 × 500 mg
Carboplatin in combination with nab-paclitaxel					
Carboplatin	500 mg/m² = 950 mg	950 mg	1 × 600 mg + 1 × 450 mg	17	17 × 600 mg + 17 × 450 mg
+ nab-paclitaxel	100 mg/m² = 190 mg	190 mg	2 × 100 mg	51	102 × 100 mg
b) <u>Adult patients with first-line treatment of metastatic squamous NSCLC without EGFR or ALK positive tumour mutations whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS)</u>					
Pembrolizumab	200 mg	200 mg	2 × 100 mg -	17	34 × 100 mg

<u>Costs:</u>

Costs of the medicinal product:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail 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 pharmaceutical costs were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

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 100 mg	1 vial	€ 3,234.94	€ 1.77	€ 181.48	€ 3,051.69
Carboplatin 600 mg	1 vial	€ 300.51	€ 1.77	€ 13.74	€ 285.00
Carboplatin 450 mg	1 vial	€ 227.91	€ 1.77	€ 10.29	€ 215.85
Cisplatin 100 mg	1 vial	€ 76.26	€ 1.77	€ 3.10	€ 71.39
Cisplatin 50 mg	1 vial	€ 47.37	€ 1.77	€ 1.73	€ 43.87
Pemetrexed 500 mg	1 vial	€ 2,533.24	€ 1.77	€ 558.64	€ 1,972.83
Appropriate comparator therapy					
Carboplatin 600 mg	1 vial	€ 300.51	€ 1.77	€ 13.74	€ 285.00
Carboplatin 450 mg	1 vial	€ 227.91	€ 1.77	€ 10.29	€ 215.85
Cisplatin 100 mg	1 vial	€ 76.26	€ 1.77	€ 3.10	€ 71.39
Cisplatin 50 mg	1 vial	€ 47.37	€ 1.77	€ 1.73	€ 43.87
Cisplatin 10 mg	1 vial	€ 17.20	€ 1.77	€ 0.30	€ 15.13
Docetaxel 160 mg	1 vial	€ 1,397.30	€ 1.77	€ 175.44	€ 1,220.09
Gemcitabine 2,000 mg	1 vial	€ 193.90	€ 1.77	€ 8.68	€ 183.45
Gemcitabine 200 mg	1 vial	€ 28.51	€ 1.77	€ 0.83	€ 25.91
nab-paclitaxel	1 vial	€ 429.03	€ 1.77	€ 23.15	€ 404.11
Paclitaxel 100 mg	1 vial	€ 360.21	€ 1.77	€ 16.57	€ 341.87
Paclitaxel 150 mg	1 vial	€ 535.25	€ 1.77	€ 24.88	€ 508.60
Pembrolizumab	1 vial	€ 3,234.94	€ 1.77	€ 181.48	€ 3,051.69
Pemetrexed	1 vial	€ 2,533.24	€ 1.77	€ 558.64	€ 1,972.83
Vinorelbine 50 mg	1 vial	€ 152.31	€ 1.77	€ 6.71	€ 143.83
Vinorelbine 10 mg	1 vial	€ 38.57	€ 1.77	€ 1.31	€ 35.49
Abbreviations: ***					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 September 2019

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

Non-prescription medicinal products are subject to the regulations on the prescribability of non-prescription medicinal products (OTC medicinal products) at the expense of statutory health

insurance. These medicinal products are not subject to the current medicinal product price regulation but rather, in accordance with Section 129, paragraph 5a of the German Social Code, Book V, (SGB V) when a non-prescription medicinal product is sold and invoiced in accordance with Section 300 SGB V, for the insured person, a pharmaceutical selling price in the amount of the selling price of the pharmaceutical company – plus the surcharges pursuant to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the 31 December 2003 version – shall apply.

