Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Pembrolizumab (New Therapeutic Indication: Colorectal cancer with MSI-H or dMMR, first-line)

of 16 September 2021

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 studies 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 benefits,
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. Costs of therapy for the statutory health insurance,
6. Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient pembrolizumab (KEYTRUDA®) was listed for the first time on 15 August 2015 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 21 January 2021, pembrolizumab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the commission of 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 16 September 2020, the pharmaceutical company submitted an application to merge the evaluation procedures of pembrolizumab according to Section 35a, paragraph 5b SGB V. At its session on 5 November 2020, the G-BA approved the application for a merger in compliance with Section 35a, paragraph 5b SGB V.

On 30 March 2021, the pharmaceutical company has 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 as monotherapy is indicated for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults".

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de), on 1 July 2021, thus initiating the written statement procedure. In addition, an oral hearing was also held.

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

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

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

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

Colorectal cancer (CRC)

KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults.

Therapeutic indication of the resolution (resolution from 16.09.2021):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer eligible for intensive therapy; first-line treatment

1 General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Appropriate comparator therapy for pembrolizumab as monotherapy:

A patient-individual treatment depending on the all-RAS mutation status, the location of the primary tumour, as well as the risk of bevacizumab-induced toxicity under the selection of

- combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX)

- combination therapy of 5-fluorouracil + folinic acid + irinotecan (FOLFIRI)

- combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) and an anti-EGFR therapy (cetuximab or panitumumab) - (only for patients with wild-type RAS)

- combination therapy of 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) and an anti-EGFR therapy (cetuximab or panitumumab) - (only for patients with wild-type RAS)

- combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) and bevacizumab

- combination therapy of 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) and bevacizumab

b) Adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer not eligible for intensive therapy; first-line treatment.

Appropriate comparator therapy for pembrolizumab as monotherapy:

- 5-fluorouracil + folinic acid ± bevacizumab

or

- capecitabine ± bevacizumab

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

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered 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 Federal Joint Committee has already determined the patient-relevant benefit shall be preferred.

4. Comparative therapy should be part of the appropriate therapy in the therapeutic indication according to the generally accepted state of medical knowledge.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1.

In terms of authorisation status, the active ingredients capecitabine, 5-fluorouracil, oxaliplatin, calcium folinate, mitomycin, irinotecan, bevacizumab, panitumumab and cetuximab are available for the first-line therapy of non-resectable or metastatic colorectal cancer.

on 2.

A non-medicinal treatment cannot be considered in this therapeutic indication.

on 3.

For first-line treatment in the therapeutic indication, no resolutions of the G-BA for medicinal products are available.

on 4.

The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication.

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

Among the approved active ingredients listed under 1.), only certain active ingredients named below will be included in the appropriate comparator therapy, considering the evidence on therapeutic benefit, the guideline recommendations and the reality of health care provision.

According to the available evidence, there are no current recommendations for mitomycin in the first-line treatment of metastatic colorectal cancer.

According to the available evidence, a fluoropyrimidine-based therapy regimen should generally be selected for the first-line treatment of non-resectable or metastatic colorectal cancer in patients who are eligible for intensive chemotherapy due to their general condition (no severe comorbidity). Evidence is available for the combination therapies consisting of 5-fluorouracil, folinic acid and oxaliplatin (FOLFOX) and 5-fluorouracil, folinic acid and irinotecan (FOLFIRI). In contrast, there is insufficient evidence for combining a fluoropyrimidine-based therapy regimen with oxaliplatin and irinotecan (FOLFOXIRI).

In addition, the anti-EGFR antibodies cetuximab and panitumumab (if a wild-type RAS is present) and the anti-VEGF antibody bevacizumab are further treatment options approved for the present therapeutic indication in first-line therapy, each of which can be combined with the fluoropyrimidine-based combination chemotherapies.

