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 Nivolumab (new therapeutic indication: MSI-H or dMMR colorectal cancer, after prior Fluoropyrimidine-based combination chemotherapy, combination with Ipilimumab)

of 20 January 2022

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1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

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

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

2. Key points of the resolution

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

On 24 June 2021, nivolumab 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 European 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, 12.12.2008, p. 7).

On 21 July 2021, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5,

Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient nivolumab with the new therapeutic indication

"in combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy."

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 November 2021, 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 nivolumab compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of nivolumab.

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 Nivolumab (Opdivo) in accordance with the product information

OPDIVO in combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy.

Therapeutic indication of the resolution (resolution of 20 January 2022):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with metastatic, mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer; after prior Fluoropyrimidine-based combination therapy

A patient-individual therapy, depending on the type and number of previous therapies, RAS and BRAF mutational status, location of the primary tumour, general condition and risk of toxicity induced by anti-VEGF and anti-VEGFR agents, selecting:

- 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ± bevacizumab or aflibercept or ramucirumab
- 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ± cetuximab or panitumumab (only for patients with wild-type RAS)

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

- 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) ± bevacizumab
- Capecitabine + oxaliplatin (CAPOX) ± bevacizumab
- 5-fluorouracil + folinic acid ± bevacizumab
- Capecitabine ± bevacizumab
- Irinotecan as monotherapy
- Panitumumab as monotherapy (only for patients with wild-type RAS)
- Cetuximab as monotherapy (only for patients with wild-type RAS)
- trifluridine/ tipiracil
- Irinotecan + cetuximab (only for patients with wild-type RAS)
- Encorafenib + cetuximab (only for patients with BRAF-V600E mutation)

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

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

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the Federal Joint Committee has already determined the patient-relevant advantage 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. For the specific treatment situation of metastatic, mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer after previous fluoropyrimidine-based combination therapy, no agents are explicitly approved apart from nivolumab in combination with ipilimumab. The active ingredients 5-fluorouracil, aflibercept, bevacizumab, calcium folinate, capecitabine, cetuximab, encorafenib, ipilimumab, irinotecan, mitomycin, oxaliplatin, panitumumab, ramucirumab, regorafenib and trifluridine/tipiracil are available as monotherapy or as part of combination therapies for the treatment of metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy, which also includes dMMR or MSI-H patients.

on 2. A non-medicinal treatment cannot be considered in this treatment setting.

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

- Encorafenib - resolution of 17 December 2020
- Trifluridine/ tipiracil - resolution of 1 October 2020
- Ramucirumab - resolution of 1 September 2016
- Regorafenib - resolution of 17 March 2016
- Aflibercept - resolution of 15 August 2013

on 4. The general state of medical knowledge, on which the findings of the G-BA are based, was illustrated by systematic research 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, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of health care provision.

For the present therapeutic indication, it is assumed that there is no indication for curative treatment or that there is no primary or secondary resectability.

In addition, it is assumed for the present therapeutic indication that the patients receive an antineoplastic therapy in the respective treatment setting.

The treatment concept of metastatic colorectal cancer in the palliative treatment setting is characterised by the sequence of different lines of therapy. For first and second-line therapy, the guidelines provide defined treatment regimens that include fluoropyrimidine, oxaliplatin and/or irinotecan-containing chemotherapy regimens.

Overall, the available evidence and the statements of the scientific-medical societies in the benefit assessment procedure show that a specific standard therapy for patients with metastatic, dMMR or MSI-H colorectal cancer after previous fluoropyrimidine-based combination therapy cannot be specified.

Thus, in principle, those therapy options that represent a standard, regardless of the dMMR or MSI-H status, are considered as appropriate comparator therapy.

The present therapeutic indication addresses a treatment setting that may correspond to a second-line therapy as well as to a third-line therapy or a subsequent line of therapy, which is why the determination of the appropriate comparator therapy was based on these different treatment settings.

