Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Durvalumab (New Therapeutic Indication: Small cell Lung Cancer, First-line, in Combination with Etoposide and either Carboplatin or Cisplatin)

From 1 April 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 trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

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

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

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

2. Key points of the resolution

The active ingredient durvalumab (Imfinzi) was listed for the first time on 15 October 2018 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 27 August 2020, durvalumab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2a 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 23 September 2020, 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 durvalumab with the new therapeutic indication (first-line treatment of adults with extensive-stage small cell lung cancer) in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 4 January 2021 on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

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

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 durvalumab (Imfinzi) in accordance with the product information

Imfinzi in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC).

Therapeutic indication of the resolution (resolution from 01.04.2021):

see approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with extensive-stage small cell lung cancer (ES-SCLC): for first-line treatment

Appropriate comparator therapy:

- Cisplatin in combination with etoposide

or

- Carboplatin in combination with etoposide

or

- Atezolizumab in combination with carboplatin and etoposide

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

on 1. Medicinal products with the following active ingredients are approved for the present therapeutic indication:

atezolizumab, carboplatin, cisplatin, cyclophosphamide, doxorubicin, epirubicin, etoposide, ifosfamide, lomustine and vincristine

on 2. As a non-medicinal treatment option, prophylactic cranial irradiation (PCI) and radiotherapy come into consideration in the present therapeutic indication. Based on currently valid guidelines, a PCI is recommended for those patients that responded to the first-line chemotherapy. Therefore, PCI is a treatment option after first-line chemotherapy in case of complete or partial remission. In addition, in accordance with the guideline recommendations, further radiotherapy interventions can in principle be considered. For patients with an initial brain metastasis, the early application of cranial radiation is recommended, for patients with very good remission of the remote metastasis also primary tumour radiation, or for patients who need symptom-oriented, palliative radiation mainly for pain relief or complication prevention. The mentioned radiotherapeutic interventions are therefore either applied after the first-line chemotherapy (and depending on the response to this) or are only considered for some of the patients in the therapeutic indication. They are therefore not determined as appropriate comparator therapy. Their use as an additional therapy option remains unaffected.

on 3. The following resolutions or guidelines of the G-BA for medical products are available:

Annex VI to Section K of the Pharmaceuticals Directive - Prescribability of approved medicinal products in non-approved therapeutic indications - Part A: Irinotecan for small cell lung cancer (SCLC), extensive disease.

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

Atezolizumab: resolution of 2 April 2020

on 4. The generally accepted state of medical knowledge for the indication was established by means of a systematic search for guidelines and reviews of clinical studies. In these guidelines, the use of etoposide in combination with either cisplatin or carboplatin is consistently recommended for the first-line treatment of small cell lung cancer in the extensive stage. According to the S3 guideline, cisplatin and carboplatin can be regarded as equally effective, however, due to the lower rate of side effects, the use of carboplatin is preferred. Other guidelines do not differentiate between carboplatin and cisplatin in their therapy recommendations. In addition, there are sometimes weaker recommendations for irinotecan in combination with a platinum derivative (cisplatin or carboplatin). Irinotecan is not approved in the present therapeutic indication, but is prescribable in accordance with Annex VI Section K of the Pharmaceuticals Directive (see under 3.). Irinotecan with a platinum preparation is only prescribable to patients who have received a platinum preparation and etoposide in first-line therapy and in

whom such serious etoposide-related side effects have been observed that continued administration of etoposide would be associated with unacceptable risks. A combination therapy consisting of irinotecan and a platinum preparation is therefore not an appropriate comparative therapy for the present therapeutic indication. With the approval of atezolizumab in combination with carboplatin and etoposide, another treatment option is available in the present therapeutic indication. The benefit assessment by the G-BA resulted in a hint of a minor additional benefit compared to carboplatin and etoposide. Furthermore, in the written statements on the present benefit assessment, clinical experts explained that atezolizumab in combination with carboplatin and etoposide is part of the current treatment standard in medical care.

In the overall view, therefore, the combination therapies of cisplatin and etoposide, carboplatin and etoposide and atezolizumab with carboplatin and etoposide are determined to be equally appropriate comparator therapies

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

Change of the appropriate comparator therapy:

Considering the original determinations, atezolizumab in combination with carboplatin and etoposide is added to the previously determined appropriate comparator therapies as an equally appropriate comparator therapy.