Evidence suggests that bevacizumab may be indicated in combination with the above chemotherapy regimens in the first-line setting for patients who are suitable for intensive chemotherapy and have a RAS mutation. Whether bevacizumab shows advantages in this therapy situation is not sufficiently clarified. The current guidelines and recommendations of the scientific-medical societies indicate the treatment with bevacizumab as a treatment option. It should be taken into account that treatment with bevacizumab may be associated with a significant disadvantage in terms of adverse events. Therefore, bevacizumab should

only be considered depending on the risk for bevacizumab-induced toxicity in accordance with comorbidity, intolerances, and patient preference.

Regarding patients with wild-type RAS, the evidence recommends anti-EGFR therapy for first-line therapy in combination with FOLFOX or FOLFIRI in the presence of a primary tumour in the left-sided colon.

Thus, according to the available evidence, patient-individual criteria (all-RAS mutation status, location of the primary tumour, risk of bevacizumab-induced toxicity) exist to determine the selection of the therapeutic regimen for patients suitable for individual therapy.

For the reasons mentioned above, a patient-individual therapy selecting the fluoropyrimidine-based combination chemotherapies FOLFOX or FOLFIRI, possibly in combination with an anti-EGFR compound (cetuximab or panitumumab) or bevacizumab and depending on the criteria of RAS mutation status, primary tumour location, and toxicity profile of bevacizumab, was determined as the appropriate comparator therapy for the subgroup.

For patients who are not eligible for intensive therapy, first-line treatment of metastatic colorectal cancer with 5-fluorouracil + folinic acid or capecitabine is recommended, in each case with or without the addition of bevacizumab. In the current S3 guideline, administering dose-reduced combination chemotherapy with oxaliplatin or irinotecan is also designated a therapy option for this patient group.

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

<u>Change of the appropriate comparator therapy:</u>

Originally, the following appropriate comparator therapy was determined for patient population b):

- 5-fluorouracil + folinic acid ± bevacizumab

or

- capecitabine ± bevacizumab

or

- combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (reduced dose) ± bevacizumab

or

- combination therapy of 5-fluorouracil + folinic acid + irinotecan (reduced dose) ± bevacizumab

The deletion of the dose-reduced combination chemotherapies with oxaliplatin or irinotecan takes into account, in particular, the written statements of the scientific-medical societies submitted in the present benefit assessment procedure as well as the statements of the representatives of the scientific-medical societies in the oral hearing.

This change in the appropriate comparator therapy has no direct consequences for assessing the additional benefit for the patient population concerned b), as no suitable data for the

benefit assessment are available even after the change in the appropriate comparator therapy.

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 metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer eligible for intensive therapy; first-line treatment.

Hint for a minor additional benefit

Justification:

The benefit assessment is based on the results of the open-label, randomised, active-controlled, multicentre KEYNOTE 177 study comparing pembrolizumab with patient-individual therapy using a chemotherapy (folinic acid + 5 fluorouracil (5-FU) + oxaliplatin [FOLFOX], used as a modified regimen mFOLFOX6, or folinic acid + 5-FU + irinotecan [FOLFIRI]) ± bevacizumab or cetuximab.

Adult patients with metastatic colorectal cancer with MSI-H or dMMR tumours were included in the study. Patients were not allowed to have received previous systemic therapy in the metastatic stage.

The patients must have a good general condition, Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1, and adequate organ functioning. Therefore, it can be assumed that the patients included in the KEYNOTE 177 study were in principle eligible for intensive therapy.

A total of 307 patients were included in the KEYNOTE 177 study and randomised in a 1:1 ratio. Before randomisation, the principal investigator determined which of the above therapies the respective patient was to receive in the event of allocation to the control arm.

Co-primary endpoints in the study were overall survival and progression-free survival (PFS). Patient-relevant secondary endpoints were morbidity, health-related quality of life, and adverse events (AEs).

For the benefit assessment, the a priori planned interim analysis after approximately 209 PFS events dated 19.02.2020 from the KEYNOTE 177 study, as prepared in the dossier, was used. The final data cut-off of 19.02.2021, the results of which were subsequently submitted by the pharmaceutical company as part of the statements, was not reassessed.

Extent and probability of the additional benefit

Mortality

Overall survival

In the KEYNOTE 177 study, no statistically significant difference in overall survival was detected between the treatment groups. Thus, no additional benefit is determined for the endpoint overall survival with pembrolizumab.