In the first or second-line therapy of metastatic colorectal cancer, the chemotherapy regimens 5-fluorouracil in combination with folinic acid and irinotecan (FOLFIRI) and 5-fluorouracil in combination with folinic acid and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin (CAPOX) are regularly used, which can be accordingly combined with anti-VEGF active ingredients (bevacizumab, aflibercept and ramucirumab) and anti-EGFR substances (cetuximab, panitumumab), depending on the marketing authorisation and mutational status. So far, the superiority of a specific sequence for the total population of patients with metastatic colorectal cancer has not been proven.

According to the unanimous therapy recommendations, a FOLFIRI-based therapy in the first line should be followed by a FOLFOX-based therapy in the second line and a FOLFOX-based therapy in the first line should be followed by a FOLFIRI-based therapy in the second line.

Aflibercept and ramucirumab are two anti-VEGF active ingredients that are approved in the present therapeutic indication and can be used after prior oxaliplatin-containing

chemotherapy. In the benefit assessment, an indication of a minor additional benefit was found for aflibercept compared to FOLFIRI (resolution of 15 August 2013), while an additional benefit for ramucirumab compared to FOLFIRI was not proven (resolution of 1 September 2016).

For patients with BRAF-V600E mutation, the combination of active ingredients of encorafenib and cetuximab is also available. In the resolution of 17 December 2020, a hint for a considerable additional benefit was found for this combination of active ingredients compared to FOLFIRI + cetuximab or irinotecan + cetuximab.

For the treatment of patients with metastatic colorectal cancer in the third line and subsequent lines of therapy, two therapy options are available with trifluridine/ tipiracil and regorafenib, which are recommended in the guidelines for subsequent lines of therapy.

Within the scope of the benefit assessment, a hint for a minor additional benefit. was identified for trifluridine/ tipiracil compared to best supportive care with the resolution of 1 October 2020.

The active ingredient regorafenib is currently off-label in Germany and therefore does not represent a treatment option in the context of the appropriate comparator therapy at this time. On the one hand, this is due to the fact that a regular supply of the medicinal product is not guaranteed in Germany; on the other, the benefit assessment in the resolution of 17 March 2016 did not identify any additional benefit compared to best supportive care.

In the case of a reduced general condition, certain intolerances or in more advanced treatment settings, monotherapies with 5-fluorouracil, capecitabine, irinotecan, cetuximab or panitumumab as well as the combination therapies of capecitabine and bevacizumab or 5-fluorouracil and bevacizumab are available as further treatment options according to their marketing authorisation.

With regard to the previously mentioned different therapy options that can be considered for an appropriate comparator therapy in the present therapeutic indication, the concrete treatment decision depends largely on patient-individual factors. These usually include the type and number of previous therapies, the RAS and BRAF mutational status, the location of the primary tumour, the general condition as well as the side effect profiles of the active ingredients and, in particular, the risk of toxicity induced by anti-VEGF and anti-VEGFR active ingredients.

In the overall assessment, therefore, a patient-individual therapy, depending on the type and number of previous therapies, the RAS and BRAF mutational status, the location of the primary tumour, the general condition and the risk of toxicity induced by anti-VEGF and anti-VEGFR active ingredients, was chosen from the above-mentioned therapy options.

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

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of nivolumab in combination with ipilimumab is assessed as follows:

<u>Adults with metastatic, mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer; after prior Fluoropyrimidine-based combination therapy</u>

An additional benefit is not proven.

Justification:

Data basis

The results of the CA209-6EP study were used by the pharmaceutical company for the benefit assessment. This is a comparison of individual arms from different studies, using data on nivolumab in combination with ipilimumab from the prospective CA209-142 (cohort 2) study and data from the Flatiron Health database for the appropriate comparator therapy. The CA209-6EP study investigates the endpoint of overall survival.

For statements on the endpoint categories of morbidity and health-related quality of life, before-after comparisons of the prospective CA209-142 (cohort 2) study were submitted by the pharmaceutical company.

