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, squamous, first line, combination with carboplatin and (nab-) paclitaxel)

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 11 March 2019, pembrolizumab (KEYTRUDA®) received marketing authorisation for a new therapeutic indication:

"KEYTRUDA, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults."

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 2 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1 number 2 VerfO on 28 March 2019.

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 carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy for pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults is:

a) Adult patients with first-line treatment of metastatic squamous NSCLC 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
   - Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel; cf Annex VI to Section K of the Pharmaceuticals Directive)

     or
   - Carboplatin in combination with nab-paclitaxel

b) Adult patients with first-line treatment of metastatic squamous NSCLC whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS[2]):
   - Pembrolizumab as monotherapy

<u>Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:</u>

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:

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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

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. With regard to the authorisation status, the active ingredients cisplatin, docetaxel, gemcitabine, ifosfamid, mitomycin, nab-paclitaxel, paclitaxel, vindesin, and vinorelbine and the monoclonal antibodies necitumumab and pembrolizumab are available, whereby in the present therapeutic indication, carboplatin is authorised in combination with nab-paclitaxel and is also prescribable off-label.

On 2. For the present therapeutic indication, it is assumed that the patients do not have an indication for definitive local therapy. A non-medicinal treatment can thus not be considered in the present therapeutic indication.

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

- Necitumumab (EGFR-expressing NSCLC): Resolution of 15 September 2016 on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V
- 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
- 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 generally accepted state of medical knowledge for the indication was established by means of a search for guidelines as well as systematic reviews of clinical studies.

Because, according to the state of medical knowledge, mutations that can be treated (e.g. activating EGFR mutations or ALK translocations) in NSCLC with squamous histology are rather isolated cases in the present therapeutic indication, corresponding mutation-specific therapy options were not considered as appropriate comparator therapy.

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[2]).

a) Adult patients with first-line treatment of metastatic squamous NSCLC whose tumours express PD-L1 with a < 50% tumour proportion score (TPS[2]):
According to the evidence available, platinum-based combination chemotherapy with a third-generation cytostatic agent is the standard treatment for the first-line treatment of metastatic squamous NSCLC with a PD-L1 expression < 50%. The active ingredients paclitaxel, gemcitabine, docetaxel, and vinorelbine are authorised for use in this therapeutic indication, although no preference can be

derived for a particular combination. 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 appropriate therapeutic option in the therapeutic indication.

Because pembrolizumab is used in combination with carboplatin and either paclitaxel or nab-paclitaxel in this therapeutic indication, it can be assumed that the patients are generally suitable for combination chemotherapy and that monochemotherapies cannot be considered as an appropriate comparator therapy.

b) Adult patients with first-line treatment of metastatic squamous NSCLC whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS[2]):
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[2]).

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 is assessed as follows:

a) Adult patients with first-line treatment of metastatic squamous NSCLC whose tumours express PD-L1 with a < 50% tumour proportion score (TPS[2]):

Hint for a considerable additional benefit.

Justification:

The benefit assessment is based on the data from the RCT KEYNOTE 407 submitted in the dossier of the pharmaceutical company.

KEYNOTE 407 is a randomised, double-blind, controlled, parallel group study, which has been ongoing since August 2016 and compares pembrolizumab in combination with carboplatin and (nab-) paclitaxel with carboplatin in combination with (nab-) paclitaxel. Of a total of 559 patients, 278 patients in the intervention arm and 281 patients in the comparator

arm were stratified by type of taxane-based chemotherapy, PD-L1 expression (< 1% vs ≥ 1%), and geographic region. The study included adults with histologically or cytologically confirmed squamous NSCLC without systemic pretreatment in the metastatic stage. PD-L1 expression was measured immunohistochemically and expressed as TPS. From the ongoing study, the 1st data cut-off of 27 October 2017 (the planned first interim analysis of the endpoint objective response rate after approximately 200 patients have been observed for 28 weeks) and the 2nd data cut-off of 3 April 2018 (a pre-specified second interim analysis after approximately 332 occurred PFS events) are available. Furthermore, according to the study protocol, a third interim analysis is planned after reaching approx. 415 PFS events and the final data cut-off for overall survival after reaching approx. 361 deaths. The present benefit assessment is based on the 2nd data cut-off of 3 April 2018.