Morbidity

Progression-free survival (PFS)

PFS was defined in the KEYNOTE 177 study as the time from randomisation to the time of disease progression or death from any cause, whichever occurs first. Disease or tumour progression was assessed according to the RECIST criteria version 1.1. The primary analysis is based on tumour assessment by a blinded independent review committee (BICR). The result shows a statistically significant prolongation of PFS by treatment with pembrolizumab compared to the control arm.

The PFS endpoint is a combined endpoint composed of endpoints of the Mortality and Morbidity categories. The endpoint component Mortality is already surveyed in the present study via the endpoint overall survival as an independent endpoint. The morbidity component "Disease progression" was assessed solely using imaging procedures (radiologically determined disease progression according to the RECIST criteria). Thus, morbidity is not primarily assessed based on disease symptoms but solely based on asymptomatic findings that are not directly relevant to the patient.

Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient relevance of the endpoint PFS.

The overall statement on the extent of the additional benefit remains unaffected.

Symptomatology (EORTC QLQ-C30 and EORTC QLQ-CR29)

The disease symptomatology of the study participants was assessed using the symptom scales of the cancer-specific questionnaire EORTC QLQ-C30 and the colorectal cancer-specific questionnaire EORTC QLQ-CR29.

For both questionnaires, the survey time points within treatment cycles differed between study arms. In the intervention arm, all surveys took place at the beginning of each new cycle, whereas in the control arm, surveys at weeks 9, 27, and 45 were mid-cycle. This leads to an unequal representation of the burden of treatment throughout the cycle in the study arms.

Thus, in contrast to the intervention arm, the control arm also considers surveys at a time of potentially higher treatment burden (mid-cycle survey). This results in a potential bias in favour of intervention.

Despite the criticism presented in IQWiG's dossier assessment, the pharmaceutical company does not present corresponding sensitivity analyses to assess a possible influence of the different survey time points within the treatment cycle in its statements.

Therefore, the submitted evaluations on symptomatology do not provide robust results and are therefore considered not usable.

Health status (EQ-5D VAS)

The health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. The uncertainties mentioned concerning the survey of disease symptomatology due to different survey time points between the study arms also apply to the survey of health-related quality of life using the EQ-5D VAS. In accordance with the explanations in the section on "Symptomatology", the evaluations presented on health-related quality of life are therefore also regarded as not usable.

<u>Quality of life</u>

Health-related quality of life was assessed using the functional scales of the cancer-specific questionnaire EORTC QLQ-C30 and the colorectal cancer-specific questionnaire EORTC QLQ-

CR29. The uncertainties mentioned concerning the assessment of disease symptomatology due to different survey times between the study arms also apply to the assessment of the health-related quality of life. In accordance with the explanations in the section on "Symptomatology", the evaluations presented on health-related quality of life are therefore also regarded as not usable.

Side effects

Adverse events (AEs in total)

In the KEYNOTE 177 study, 97.4% of patients in the intervention arm and approx. 99.3% of patients in the comparator arm experienced an adverse event. The results for the endpoint "Total adverse events" are only presented additionally.

Serious AEs

For the endpoint serious adverse events (SAEs), there was a statistically significant difference in the benefit of pembrolizumab compared to FOLOFX/FOLFIRI ± bevacizumab or cetuximab.

Severe AE (CTCAE grade ≥ 3)

For the endpoint severe AEs (CTCAE grade ≥ 3), there was a statistically significant difference in the benefit of pembrolizumab compared to FOLOFX/FOLFIRI ± bevacizumab or cetuximab.

Discontinuation because of AEs

There was no statistically significant difference between the treatment arms for the endpoint Discontinuation because of AEs (CTCAE grade ≥ 3).

Immune-mediated severe AEs (CTCAE grade ≥ 3)

There was no statistically significant difference between the treatment groups for the endpoint immune-mediated severe AEs (CTCAE grade ≥ 3).