Statements on side effects were made on the basis of a descriptive comparison. Results on nivolumab in combination with ipilimumab from the CA209-142 (cohort 2) study were compared with results from freely available study data.

CA209-142 (cohort 2, data source for the intervention arm of the CA209-6EP study)

The CA209-142 study is an ongoing, open-label, non-controlled, multicentre, prospective phase II cohort study with a total of 7 cohorts. For the CA209-6EP study, only data from cohort 2 of the CA209-142 study were considered by the pharmaceutical company. Cohort 2 comprises 119 adults with dMMR or MSI-H, metastatic or recurrent colorectal cancer after progression during or after ≥ 1 fluoropyrimidine-based combination chemotherapy or intolerance to this therapy who had an ECOG ≤ 1.

The primary endpoint of the CA209-142 study is the objective response rate. In addition, the overall survival and other patient-relevant endpoints of the endpoint categories of morbidity, health-related quality of life and side effects are assessed.

Flatiron Health database (data source for the comparator arm of the CA209-6EP study)

The CA209-6EP study uses data from the Flatiron Health database as a comparison for cohort 2 of the CA209-142 study. For this purpose, evaluations of adults with dMMR and/or MSI-H, metastatic colorectal cancer who had received at least 1 prior therapy with a fluoropyrimidine combined with oxaliplatin or irinotecan and had received standard chemotherapy in the subsequent line of therapy were used (Flatiron cohort).

Comparison data

CA209-6EP

As the primary analysis, an Inverse Probability of Treatment Weighting (IPTW) method based on the propensity score is applied by the pharmaceutical company in the dossier for the benefit assessment. Sensitivity analyses presented include an unadjusted comparison using a univariate regression model, a multivariate regression model using the confounders identified by the pharmaceutical company as covariates, a propensity score matching and an IPTW complete cases analysis.

Within the framework of the written statement procedure, the pharmaceutical company submitted, among other things, a recalculation of the indirect comparison for the endpoint of overall survival. Propensity score matching is now used as the primary analysis in the pharmaceutical company's statement. In addition, the statement provides further information

on the influence of the unconsidered potential confounders on the results of the indirect comparison.

Before-after comparisons of the CA209-142 (cohort 2) study

For the endpoint categories of morbidity and health-related quality of life, the pharmaceutical company conducted before-after comparisons with data from the CA209-142 (cohort 2) study.

Disease symptomatology and health-related quality of life will be assessed in the CA209-142 study using the EORTC QLQ-C30 cancer-specific questionnaire. The health status is assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire.

Comparison with individual arms of randomised controlled trials

For statements on side effects, freely available study data were used in the dossier for the benefit assessment of 4 different options of the appropriate comparator therapy, and these results were compared with the results for nivolumab in combination with ipilimumab from the CA209-142 (cohort 2) study. According to the pharmaceutical company, the selected 4 different options of the appropriate comparator therapy are the 4 most frequent therapies used in the patients from the Flatiron Health database (total share: 39.7%).

In the context of the written statement procedure, the pharmaceutical company also submitted further descriptive comparisons of the adverse events to other therapy options of the appropriate comparator therapy. For this purpose, freely available study data were compared with the propensity score matching population of the comparison CA209-6EP, which was subsequently submitted in the written statement procedure.

Assessment

There is no randomised controlled trial for the comparison of nivolumab in combination with ipilimumab and the appropriate comparator therapy. As the pivotal study CA209-142 is a non-controlled study, a comparison of individual arms from different studies in the form of the CA209-6EP study (cohort 2 of the CA209-142 study vs data from the Flatiron Health database), a before-after comparison of the CA209-142 study and a comparison of data from the CA209-142 study with individual arms from randomised controlled trials were performed by the pharmaceutical company for the assessment of additional benefit.