Patients were treated until disease progression, complete response, occurrence of unacceptable side effects, or discontinuation of the study at the discretion of the physician or patient. With regard to the type of follow-up therapy, there was no restriction in either arm. If suitable, a change from a comparator arm to a pembrolizumab monotherapy was permitted after disease progression. At the time of the 2nd data cut-off of 3 April 2018, 26.7% of the patients had switched from the comparator arm to pembrolizmab monotherapy in accordance with the study protocol. Censoring took place at the time of the respective data cut-off.

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 157 patients in the intervention arm and 153 patients in the control arm.

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 407 study, overall survival was defined as the period from randomization to death of any cause.

There is a statistically significant difference between pembrolizumab in combination with carboplatin-based chemotherapy over carboplatin-based chemotherapy (hazard ratio (HR): 0.56; [95% confidence interval (CI): 0.38; 0.82]; p value = 0.003). At the time of the data cut-

off of 3 April 2018, the median survival time was 14.4 months for the assessment-relevant TPC sub-population with PD-L1 expression < 50% (TPS) in the intervention arm and 11.1 months in the comparator arm and thus differed by an absolute difference of 3.3 months between the study arms in favour of the intervention.

Based on the results of the KEYNOTE 407 study, the overall survival endpoint was significantly improved for pembrolizumab in combination with carboplatin-based chemotherapy compared with carboplatin-based chemotherapy.

Morbidity

Symptomology

The symptom scales of the EORTC QLQ-C30 and EORTC QLQ-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.

For the endpoint dysphagia surveyed by EORTC QLQ-LC13, there is a statistically significant difference in favour of pembrolizumab in combination with carboplatin and (nab-) paclitaxel (HR: 0.52; 95% CI [0.31; 0.86]; p = 0.011).

Health status

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 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 the treatment arms, neither on the basis of an MID of 7 nor of 10 points.

Quality of life

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.

For the endpoint physical function, there is a statistically significant difference in favour of pembrolizumab in combination with carboplatin and (nab-) paclitaxel (HR: 0.71; 95% CI [0.52; 0.96]; p = 0.028).

Side effects

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

For the endpoints “serious adverse events (SAE)” and “immune-mediated SAE”, there are no usable statements. The background is that the therapy changers from the control arm to the permitted pembrolizumab monotherapy were only included in the evaluation of the event time analysis until the time of the therapy change (i.e. until 21 days after discontinuation of therapy in the control arm), whereas the follow-up of the endpoints “SAE” and “immune-mediated SAE” was 90 days as planned. Because a relevant proportion of therapy changers amounting to 23% of the control arm) is present on pembrolizumab monotherapy, which is affected by this premature censoring, the data available are not usable.

For the endpoint AE (CTCAE grade ≥ 3), there is a statistically significant difference to the advantage of pembrolizumab in combination with carboplatin and (nab-) paclitaxel (HR: 0.69; 95% CI [0.53; 0.90]; p = 0.006).

For the endpoint immune-mediated AE, there is a statistically significant difference to the disadvantage of pembrolizumab in combination with carboplatin and (nab-) paclitaxel (HR: 3.09; 95% CI [1.66; 5.77]; p < 0.001).

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

Overall assessment

For the benefit assessment of pembrolizumab in combination with carboplatin and (nab-) paclitaxel for the first-line treatment of adult patients with metastatic squamous NSCLC and a PD-L1 expression of < 50% (TPS), the results on overall survival, morbidity, health-related quality of life, and side effects from the KEXNOTE 407 study are available.

In the endpoint category mortality, there is a statistically significant difference for overall survival between the study arms; the median overall survival in the intervention arm is extended by 3.3 months. Pembrolizumab in combination with carboplatin and (nab-) paclitaxel leads to a significant improvement of overall survival compared with carboplatin and (nab-) paclitaxel.