Immune-mediated SAEs

For the endpoint of immune-mediated SAEs, there is a statistically significant difference to the disadvantage of pembrolizumab compared to FOLOFX/FOLFIRI ± bevacizumab or cetuximab.

Specific AEs

For the specific AEs mucositis (AEs), decreased appetite (AEs), peripheral neuropathy (AEs), peripheral sensory neuropathy (AEs), epistaxis (AEs), alopecia (AEs), palmar-plantar erythrodysesthesia syndrome (AEs), gastrointestinal disorders (severe AEs), fatigue (severe AEs), infections and infestations (severe AEs), and hypokalaemia (severe AEs), and for the endpoint blood and lymphatic system disorders (SOC, severe AEs), there is a statistically significant difference in the benefit of pembrolizumab compared to FOLOFX/FOLFIRI ± bevacizumab or cetuximab.

For the endpoint arthralgia (AEs), there is a statistically significant difference to the disadvantage of pembrolizumab compared to FOLOFX/FOLFIRI ± bevacizumab or cetuximab.

Overall, the results on side effects show predominantly positive effects for pembrolizumab compared to patient-individual therapy with FOLOFX/FOLFIRI ± bevacizumab or cetuximab. In particular, the benefits in serious adverse events and severe adverse events represent a significant improvement in therapeutic benefit. In detail, there are disadvantages in the immune-mediated SAEs and predominantly advantages in the specific AEs.

Overall assessment / conclusion

For the assessment of the additional benefit of pembrolizumab as monotherapy for the first-line treatment of high-frequency microsatellite instability (MSI-H) or with mismatch repair deficiency (dMMR) metastatic colorectal cancer, results of the KEYNOTE 177 study are available for the endpoint categories mortality, morbidity, quality of life and side effects. The study will compare with pembrolizumab as monotherapy with treatment with FOLOFX or FOLFIRI ± bevacizumab or cetuximab.

Regarding overall survival, there are no signs of statistically significant differences between the treatment groups. Thus, no additional benefit is determined for the endpoint overall survival with pembrolizumab.

For the endpoint categories morbidity and health-related quality of life, no usable data are available based on the analyses submitted by the pharmaceutical company for the measurement instruments EORTC QLQ-C30, EORTC QLQ-CR29, nor EQ-5D VAS. This is due to differences in the survey time points within the treatment cycle in the study arms, which means that the burden of treatment throughout the cycle is not reflected equally in the study arms. The pharmaceutical company does not submit corresponding sensitivity analyses to evaluate a possible influence of the different survey time points in the treatment cycle. An assessment of the effect of therapy with pembrolizumab compared to the comparator therapy on disease-specific symptomatology, health status, and health-related quality of life of patients is therefore not possible based on the data submitted by the pharmaceutical company for the benefit assessment. Thus, no additional benefit is identified for the endpoint categories morbidity and health-related quality of life.

The results on side effects show predominantly positive effects for pembrolizumab compared to patient-individual therapy with FOLOFX/FOLFIRI ± bevacizumab or cetuximab. In particular, the benefits in serious adverse events and severe adverse events represent a significant improvement in therapeutic benefit. In detail, there are disadvantages in the immune-mediated SAEs and predominantly advantages in the specific AEs.

In the overall consideration of the present results, there is a relevant difference in favour of the treatment with pembrolizumab only in the side effects. There was no statistically significant difference in overall survival, and no usable data were available for the endpoint categories morbidity and health-related quality of life. Thus, in the patient-relevant endpoint categories of mortality, morbidity and health-related quality of life, no benefit could be demonstrated for treatment with pembrolizumab compared to the comparator arm.

In the synopsis of the results and considering the therapeutic indication, the G-BA identifies a minor additional benefit for pembrolizumab as monotherapy is indicated for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer compared with the appropriate comparator therapy.