CA209-6EP

The evaluations presented in the dossier for the CA209-6EP study are not suitable for the assessment of the additional benefit of nivolumab in combination with ipilimumab especially due to relevant uncertainties arising from the identification, completeness and adjustment of the confounders:

Accordingly, the information obtained for the search for confounders is not suitable for ensuring the completeness of the results, among other things, because observational studies were possibly not taken into account as an important source for the identification of confounders. Furthermore, the selection of relevant confounders is inadequate. Thus, it is unclear why potential confounders mentioned in less than 3 publications identified by the pharmaceutical company are not taken into account. The non-consideration of the confounders "number of metastatic sites/ organs", "primary tumour resection" and "region", which were identified as relevant by the pharmaceutical company, also results in relevant uncertainties with regard to the results and the observed effects of the endpoint of overall survival of the CA209-6EP study.

In the IPTW analysis primarily used for the benefit assessment in the dossier, weighting is done according to propensity scores. The propensity scores are based on the confounders considered by the pharmaceutical company. The results of this analysis are not suitable for the assessment of the additional benefit of nivolumab in combination with ipilimumab since the requirement of sufficient overlap for the application of the method, measured by the propensity score of the compared cohorts (cohort 2 of the CA209-142 study and the Flatiron cohort), is not fulfilled. This applies equally to the IPTW complete cases analysis. The unadjusted calculations are not suitable for deriving a statement due to the present situation of a non-randomised study. With regard to propensity score matching, the dossier lacked information on patient characteristics and the therapies used in the comparator arm.

In addition to the relevant uncertainties arising from the identification, completeness and adjustment of the confounders, other uncertainties remain.

On the one hand, these result from inclusion and exclusion criteria of the nivolumab study that were not applied to the Flatiron cohort. For example, only patients who showed complete reduction of the side effects of a previous therapy, with a few exceptions, were enrolled in the CA209-142 study. This criterion was not applied to the Flatiron Health database. As a result, 100% of the patients in the Flatiron cohort made the switch from the last prior therapy to the appropriate comparator therapy within three months. In cohort 2 of the CA209-142 study, this only applies to 50% of patients. As a result, there is a relevant selection difference.

In addition, 26.7% of the patients in the Flatiron cohort received a therapy option that deviated from the appropriate comparator therapy.

Overall, the evaluations presented in the dossier for the CA209-6EP study are therefore not suitable for assessing the additional benefit of nivolumab in combination with ipilimumab.

Within the framework of the written statement procedure, a recalculation of the indirect comparison was submitted by the pharmaceutical company, taking into account the therapy options exclusively covered by the appropriate comparator therapy, and using propensity score matching as the primary analysis. Further information on the influence of the unconsidered potential confounders on the results of the indirect comparison was also provided in the statement.

Relevant uncertainties remain even when taking into account the information and evaluations submitted with the statement.

Accordingly, the search strategy presented with the statement is also not suitable for ensuring adequate identification and completeness of the confounders. Four further literature sources/ studies were identified as part of a second review carried out for the statement during the initial literature search. However, the original search strategy was not designed to identify observational studies which also makes the search presented in the statement unsuitable.

Furthermore, the evaluations and presentations submitted in the statement are not suitable to legitimise the non-consideration of (potential) confounders. In particular, the causal graphs are neither literature-based nor are the connections between individual (potential) confounders established in the causal graphs plausible. Consequently, confounders are identified by the pharmaceutical company, but these are partly not included in the data set or are not taken into account (region characteristic).

The sensitivity analyses submitted by the pharmaceutical company to estimate the influence of the unconsidered confounders on the observed effect support an amplification of the effect up to an effect reversal.

In the overall assessment, relevant multifactorial uncertainties remain, even when taking into account the information and evaluations submitted by the pharmaceutical company in the

written statement procedure. These relate, in particular to the identification and completeness of the confounders and the consequences of not taking identified confounders into account. The evaluations presented for the CA209-6EP study are therefore not suitable for assessing the additional benefit of nivolumab in combination with ipilimumab.

Before-after comparisons of the CA209-142 (cohort 2) study

The results of the before-after comparisons of the CA209-142 (cohort 2) study are not suitable for the assessment of the additional benefit of nivolumab in combination with ipilimumab in the endpoint categories of morbidity and health-related quality of life, as they do not allow a comparison with the appropriate comparator therapy.