Advantages of pembrolizumab in combination with carboplatin and (nab-) paclitaxel can also be observed in terms of morbidity. This shows a positive effect in the symptomology because of the reduction of the symptom dysphagia.

For health-related quality of life, an advantageous effect for pembrolizumab in combination with carboplatin and (nab-) paclitaxel is shown in the functional scale of physical function.

In the endpoint category side effects there are no usable statements for serious adverse events (SAE) and for the specific adverse event of the immune-mediated SAE. In addition, pembrolizumab in combination with carboplatin and (nab-) paclitaxel shows a reduction of AE (CTCAE grade ≥ 3) and an increase of immune-mediated AE in the area of specific AE.

Overall, the G-BA found a considerable additional benefit for pembrolizumab in combination with carboplatin and (nab-) paclitaxel over carboplatin and (nab-) paclitaxel based on the overall survival endpoint.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the randomized, double-blind controlled KEYNOTE 407 study. The risk of bias at the study level is classified as low.

At the endpoint level, the bias risk of bias for the endpoints overall survival is also considered low.

Because of the lack of usable evaluations on the endpoints serious adverse events (SAE) and immune-mediated SAE, the KEYNOTE 407 study does not allow a full assessment of the endpoint category side effects. There is thus a relevant uncertainty when determining the

extent of the additional benefit. 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 whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS[2]):

An additional benefit is not proven.

Justification:

In the absence of a direct comparative study to demonstrate an additional benefit for patient group b), the pharmaceutical company presents an adjusted indirect comparison in the dossier. The RCT KEYNOTE 407 is found on the intervention side and the RCT KEYNOTE 042 is found on the appropriate comparator therapy side, whereby the bridge comparator consists of carboplatin-based chemotherapy of carboplatin in combination with (nab-) paclitaxel.

The KEYNOTE 407 RCT was described in the section on patient population a).

KEYNOTE 042 is a randomized, open, controlled study that started in November 2014 and is currently ongoing. Adult patients with histologically or cytologically confirmed locally advanced or metastatic NSCLC without systematic pretreatment with PD-L1 tumour expression ≥ 1% were included. 1274 patients stratified by histology, geographical region, EGOC-PS, 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. Patients were treated until disease progression, until unacceptable side effects occurred, until the study was discontinued at the discretion of the investigator or the patient, or until complete response. In both treatment arms, the patients could be treated with follow-up therapies after discontinuation of the study medication. In the case of disease progression and corresponding suitability, a change from the comparison group to the intervention group was not explicitly part of the study design. For the indirect comparison, the study population of the KEYNOTE 042 study was restricted to patients with squamous NSCLC in the metastatic stage for whom a therapy carboplatin in combination with paclitaxel was defined as the platinum-based chemotherapy prior to randomisation. From the KEYNOTE 024 study, also identified in connection with the implementation of the indirect comparison, only a sub-population of six patients would be relevant. Because of the low number of patients in the KEYNOTE 024 study, the pharmaceutical company did not include these patients in the indirect comparison.

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 in both studies. 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 55 or 57 patients in the intervention arm for KEYNOTE 407 or KEYNOTE 042 and 53 or 63 patients in the comparator arm for KEYNOTE 407 or KEYNOTE 042.

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.

When assessing the indirect comparison presented, it should be taken into account that not all patient-relevant endpoints have usable evaluations from the indirect comparison. Thus, evaluations in the endpoint categories morbidity and health-related quality of life are completely absent because endpoints of these categories were not collected in the KEYNOTE 042 study. In addition, in the endpoint category side effects in particular, evaluations of serious adverse events and specific adverse events are missing.

On the other hand, it must be considered that the KEYNOTE 042 study is an open-ended study. A higher risk of bias can thus be assumed on the side of the comparative therapy than on the side of the intervention for further endpoints in the category side effects.

Furthermore, taking into account the fact that results from adjusted, indirect comparisons per se show little certainty of results, the G-BA therefore comes to the overall conclusion that in the present case it is not possible to weigh up positive and negative effects from the indirect comparison submitted. An additional benefit of pembrolizumab in combination with carboplatin and (nab-) paclitaxel compared with pembrolizumab is not proven.