The change is made in consideration of the resolution about the benefit assessment of atezolizumab in combination with carboplatin and etoposide from 2 April 2020 and the importance of this treatment option in current care, as put forward in the opinions of medical societies and experts.

This change to the appropriate comparator therapy has no effects on the present assessment of the additional benefit, nor does it require the benefit assessment to be carried out again.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of durvalumab with etoposide and either carboplatin or cisplatin is assessed as follows:

There is a hint of a minor added benefit for first-line treatment in adult patients with extensive-stage small cell lung cancer (ES-SCLC).

Justification:

The pharmaceutical company has submitted data from the randomised, open phase III CASPIAN study for the benefit assessment.

In the main cohort (global cohort) included a total of 805 adult patients with ES-SCLC who had not received prior systemic therapy in stage ES-SCLC and which were suitable for platinum-based chemotherapy as first-line treatment for ES-SCLC. The study includes three study arms, wherein for the present marketing authorisation only the comparison between the intervention arm durvalumab in combination with chemotherapy (etoposide and either carboplatin or cisplatin) and the comparator arm chemotherapy (etoposide and either carboplatin or cisplatin) is relevant. 268 patients were randomly assigned to treatment with durvalumab in combination with chemotherapy and 269 patients to treatment with chemotherapy. This was done stratified after the planned platinum-based chemotherapy for cycle 1 (cisplatin or carboplatin).

In addition to the global cohort, the pharmaceutical company presented data from a Chinese cohort with an identical study protocol and statistical analysis plan for the global study population, but with a separate analysis. A total of 61 patients were randomly assigned to the intervention arm and 62 patients to the comparator arm. The recruitment took place after the

global cohort had completed its recruitment phase. According to the pharmaceutical company, the recruitment was carried out for the purpose of marketing authorisation in China.

Patients with brain metastases were included in the study if they were asymptomatic at the start of the study or, if previously treated, were stable without treatment with steroids and anticonvulsants for at least one month before the start of the study treatment. In the global cohort, 10% of the patients had brain metastases at the start of the study and, in the China cohort, 15.5% of the patients.

The average age of the patients in the global cohort was around 62 years and the majority were male. The proportion of women was around 30%. Very few patients had already received radiotherapy or chemotherapy prior to study entry.

In the comparator arm, the patients received chemotherapy for a total of 4 cycles. In cycle 5 and 6, up to 2 further cycles of chemotherapy could be administered at the investigator's discretion. In accordance with the statements made by the clinical experts in the written statement procedure, this approach reflects the German health care context. However, it is unclear whether giving more than 4 cycles of chemotherapy leads to a better chance of survival. Especially for patients who were treated with 6 cycles of chemotherapy, a higher toxicity can not be excluded while the benefit is uncertain.

In addition, the patients received therapies as part of the permitted concomitant treatment until progression. In the comparator arm, but not in the intervention arm, this included prophylactic cranial irradiation (PCI) as specified by the investigator. In the global cohort, 8.2% of the patients in the comparator arm received PCI , which, according to the explanations of the clinical experts in the written statement procedure adequately reflects the reality of medical care. Prophylactic cranial irradiation is recommended for patients who have responded to first-line chemotherapy. According to the statements of the experts in the written statement procedure, this recommendation is currently being discussed in specialist circles due to more recent study data.

Treatment continued until disease progression, unacceptable toxicity, the start of another tumour therapy, withdrawal of consent, or until death. Treatment could continue to be administered after progression provided the clinical benefit continued. This remained at the investigator's discretion. As a subsequent antineoplastic therapy after discontinuation of the study medication, the patients were able to receive consolidating thoracic radiotherapy. Consolidating thoracic irradiation was prohibited in both study arms. In the written statement procedure the clinical experts reported the lack of final assessment of the present evidence on the clinical importance of consolidating thoracic irradiation. Palliative radiation treatment outside the thorax of non-target lesions was allowed in both study arms as additional concomitant treatment.

The primary endpoint of the CASPIAN study is overall survival. Furthermore, endpoints for morbidity, the health-related quality of life and adverse events, amongst others, are surveyed.

The currently ongoing study started in April 2017 and is being carried out in 209 centres in North and South America, Europe and Asia.