Comparison with individual arms of RCTs

The large uncertainties associated with the descriptive comparison of individual arms from different studies, with a simultaneous lack of large effects, do not allow an assessment of the additional benefit of nivolumab in combination with ipilimumab in the endpoint category of side effects. A comparability of the therapies with regard to side effects in the sense of equivalence cannot be derived from this database either. Overall, the descriptive comparison is not suitable for assessing the additional benefit of nivolumab in combination with ipilimumab.

Conclusion

Overall, the data presented are not suitable to demonstrate an additional benefit of nivolumab in combination with ipilimumab compared to the appropriate comparator therapy, which is why an additional benefit of nivolumab in combination with ipilimumab for the treatment of metastatic, mismatch repair deficient or microsatellite instability-high colorectal cancer in adults after previous fluoropyrimidine-based combination chemotherapy is not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the medicinal product Opdivo with the active ingredient nivolumab.

The therapeutic indication assessed here is as follows:

“Opdivo O in combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy.”

The G-BA defined a patient-individual therapy as an appropriate comparator therapy, depending on the type and number of previous therapies, the RAS and BRAF mutational status, the localisation of the primary tumour, the general condition and the risk of toxicity induced by anti-VEGF and anti-VEGFR active ingredients, selecting:

- 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ± bevacizumab or aflibercept or ramucirumab
- 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ± cetuximab or panitumumab (only for patients with wild-type RAS)
- 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) ± bevacizumab
- Capecitabine + oxaliplatin (CAPOX) ± bevacizumab

- 5-fluorouracil + folinic acid ± bevacizumab
- Capecitabine ± bevacizumab
- Irinotecan as monotherapy
- Panitumumab as monotherapy (only for patients with wild-type RAS)
- Cetuximab as monotherapy (only for patients with wild-type RAS)
- trifluridine/ tipiracil
- Irinotecan + cetuximab (only for patients with wild-type RAS)
- Encorafenib + cetuximab (only for patients with BRAF-V600E mutation)

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The benefit assessment is based on the pivotal, non-controlled CA209-142 study. For the endpoint of overall survival, a comparison of individual arms from different studies (CA209-6EP study) was presented using different methods. For morbidity and health-related quality of life, a before-after comparison of the CA209-142 study data was presented, and for side effects, a descriptive comparison of the CA209-142 study data with single arms of randomised controlled trials was presented.

Overall, the data are not suitable to demonstrate an additional benefit of nivolumab in combination with ipilimumab compared to the appropriate comparator therapy, which is why an additional benefit of nivolumab in combination with ipilimumab 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 G-BA bases its resolution on the patient numbers from the dossier submitted by the pharmaceutical company. The procedure of the pharmaceutical company is mathematically comprehensible by far.

Significant uncertainties arise from the fact that the percentage values for progression to stage IV can deviate, the underlying data are partly of limited up-to-dateness and/or are based on deviating populations, and the calculation is generally restricted - instead of only for the lower limit - to patients with initiation of the 2nd line of therapy.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Opdivo (active ingredient: nivolumab) at the following publicly accessible link (last access: 06 January 2022):

https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf

Treatment with nivolumab should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of adults with metastatic colorectal cancer, specialists in internal medicine and gastroenterology, and other doctors from specialist groups participating in the Oncology Agreement.

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

In accordance with the Medicines Agency requirements regarding additional risk minimisation measures, the pharmaceutical company must provide healthcare professionals and patients with a patient card. The patient card contains, in particular, instructions on the management of immune-mediated side effects potentially occurring with nivolumab as well as on infusion-related reactions. The prescribing doctors must discuss the risks of therapy with nivolumab with the patients.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 January 2022).

The annual treatment costs shown refer to the first year of treatment.

The (daily) doses recommended in the product information or in the labelled publications were used as the basis for calculation.

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.