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 carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults.”

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

a) Adult patients with first-line treatment of metastatic squamous NSCLC whose tumours express PD-L1 with a < 50% tumour proportion score (TPS)

and

b) Adult patients with first-line treatment of metastatic squamous NSCLC whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS).

About patient group a)

The G-BA determined cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel) *or* carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel; *cf* Annex VI to Section K of the Pharmaceuticals Directive) *or* carboplatin in combination with nab-paclitaxel to be an appropriate comparator therapy.

For this patient group, the pharmaceutical company presents the results of the randomised, double-blind, controlled KEYNOTE 407 study in which pembrolizumab in combination with carboplatin and (nab-) paclitaxel is compared with carboplatin in combination with (nab-) paclitaxel. The benefit assessment is based on all patients who were treated according to the criteria of the AM-RL.

In the endpoint category mortality, there is a statistically significant difference for overall survival between the study arms; the median overall survival in the intervention arm is extended by 3.3 months. There is a significant improvement in overall survival.

Advantages of pembrolizumab in combination with carboplatin and (nab-) paclitaxel can also be observed in terms of morbidity (reduction of the symptom of dysphagia) and in health-related quality of life (beneficial effect on physical function).

In the endpoint category side effects there are no usable statements for serious adverse events (SAE) and for the specific adverse event of the immune-mediated SAE. In addition, pembrolizumab in combination with carboplatin and (nab-) paclitaxel shows a reduction of AE (CTCAE grade ≥ 3) and an increase of immune-mediated AE in the area of specific AE.

In the overall view, the G-BA notes a considerable additional benefit based mainly on the advantage in the overall survival endpoint.

However, the data are limited, in particular because of uncertainties regarding inappropriate evaluations of some endpoints in the side effects category. As a result, 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 of the randomised, double-blind, controlled phase III KEYNOTE 407 study (pembrolizumab in combination with carboplatin and (nab-) paclitaxel vs. carboplatin and (nab-) paclitaxel) and the randomized, open, controlled KEYNOTE 042 study (pembrolizumab vs platinum-based chemotherapy) via the bridge comparator of carboplatin-based chemotherapy.

Because of the lack of numerous evaluations of patient-relevant endpoints in indirect comparisons and taking into account the fact that results from adjusted, indirect comparisons per se show a low degree of certainty of results, it is not possible to conclusively weigh up positive and negative effects. An additional benefit of pembrolizumab in combination with carboplatin and (nab-) paclitaxel compared with pembrolizumab is not proven.

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

In order to enable a consistent consideration of the number of patients 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 G-BA uses the following derivation of patient numbers:

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 six 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. A squamous histology is present in 35.9% of Stage IIIB/IV NSCLC patients. [5]

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

5a. The proportion of patients with Stage IV NSCLC with PD-L1 expressing tumours (TPS < 50%) is 71.1%. [4]

5b. The proportion of patients with Stage IV NSCLC with PD-L1 expressing tumours (TPS ≥ 50%) is 28.9%. [4]

6. Number of SHI patients: 85.9%. [6]

For

a) adult patients with first-line treatment of metastatic squamous NSCLC whose tumours express PD-L1 with a < 50% tumour proportion score (TPS):

   this results in approx. 3800 to 3960 patients

b) adult patients with first-line treatment of metastatic squamous NSCLC whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS):

   this results in approx. 1540 to 1610 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: 11 June 2019):

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

[3] Resolution on osimertinib of 17 January 2019
[4] Resolution on pembrolizumab of 3 August 2017
[5] Resolution on afatinib of 20 October 2016
[6] Dossier of the pharmaceutical company

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.