Regarding the cohort in China, the study started in May 2018 and is being carried out in 28 centres in China and Taiwan. There are two data cut-offs for the global cohort. The first data cut-off from 11 March 2019 is the a priori planned interim analysis of overall survival (after approx. 318 events). The later data cut-off from 27 January 2020 is the final analysis of overall survival (after approx. 425 events). For the present benefit assessment, the later data cut-off of the global cohort of 27 January 2020 was used.

For the Chinese cohort, a data cut-off is present, that is used for the present benefit assessment. This is an analysis of overall survival (planned after events in approx. 60% of patients).

The two cohorts of the CASPIAN study are suitable for a meta-analytical summary. For the present assessment, the meta-analytical summary of the two cohorts is used, which is based

on patient-individual data (IPD meta-analysis). The results of the individual cohorts are only considered if there is significant heterogeneity between the cohorts (p-value of the interaction test of cohort and treatment <0.05). The heterogeneity test and subgroup analyses for the assessment of the endpoint morbidity and quality of life by submitted in the written statement procedure by the pharmaceutical company are used.

Extent and probability of the additional benefit

Mortality

Overall survival

In the global cohort of the CASPIAN study, there was a statistically significant prolongation in overall survival from treatment with durvalumab in combination with chemotherapy compared to chemotherapy alone. There is no statistically significant difference for the cohort in China.
The meta-analysis from the two cohorts shows a statistically significant prolongation in overall survival through treatment with durvalumab in combination with chemotherapy compared to chemotherapy alone. The extent of this effect assessed as a small improvement in overall survival.

Morbidity

Progression-free survival (PFS)

Progression-free survival (PFS) is defined in the study as the time from randomisation to the first objective disease progression (assessed by the investigator or the investigator based on the RECIST version 1.1) or death for any reason without prior progression, regardless of whether the patient discontinued the randomised therapy or received other antineoplastic therapy before progression.
For the PFS in the global cohort, there was a statistically significant difference in the advantage of durvalumab in combination with chemotherapy compared to chemotherapy alone. In the Chinese cohort no statistically significant difference was detected between the treatment arms. In the meta-analysis from the two cohorts, the PFS presented a statistically significant difference between the treatment arms to the advantage of durvalumab in combination with chemotherapy compared to chemotherapy alone.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component mortality is already surveyed via the endpoint overall survival as an independent endpoint. The morbidity component assessment is not done in a symptom-related manner but exclusively by means of imaging (disease progression assessed by radiology according to the RECIST criteria).

Taking into consideration the aforementioned aspects, there are different views 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

The symptomatology of the CASPIAN study patients is assessed using the symptom scales of the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires.

In the dossier, the pharmaceutical company presented time-to-event analyses, operationalised as the time to the first deterioration by ≥ 10 points, which, however, only included data up to cycle 6 (approx. 4.2 months). As part of the written statement procedure, the pharmaceutical

company submits time-to-event analysis over the entire assessment period, for which, however, analyses are missing, in particular for subgroups. The presented time-to-event analysis are therefore not used.

In addition, the pharmaceutical company submitted in the dossier additionally MMRM analyses (Mixed Model for Repeated Measures). These analyses were pre-specified, showing results for the mean change in symptoms from baseline up to progression or up to month 12 (whichever occurred earlier).

For the symptoms nausea and vomiting, loss of appetite, diarrhoea and alopecia there is a statistically significant difference between treatment groups to the advantage of durvalumab in combination with chemotherapy. The standardised mean difference in the form of Hedges'g is used to assess the relevance of the result. The 95% confidence interval of the mean difference is not completely outside the irrelevance range [−0.2; 0.2]. Therefore, for the endpoints nausea and vomiting, loss of appetite, diarrhoea and alopecia, it cannot be derived that the effect is relevant.

Health status (EQ-5D, visual analogue scale)

The health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire.

In the dossier, the pharmaceutical company presented time-to-event analysis, operationalised as time up to clinically relevant deterioration of 7 and 10 points, which, however, only included data up to cycle 6 (approx. 4.2 months). As part of the written statement procedure, the pharmaceutical company submits time-to-event analysis over the entire assessment period, for which, however, analyses are missing, in particular for subgroups. The presented time-to-event analysis are therefore not used.

For the present assessment, the pharmaceutical company submits additional MMRM analyses in the dossier. These analyses were pre-specified, showing results for the mean change in symptoms from baseline up to progression or up to month 12 (whichever occurred earlier).