Cost per package	Costs after deduction of statutory rebates[10]	Cost per service[11]	Treatment days per year	Cost per patient per year
Cisplatin				
Antiemetic 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.				
Forced diuresis with mannitol 10% infusion solution, 37.5 g/day				
10 × 500 ml: € 102.36	€ 93.10 (€ 5.12; € 4.14)	€ 9.31	17	€ 158.27
Hydration: sodium chloride 0.9% infusion solution, 3–4.4 l/day				
10 × 1,000 ml: € 35.47 10 × 500 ml: € 22.72	€ 32.58 (€ 1.77; € 1.12) € 20.89 (€ 1.14; € 0.69)	€ 9.77 – 15.12	17	€ 166.16 – 257.06
Pemetrexed				
Pre-medication: Dexamethasone 2 x 4 mg/day, oral				
100 × 4 mg: € 79.21 (FB)	€ 72.04 (€ 1.77; € 5.40)	€ 1.44	51	€ 73.48
Folic acid: 350 – 1,000 µg/day[12], oral				
100 x 400 µg: € 15.55	€ 12.63 (€ 0.78; € 2.14)	€ 0.13 – 0.25	365	€ 46.10 – 92.20
Vitamin B12: 1,000 µg/day, i.m.				
10 x 1,000 µg: € 7.40 (FB)	€ 6.71 (€ 0.37; € 0.32)	€ 0.67	6	€ 4.03
Paclitaxel				
Pre-medication: Dexamethasone 2 x 20 mg/day, oral				
20 × 20 mg: € 53.75 (FB)	€ 51.98 (€ 1.77; € 0.00)	€ 5.20	17	€ 88.37
Antihistamine: Dimetindene 1 mg per 10 kg BW, i.v.				
5 × 4 mg:	€ 14.82	€ 5.93[13]	17	€ 100.78

10 Section 130 SGB V and Section 130a SGB V

11 Proportionate costs of costs per package for consumption per treatment day

12 The cost of folic acid is calculated on the basis of the single dose of 400 µg of the non-divisible tablets available for cost calculation, based on a dose range of 400–800 µg per day, even if a dose range of 350–1000 µg is specified in the product information.

13 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 used as a basis (average height: 1.72 m, average body weight: 77 kg).

€ 18.56	(€ 1.77; € 1.97)			
Ranitidine: 50 mg/day, i.v.				
5 × 50 mg: € 15.02	€ 13.06 (€ 1.77; € 0.19)	€ 2.61	17	€ 44.40

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 retail price publicly accessible in the directory services in accordance with 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: arbitral award to determine the mg prices for parenteral preparations from proprietary medicinal products in oncology in the Hilfstaxe according to Section 129, paragraph 5c, sentences 2–5 SGB V of 19 January 2018), surcharges for the production of parenteral preparations containing cytostatic products of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall be payable. These additional costs are not added to the pharmacy retail 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 production and is only an approximation of the treatment costs. This presentation does not take into account, for example, the discounts 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 7 November 2017.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. At its session on 5 September 2018, the working group Section 35a redefined the appropriate comparator therapy.

On 28 March 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 2 VerfO.

By letter dated 29 March 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.

Source: German Federal Office For Statistics, Wiesbaden 2018: https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koermasse5239003179004.pdf?__blob=publicationFile

The dossier assessment by the IQWiG was submitted to the G-BA on 27 June 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 1 July 2019. The deadline for submitting written statements was 22 July 2019.

The oral hearing was held on 5 August 2019.

By letter dated 5 August 2019, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 20 August 2019.

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 10 September 2019, and the proposed resolution was approved.

At its session on 19 September 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	7 November 2017	Determination of the appropriate comparator therapy
Working group Section 35a	5 September 2018	Adjustment of the AWG according to positive opinion Confirmation of the appropriate comparator therapy
Working group Section 35a	31 July 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	5 August 2019	Conduct of the oral hearing and Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	13 August 2019 20 August 2019 3 September 2019	Consultation on the dossier assessment by the IQWiG and the evaluation of the written statement procedure
Subcommittee Medicinal product	10 September 2019	Concluding discussion of the proposed resolution
Plenum	19 September 2019	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 19 September 2019

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

Prof Hecken