Reliability of data (probability of additional benefit)

The overall risk of bias at the study level in the randomised, open-label Phase III KEYNOTE 177 study is considered low.
The risk of bias in the endpoint overall survival is considered high due to a high rate of progression-related switching of the control arm to follow-up therapy with pembrolizumab or other anti-PD-1/PD-L1 therapy. Also, the direction of the bias cannot be determined due to the change in therapy.
The endpoint categories morbidity and health-related quality of life are given high priority in the present treatment situation. However, in the absence of usable data on these endpoints, no statements can be made regarding the impact of pembrolizumab on patient morbidity and health-related quality of life.
All in all, the available data are subject to uncertainties, which leads to a limitation of the reliability of data. The reliability of data for the additional benefit is classified in the category "hint".

b) Adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer not eligible for intensive therapy; first-line treatment

The additional benefit is not proven for pembrolizumab for the first-line treatment of adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer not eligible for intensive therapy.

Justification:

The pharmaceutical company did not present any data that would have been suitable for the assessment of the additional benefit compared with the appropriate comparator therapy.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient pembrolizumab. The therapeutic indication assessed here is as follows:

KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults.

In the therapeutic indication to be considered, 2 patient groups were distinguished:

a) Adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer eligible for intensive therapy; first-line treatment

and

b) Adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer not eligible for intensive therapy; first-line treatment.

About patient group a)

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

A patient-individual treatment depending on the all-RAS mutation status, the location of the primary tumour, as well as the risk of bevacizumab-induced toxicity under selection of

- combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX)

- combination therapy of 5-fluorouracil + folinic acid + irinotecan (FOLFIRI)

- combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) and an anti-EGFR therapy (cetuximab or panitumumab) - (only for patients with wild-type RAS)

- combination therapy of 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) and an anti-EGFR therapy (cetuximab or panitumumab) - (only for patients with wild-type RAS)

- combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) and bevacizumab

- combination therapy of 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) and bevacizumab

The results of the KEYNOTE 177 study were used to assess the additional benefit. The study compares pembrolizumab with FOLOFX or FOLFIRI ± bevacizumab or cetuximab.

Regarding overall survival, there are no signs of statistically significant differences between the treatment groups.

No usable data are available for the endpoint categories morbidity and health-related quality of life, as different survey time points in the study arms unequally reflect the burdens of the therapies in the patient-reported endpoints.

The results on side effects show predominantly positive effects for pembrolizumab. In particular, the benefits in serious adverse events and severe adverse events represent a significant improvement in therapeutic benefit.

Uncertainties exist due to a high rate of progression-related changes in therapy to a follow-up therapy not compliant with marketing authorisation as well as no usable data on the endpoint categories morbidity and health-related quality of life. The reliability of data for the additional benefit is classified in the category "hint".

In the overall consideration of the present results, there is a relevant difference in favour of the treatment with pembrolizumab only in the side effects. In the patient-relevant endpoint categories mortality, morbidity and health-related quality of life, however, no advantage can be proven for the treatment with pembrolizumab compared to the comparator arm. As a result, the G-BA found a hint of minor additional benefit compared with the appropriate comparator therapy.

About patient group b)

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

- 5-fluorouracil + folinic acid ± bevacizumab

or

- capecitabine ± bevacizumab

The pharmaceutical company did not present any data that would have been suitable for the assessment of the additional benefit compared with the appropriate comparator therapy. The additional benefit is not proven.

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

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

The number of approx. 310-560 patients reported by the pharmaceutical company for both patient groups together represent a potential underestimation because the patients who developed the disease in previous years and whose disease progressed to the metastatic stage in the current year are not taken into account.

Therefore, IQWIG performed its own calculations. For this purpose, some 13,927 to 21,800 patients are assumed for the overall incidence in stage IV - i.e. taking into account patients whose disease has progressed from an earlier stage to stage IV as well as patients with newly diagnosed diseases - analogous to the calculations in the benefit assessment resolution on encorafenib (resolution of the G-BA of 17 December 2020). The values estimated by the company are used for the percentage of patients with MSI-H or dMMR, as well as the SHI share. For the proportion values for subpopulations a) and b), the upper limits of the range calculated by the company are assumed, as all of the 10 most frequent intensive and non-intensive chemotherapies were taken into account in their derivation.

It should be noted that - especially due to the limited currentness of the data underlying the overall incidence in stage IV as well as the uncertainties in determining the MSI-H and dMMR percentages in patients with first-line metastatic colorectal cancer - these patient numbers are also subject to uncertainty.