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

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				
Initial treatment				
Nivolumab	1 x per 21 day cycle	4	1	4
Ipilimumab	1 x per 21 day cycle	4	1	4
Follow-up treatment				
Nivolumab	1 x per 14 day cycle	20.1	1	20.1
Appropriate comparator therapy				
FOLFOX (5-Fluorouracil + Folinic acid + Oxaliplatin) ± Bevacizumab				

[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)	Treatment days/ patient/ year
FOLFOX 4				
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 if necessary				
Bevacizumab	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 Aflibercept or Ramucirumab 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
Plus Bevacizumab or Aflibercept or Ramucirumab or Cetuximab or Panitumumab if necessary				
Bevacizumab	1 x on day 1 of a 14 day cycle	26.1	1	26.1
Aflibercept	1 x on day 1 of a 14 day cycle	26.1	1	26.1
Ramucirumab	1 x on day 1 of a 14 day cycle	26.1	1	26.1

[3] In view of different FOLFIRI protocols, the information from the Cyramza® (ramucirumab) product information, last revised August 2020, Zaltrap® (aflibercept), as of November 2020 and Peeters et al. 2010 (DOI: 10.1200/JCO.2009.27.6055) is used.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
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
5-Fluorouracil + Folinic acid ± 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
Plus Bevacizumab if necessary				
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 a 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
CAPOX (Capecitabine + Oxaliplatin) ± Bevacizumab				
CAPOX				
Oxaliplatin	1 x on day 1 of a 21 day cycle	8	1	8
Capecitabine	2 x on day 1-14 of a 21 day cycle	8	14	112
Plus Bevacizumab if necessary				
Bevacizumab	1 x on day 1 of a 21 day cycle	17.4	1	17.4
Irinotecan ± Cetuximab				
Irinotecan	1 x on day 1 of a 21 day cycle	17.4	1	17.4
Plus Cetuximab if necessary				
Cetuximab	1 x every 7 days	52.1	1	52.1
Trifluridine/ Tipiracil				
Trifluridine/ Tipiracil	2 x daily on day 1-5 and 8-12 of a 28 day cycle	13	10	130

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Cetuximab				
Cetuximab	1 x every 7 days	52.1	1	52.1
Panitumumab				
Panitumumab	1 x on day 1 of a 14 day cycle	26.1	1	26.1
Encorafenib + Cetuximab				
Encorafenib	1 x daily	365	1	365
Cetuximab	1 x every 7 days	52.1	1	52.1