According to the requirements for risk minimisation activities in the EPAR (European Public Assessment Report), the pharmaceutical company must provide the following information material on pembrolizumab:

- Training and information material for doctors/medical professionals
- Training and information material for the patient

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 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, 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
+ carboplatin	1 x per 21-day cycle	17 cycles	1	17
+ nab-paclitaxel	3 x per 21-day cycle	17 cycles	3	51
	or			
+ paclitaxel	1 x per 21-	17 cycles	1	17

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
	day cycle			
Appropriate comparator therapy				
a) Adult patients with first-line treatment of metastatic squamous NSCLC whose tumours express PD-L1 with a < 50% tumour proportion score (TPS[2])				
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
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 whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS[2])				
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.[7]

[7] 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
Medicinal product to be assessed					
Pembrolizumab	200 mg	200 mg	2 × 100 mg -	17	34 × 100 mg
Carboplatin	500 mg/m^2 = 950 mg	950 mg	1 × 600 mg + 1 × 450 mg	17	17 × 600 mg + 17 × 450 mg
+ nab-paclitaxel	100 mg/m^2 = 190 mg	190 mg	2 × 100 mg	51	102 × 100 mg
	or				
+ paclitaxel	175 mg/m^2 = 332.5 mg	332.5 mg	2 × 100 mg + 1 × 150 mg	17	34 × 100 mg + 17 × 150 mg
Appropriate comparator therapy					
a) Adult patients with first-line treatment of metastatic squamous NSCLC whose tumours express PD-L1 with a < 50% tumour proportion score (TPS^2)					
Cisplatin or carboplatin in combination with a third generation cytostatic agent					
Cisplatin	75 mg/m^2 = 142.5 mg	142.5 mg	1 × 100 mg + 1 × 50 mg	17	17 × 100 mg + 17 × 50 mg
	80 mg/m^2 = 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/m^2 = 190 mg	190 mg	2 × 100 mg	17	34 × 100 mg
Carboplatin	500 mg/m^2 = 950 mg	950 mg	1 × 600 mg + 1 × 450 mg	17	17 × 600 mg + 17 × 450 mg
+ vinorelbine	25 mg/m^2 = 47.5 mg	47.5 mg	1 × 50 mg	34	34 × 50 mg
	30 mg/m^2 = 57 mg	57 mg	1 × 50 mg + 1 × 10 mg	34	34 × 50 mg + 34 × 10 mg
+ gemcitabine	1250 mg/m^2 = 2375 mg	2375 mg	1 × 2000 mg + 2 × 200 mg	34	34 × 2000 mg + 68 × 200 mg
+ docetaxel	75 mg/m^2 = 142.5 mg	142.5 mg	1 × 160 mg	17	17 × 160 mg
+ paclitaxel	175 mg/m^2 = 332.5 mg	332.5 mg	2 × 100 mg + 1 × 150 mg	17	34 × 100 mg + 17 × 150 mg
Carboplatin in combination with nab-paclitaxel					
Carboplatin	500 mg/m^2 = 950 mg	950 mg	1 × 600 mg + 1 × 450 mg	17	17 × 600 mg + 17 × 450 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
+ nab-paclitaxel	100 mg/m^2 = 190 mg	190 mg	2 × 100 mg	51	102 × 100 mg
b) Adult patients with first-line treatment of metastatic squamous NSCLC whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS^2)					
Pembrolizumab	200 mg	200 mg	2 × 100 mg -	17	34 × 100 mg

Costs:

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
nab-paclitaxel	1 vial	€ 429.03	€ 1.77	€ 23.15	€ 429.03
Paclitaxel 100 mg	1 vial	€ 360.21	€ 1.77	€ 16.57	€ 360.21
Paclitaxel 150 mg	1 vial	€ 535.25	€ 1.77	€ 24.88	€ 535.25
Appropriate comparator therapy					

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
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
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[8]	Cost per service[9]	Treatment days per year	Cost per patient per year
Cisplatin				
Antiemetic treatment				
In clinical practice, appropriate antiemetic 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
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: € 18.56	€ 14.82 (€ 1.77; € 1.97)	€ 5.93[10]	17	€ 100.78
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

8 Section 130 SGB V and Section 130a SGB V

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

10 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). Source: German Federal Office For Statistics, Wiesbaden 2018: https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile

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 29 January 2019.

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.

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	29 January 2019	Determination 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