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: 1 September 2021):
https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf

Treatment with pembrolizumab should only be initiated in patients with metastatic colorectal cancer and monitored by specialists in internal medicine, haematology, oncology, gastroenterology specialists, and specialists participating in the Oncology Agreement.

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

In accordance with the Medicines Agency requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient pass. The training material for health professionals and the patient pass contain, in particular, instructions on the management of immune-mediated side effects potentially occurring with KEYTRUDA as well as on infusion-related reactions. The prescribing doctor must discuss with the patient the risks of therapy with KEYTRUDA. The patient pass should be made available to 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 2021).

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

The average body measurements were applied for dosages depending on body weight or surface (average body height: 1.72 m, average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916)[2]

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Pembrolizumab	1 x per 21 day cycle	17.4 cycles	1	17.4
	or			
	1 x per 42 day cycle	8.7 cycles	1	8.7
Appropriate comparator therapy				
a) Adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer eligible for intensive therapy; first-line treatment				
FOLFOX (5-fluorouracil + folinic acid + oxaliplatin) ± bevacizumab or cetuximab or panitumumab				
FOLFOX 4				

2 Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Oxaliplatin	1 x on day 1 of a 14 day cycle	12	1	12
Folinic acid	1 x on day 1 + 2 of a 14 day cycle	12	2	24
5-fluorouracil	1 x on day 1 + 2 of a 14 day cycle	12	2	24
plus bevacizumab or cetuximab or panitumumab if necessary				
Bevacizumab	1 x on day 1 of a 14 day cycle	26.1	1	26.1
Cetuximab	1 x every 7 days	52.1	1	52.1
Panitumumab	1 x on day 1 of a 14 day cycle	26.1	1	26.1
FOLFOX 6				
Oxaliplatin	1 x on day 1 of a 14 day cycle	12	1	12
Folinic acid	1 x on day 1 of a 14 day cycle	12	1	12
5-fluorouracil	1 x on day 1 of a 14 day cycle	12	1	12
FOLFIRI (5-fluorouracil, folinic acid, irinotecan) ± bevacizumab or cetuximab or panitumumab[3]				
FOLFIRI				
Irinotecan	1 x on day 1 of a 14 day cycle	26.1	1	26.1
Folinic acid	1 x on day 1 of a 14 day cycle	26.1	1	26.1
5-fluorouracil	1 x on day 1 of a 14 day cycle	26.1	1	26.1

[3] In view of different FOLFIRI protocols, the dosing of the FIRE-3 study is used as an example: https://clinicaltrials.gov/ct2/show/NCT00433927 [last accessed 25.08.2021]

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
plus bevacizumab or cetuximab or panitumumab if necessary				
Bevacizumab	1 x on day 1 of a 14 day cycle	26.1	1	26.1
Cetuximab	1 x every 7 days	52.1	1	52.1
Panitumumab	1 x on day 1 of a 14 day cycle	26.1	1	26.1
b) Adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer not eligible for intensive therapy; first-line treatment.				
5-fluorouracil ± bevacizumab				
5-fluorouracil (de Gramont)				
Folinic acid	1 x on day 1 + 2 of a 14 day cycle	26.1	2	52.2
5-fluorouracil	1 x on day 1 + 2 of a 14 day cycle	26.1	2	52.2
if necessary, plus bevacizumab				
Bevacizumab	1 x on day 1 of a 14 day cycle	26.1	1	26.1
Capecitabine ± bevacizumab				
Capecitabine	2 x daily on day 1 - 14 of an 21 day cycle	17.4	14	243.6
plus bevacizumab if necessary				
Bevacizumab	1 x on day 1 of a 21 day cycle	17.4	1	17.4