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Initial treatment					
Nivolumab	3 mg/kg BW	231 mg	2 x 100 mg + 1 x 40 mg	4	8 x 100 mg + 4 x 40 mg
Ipilimumab	1 mg/kg BW	77 mg	2 x 50 mg	4	8 x 50 mg
Follow-up treatment					
Nivolumab	240 mg	240 mg	2 x 100 mg + 1 x 40 mg	20.1	40.2 x 100 mg + 20.1 x 40 mg
Appropriate comparator therapy					
FOLFOX (5-Fluorouracil + Folinic acid + Oxaliplatin) ± Bevacizumab					
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 if necessary					
Bevacizumab	5 mg/kg BW - 10 mg/kg BW	385 mg - 770 mg	1 x 400 mg - 2 x 400 mg	26.1	26.1 x 400 mg - 52.2 x 400 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
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	760 mg	1 x 1,000 mg	12	72 x 1,000 mg
	2,400 mg/m²	4,560 mg	5 x 1,000 mg		
FOLFIRI (5-Fluorouracil, Folinic acid, Irinotecan) +/- Bevacizumab or Aflibercept or Ramucirumab 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	760 mg	1 x 1,000 mg	26.1	156.6 x
	2,400 mg/m²	4,560 mg	5 x 1,000 mg		1,000 mg
Plus Bevacizumab or Aflibercept or Ramucirumab or Cetuximab or Panitumumab if necessary					
Bevacizumab	5 mg/kg BW	385 mg	1 x 400 mg	26.1	26.1 x 400 mg
Aflibercept	4 mg/kg	308 mg	2 x 200 mg	26.1	52.2 x 200 mg
Ramucirumab	8 mg/kg	616 mg	1 x 500 mg + 2 x 100 mg	26.1	26.1 x 500 mg + 52.2 x 100 mg
Cetuximab	Initial dose in week 1: 400 mg/m² BSA	760 mg	1 x 500 mg + 3 x 100 mg	1	52.1 x 500 mg + 3 x 100 mg
	From week 2: 250 mg/m²	475 mg	1 x 500 mg	51.1	
Panitumumab	6 mg/kg BW	462 mg	1 x 400 mg +	26.1	26.1 x 400 mg +
			1 x 100 mg		26.1 x 100 mg
5-Fluorouracil + Folinic acid ± 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
	600 mg/m²	1,140 mg	2 x 1,000 mg		1,000 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Plus Bevacizumab if necessary					
Bevacizumab	5 mg/kg BW	385 mg	1 x 400 mg	26.1	26.1 x 400 mg
Capecitabine ± Bevacizumab					
Capecitabine	1250 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	7.5 mg/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
CAPOX (Capecitabine + Oxaliplatin) ± Bevacizumab					
CAPOX					
Oxaliplatin	130 mg/m²	247 mg	1 x 200 mg + 1 x 50 mg	8	8 x 200 mg + 8 x 50 mg
Capecitabine	1,000 mg/m² = 1,900 mg	3,800 mg	8 x 500 mg	112	896 x 500 mg
Plus Bevacizumab if necessary					
Bevacizumab	7.5 mg/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
Irinotecan +/- Cetuximab					
Irinotecan	350 mg/m²	665 mg	1 x 500 mg + 2 x 100 mg	17.4	17.4 x 500 mg + 34.8 x 100 mg
Plus Cetuximab if necessary					
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:	475 mg	1 x 500 mg	51.1	
Trifluridine/ Tipiracil					
Trifluridine/ Tipiracil	35 mg/m²	65 mg	6 x 15 mg + 2 x 20 mg	130	780 x 15 mg + 260 x 20 mg
Cetuximab					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Cetuximab	Initial dose in week 1: 400 mg/m² BSA	760 mg	1 x 500 mg + 3 x 100 mg	1	52.1 x 500 mg + 3 x 100 mg
	From week 2:	475 mg	1 x 500 mg	51.1	
Panitumumab					
Panitumumab	6 mg/kg BW	462 mg	1 x 400 mg + 1 x 100 mg	26.1	26.1 x 400 mg + 26.1 x 100 mg
Encorafenib + Cetuximab					
Encorafenib	300 mg	300 mg	4 x 75 mg	365	1460 x 75 mg
Cetuximab	Initial dose in week 1: 400 mg/m² BSA	760 mg	1 x 500 mg + 3 x 100 mg	1	52.1 x 500 mg + 3 x 100 mg
	From week 2: 250 mg/m² BSA	475 mg	1 x 500 mg	51.1	

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of usage. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					

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
Nivolumab 100 mg	1 CIS	€ 1,344.47	€ 1.77	€ 73.81	€ 1,268.89
Nivolumab 40 mg	1 CIS	€ 544.56	€ 1.77	€ 29.53	€ 513.26
Ipilimumab 50 mg	1 CIS	€ 3,849.30	€ 1.77	€ 216.54	€ 3,630.99
Appropriate comparator therapy					
Bevacizumab 100 mg	1 CIS	€ 396.98	€ 1.77	€ 21.35	€ 373.86
Bevacizumab 400 mg	1 CIS	€ 1,553.30	€ 1.77	€ 85.42	€ 1,466.11
Capecitabine 300 mg[4]	30 FCT	€ 36.33	€ 1.77	€ 1.98	€ 32.58
Capecitabine 500 mg[4]	120 FCT	€ 151.81	€ 1.77	€ 11.11	€ 138.93
Capecitabine 500 mg[4]	60 FCT	€ 87.64	€ 1.77	€ 6.04	€ 79.83
Cetuximab 500 mg	1 INF	€ 1,499.64	€ 1.77	€ 82.40	€ 1,415.47
Cetuximab 100 mg	1 INF	€ 308.96	€ 1.77	€ 16.48	€ 290.71
5-Fluorouracil 1,000 mg[4]	5 SFI	€ 37.41	€ 1.77	€ 2.07	€ 33.57
5-Fluorouracil 1,000 mg[4]	1 SFI	€ 16.64	€ 1.77	€ 0.42	€ 14.45
Folinic acid 500 mg[4]	10 IIS	€ 1,934.13	€ 1.77	€ 153.10	€ 1,779.26
Folinic acid 500 mg[4]	5 SFI	€ 973.15	€ 1.77	€ 76.08	€ 895.30
Folinic acid 500 mg[4]	1 SFI	€ 200.93	€ 1.77	€ 15.00	€ 184.16
Folinic acid 800 mg[4]	5 SFI	€ 1,499.02	€ 1.77	€ 117.67	€ 1,379.58
Folinic acid 800 mg[4]	1 SFI	€ 304.62	€ 1.77	€ 23.20	€ 279.65
Irinotecan 40 mg	1 CIS	€ 85.56	€ 1.77	€ 9.41	€ 74.38
Irinotecan 100 mg	1 CIS	€ 196.36	€ 1.77	€ 8.78	€ 185.81
Irinotecan 300 mg	1 CIS	€ 573.90	€ 1.77	€ 71.20	€ 500.93
Irinotecan 500 mg	1 CIS	€ 940.09	€ 1.77	€ 44.08	€ 894.24
Oxaliplatin 200 mg	1 CIS	€ 399.29	€ 1.77	€ 18.41	€ 379.11
Oxaliplatin 200 mg	1 CIS	€ 628.26	€ 1.77	€ 29.28	€ 597.21
Oxaliplatin 50 mg	1 CIS	€ 164.89	€ 1.77	€ 7.29	€ 155.83
Panitumumab 400 mg	1 CIS	€ 2,578.98	€ 1.77	€ 144.00	€ 2,433.21

[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	€ 661.46	€ 1.77	€ 36.00	€ 623.69
Ramucirumab 500 mg	1 CIS	€ 2,141.31	€ 1.77	€ 119.00	€ 2,020.54
Ramucirumab 100 mg	1 CIS	€ 441.14	€ 1.77	€ 23.80	€ 415.57
Aflibercept 200 mg	1 CIS	€ 769.87	€ 1.77	€ 0.00	€ 768.10
Tipiracil/ Trifluridine 15 mg	60 FCT	€ 2,348.73	€ 1.77	€ 0.00	€ 2,346.96
Tipiracil/ Trifluridine 20 mg	60 FCT	€ 3,112.42	€ 1.77	€ 0.00	€ 3,110.65
Encorafenib 75 mg	168 HC	€ 6,235.15	€ 1.77	€ 0.00	€ 6,233.38
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: 01 January 2022

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

According to the product information on cetuximab (Erbitux), patients must be pretreated 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 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 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 rather follow the rules for calculating in the Hilfstaxe. The cost

representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active 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 25 August 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

The appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 10 August 2021.

On 21 July 2021 the pharmaceutical company submitted a dossier for the benefit assessment of nivolumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 22 July 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 nivolumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 October 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 November 2021. The deadline for submitting written statements was 22 November 2021.

The oral hearing was held on 6 December 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 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 11 January 2022, and the proposed resolution was approved.

At its session on 20 January 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation

Subcommittee Medicinal product	25 August 2020	Implementation of the appropriate comparator therapy
Subcommittee Medicinal product	10 August 2021	New implementation of the appropriate comparator therapy
Working group Section 35a	1 December 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	6 December 2021	Conduct of the oral hearing
Working group Section 35a	15 December 2021 5 January 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	11 January 2022	Concluding discussion of the draft resolution
Plenum	20 January 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 January 2022

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

Prof. Hecken