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	8.7	34.8 x 100 mg
Appropriate comparator therapy					
a) Adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer eligible for intensive therapy; first-line treatment					
FOLFOX (5-fluorouracil + folinic acid + oxaliplatin) ± bevacizumab or cetuximab or panitumumab					
FOLFOX 4					
Oxaliplatin	85 mg/m^2	161.5 mg	1 x 200 mg	12	12 x 200 mg
Folinic acid	200 mg/m^2	380 mg	1 x 500 mg	24	24 x 500 mg
5-fluorouracil	400 mg/m^2	760 mg	1 x 1,000 mg	24	72 x 1,000 mg
	600 mg/m^2	1,140 mg	2 x 1,000 mg		
plus bevacizumab or cetuximab or panitumumab if necessary					
Bevacizumab	5 mg/kg KG --	385 mg -	1 x 400 mg-	26.1	26.1 x 400 mg-
	10mg/kg bw	770 mg	2 x 400 mg		52.2 x 400 mg
Cetuximab	Initial dose in week 1: 400 mg/m2 BSA	760 mg	1 x 500 mg +	1	52.1 x 500 mg +
			3 x 100 mg		3 x 100 mg
	from week 2: 250 mg/m^2	475 mg	1 x 500 mg	51.1	
Panitumumab	6mg/kg bw	462 mg	1 x 400 mg +	26.1	26.1 x 400 mg +

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
			1 x 100 mg		26.1 x 100 mg
FOLFOX 6					
Oxaliplatin	85 mg/m²	161.5 mg	1 x 200 mg	12	12 x 200 mg
Folinic acid	400 mg/m²	760 mg	1 x 800 mg	12	12 x 800 mg
5-fluorouracil	400 mg/m² 2,400 mg/m²	760 mg 4,560 mg	1 x 1,000 mg 5 x 1,000 mg	12	72 x 1,000 mg
FOLFIRI (5-fluorouracil, folinic acid, irinotecan) +/- bevacizumab or cetuximab or panitumumab					
FOLFIRI					
Irinotecan	180 mg/m²	342 mg	1 x 300 mg + 2 x 40 mg	26.1	26.1 x 300 mg + 52.2 x 40 mg
Folinic acid	400 mg/m²	760 mg	1 x 800 mg	26.1	26.1 x 800 mg
5-fluorouracil	400 mg/m² 2,400 mg/m²	760 mg 4,560 mg	1 x 1,000 mg 5 x 1,000 mg	26.1	156.6 x 1,000 mg
plus bevacizumab or cetuximab or panitumumab if necessary					
Bevacizumab	5mg/kg bw	385 mg	1 x 400 mg	26.1	26.1 x 400 mg
Cetuximab	Initial dose in week 1: 400 mg/m2 BSA	760 mg	1 x 500 mg +	1	52.1 x 500 mg +
			3 x 100 mg		3 x 100 mg
	from week 2: 250 mg/m²	475 mg	1 x 500 mg	51.1	

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Panitumumab	6mg/kg bw	462 mg	1 x 400 mg +	26.1	26.1 x 400 mg +
			1 x 100 mg		26.1 x 100 mg
b) Adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer not eligible for intensive therapy; first-line treatment.					
5-fluorouracil ± bevacizumab					
5-fluorouracil (de Gramont)					
Folinic acid	200 mg/m²	380 mg	1 x 500 mg	52.2	52.2 x 500 mg
5-fluorouracil	400 mg/m²	760 mg	1 x 1,000 mg	52.2	156.6 x 1,000 mg
	600 mg/m²	1,140 mg	2 x 1,000 mg		
plus bevacizumab if necessary					
Bevacizumab	5mg/kg bw	385 mg	1 x 400 mg	26.1	26.1 x 400 mg
Capecitabine ± bevacizumab					
Capecitabine	1,250 mg/m² = 2,375 mg	4600 mg	8 x 500 mg + 2 x 300 mg	243.6	1,948.8 x 500 mg + 487.2 x 300 mg
plus bevacizumab if necessary					
Bevacizumab	7.5mg/kg bw	577.5 mg	1 x 400 mg + 2 x 100 mg	17.4	17.4 x 400 mg + 34.8 x 100 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both based on the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined based on consumption. The required number of packs of a particular potency was first determined based on consumption

to calculate the annual treatment costs. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Pembrolizumab 100 mg	1 CIS	€ 3,037.06	€ 1.77	€ 170.17	€ 2,865.12
Appropriate comparator therapy					
Bevacizumab 100 mg	1 CIS	€ 396.75	€ 1.77	€ 21.35	€ 373.63
Bevacizumab 400 mg	1 CIS	€ 1,553.06	€ 1.77	€ 85.42	€ 1,465.87
Capecitabine 300 mg[4]	30 FCT	€ 36.09	€ 1.77	€ 1.98	€ 32.34
Capecitabine 500 mg[4]	120 FCT	€ 151.57	€ 1.77	€ 11.11	€ 138.69
Cetuximab 500 mg	1 INF	€ 1,499.40	€ 1.77	€ 82.40	€ 1,415.23
Cetuximab 100 mg	1 INF	€ 308.72	€ 1.77	€ 16.48	€ 290.47
5-fluorouracil 1,000 mg[4]	5 SFI	€ 37.18	€ 1.77	€ 2.07	€ 33.34
5-fluorouracil 1,000 mg[4]	1 SFI	€ 16.40	€ 1.77	€ 0.42	€ 14.21
Folinic acid 500 mg[4]	10 IIS	€ 1,933.89	€ 1.77	€ 153.10	€ 1,779.02
Folinic acid 500 mg[4]	5 SFI	€ 972.91	€ 1.77	€ 76.08	€ 895.06
Folinic acid 500 mg[4]	1 SFI	€ 200.69	€ 1.77	€ 15.00	€ 183.92
Folinic acid 800 mg[4]	5 SFI	€ 1,498.78	€ 1.77	€ 117.60	€ 1,379.41
Folinic acid 800 mg[4]	1 SFI	€ 304.38	€ 1.77	€ 23.20	€ 279.41
Irinotecan 40 mg	1 CIS	€ 85.32	€ 1.77	€ 9.41	€ 74.14
Irinotecan 300 mg	1 CIS	€ 573.66	€ 1.77	€ 71.20	€ 500.69
Irinotecan 500 mg	1 CIS	€ 939.85	€ 1.77	€ 44.08	€ 894.00
Oxaliplatin 200 mg	1 CIS	€ 399.05	€ 1.77	€ 18.41	€ 378.87
Panitumumab 400 mg	1 CIS	€ 2,578.74	€ 1.77	€ 144.00	€ 2,432.97

4 Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Panitumumab 100 mg	1 CIS	€ 661.22	€ 1.77	€ 36.00	€ 623.45
Abbreviations: FCT = film-coated tablets; HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; IIS = injection/infusion solution; SFI = solution for injection; INF = infusion solution					

LAUER-TAXE® last revised: 1 September 2021

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 considered 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.

According to the product information on cetuximab (Erbitux®), patients must be pre-treated with an antihistamine and a corticosteroid for at least 1 hour prior to the first administration of cetuximab. This premedication is also recommended before all further infusions. The product information does not provide any specific information why the necessary costs cannot be quantified for the premedication.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe)(Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but instead follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy sales price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 23 June 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy defined by the G-BA took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 09 February 2021.

On 30 March 2021, the pharmaceutical company submitted a dossier for the benefit assessment of pembrolizumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 31 March 2021 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 29 June 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 01 July 2021. The deadline for submitting written statements was 22 July 2021.

The oral hearing was held on 9 August 2021.

By letter dated 11 August 2021, the IQWiG was commissioned with a supplementary assessment. The addenda prepared by IQWiG was submitted to the G-BA on 27 August 2021.

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 the representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 7 September 2021, and the proposed resolution was approved.

At its session on 16 September 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Sub-committee Medicinal product	23 June 2020	Determination of the appropriate comparator therapy
Sub-committee Medicinal product	9 February 2021	New determination of the appropriate comparator therapy
Working group Section 35a	4 August 2021	Information on statements received; preparation of the oral hearing
Sub-committee Medicinal product	9 August 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	18 August 2021 1 September 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Sub-committee Medicinal product	7 September 2021	Final discussion of the draft resolution
Plenum	16 September 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 September 2021

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

Prof. Hecken