For the MMRM analyses, there was no statistically significant difference between the treatment groups for the health status recorded with the EQ-5D.

Health status (PGIC)

The health status was also assessed using the PGIC questionnaire.

In the dossier, the pharmaceutical company presented time-to-event analysis for the analysis time cycle 6 day 1 (for the global cohort and meta-analysis) and cycle 7 day 1 (for the Chinese cohort) for the proportion of patients with improvement or deterioration. Furthermore, the pharmaceutical company included time-to-event analysis, operationalised as time up to deterioration (categories "much worse" and "very much worse") as part of the written statement procedure.

The data subsequently submitted by the pharmaceutical company for the time up to deterioration of PGIC based on the meta-analysis are not suitable for the benefit assessment, because it is unclear whether all available data are reported in the time-to-event analysis or if only assessments up to cycle 6 were taken into account. In addition, there are no further analyses, particularly on subgroups. The PGIC evaluations presented are therefore not used for the benefit assessment.

<u>Quality of life</u>

The health-related quality of life is reported by the patients in the CASPIAN study and assessed using the functional scales of the EORTC-QLQ-C30 questionnaire.

In the dossier, the pharmaceutical company presented responder analyses, operationalised as time up to clinically relevant deterioration, which, however, only included data up to cycle 6 (approx. 4.2 months). As part of the written statement procedure, the pharmaceutical company submits time-to-event analysis over the entire assessment period, for which, however, analyses are missing, in particular for subgroups. The presented time-to-event analysis are therefore not used.

For the present assessment, the pharmaceutical company submits additional MMRM analyses in the dossier. These analyses were pre-specified, showing results for the mean change in symptoms from baseline up to progression or up to month 12 (whichever occurred earlier).

Overall, for the health-related quality of life there was no statistically significant difference between treatment groups.

Side effects

In its dossier, the pharmaceutical company presents evaluations of the endpoints on side effects from the time of the first dose of the study treatment until 90 days after taking the last dose of the study medication or until the start of a subsequent antineoplastic therapy, whichever occurred first. As part of the written statement procedure, the pharmaceutical company also analyses the data on adverse events up to 90 days after discontinuation of study drug regardless of the start of a subsequent therapy. These are incomplete due to lack of analyses, in particular based on system organ classes (SOC) and preferred terms (PT). Therefore, the evaluations submitted later cannot be used. Also no relevant differences are detected in the observed effects that are relevant for dossier assessment.

Adverse events (AE) in total

In the CASPIAN study, AEs occurred in almost all study participants in both cohorts. The results were only presented as a supplement.

Serious AE (SAE)

Regarding SAE the meta-analysis of both cohorts of the CASPIAN study showed no statistically significant difference between the treatment arms.

However, this endpoint presented a modification effect on the feature brain metastases at start of study. There was no statistically significant difference between the study arms for patients without brain metastases at the start of the study. In contrast, there was a statistically significant difference to the advantage of durvalumab in combination with chemotherapy for patients with brain metastases at the start of the study. This effect modification was only shown in one further endpoint on AEs and in no benefit endpoint. The corresponding subgroup results are presented, but do not lead to any specific statements in this regard in the overall assessment.

severe AEs (CTCAE grade ≥ 3) , therapy discontinuation due to AEs

In the meta-analysis of the time-to-event analysis for the study cohorts, there was no statistically significant difference between treatment groups.

Specific AE

Immune-mediated SAEs

There was statistically significant heterogeneity between the cohorts for the endpoint immune-mediated SAEs. Overall, for the health-related quality of life there was no statistically significant difference between treatment groups. No effect estimators are available for the cohort in China.

Immune-mediated severe AE

There was no statistically significant difference between the treatment arms for the endpoint immune-mediated severe AEs (CTCAE grade ≥ 3). However, there was an effect modification by the characteristic gender. For men, there was no statistically significant difference between the treatment arms. No effect estimator is available for women. This effect modification was not present in any further endpoint. It can not be ruled out that gender-independent factors underlie the effect modifications observed. In the written statement procedure, the lack of a gender-specific effect in therapy with immune checkpoint inhibitors in the present therapeutic indication was emphasised.

Overall, there are uncertainties regarding the clinical relevance of these gender-specific effect modification and therefore this is not considered further in this assessment.

PRO-CTCAE

No evaluable evaluations were available for the global cohort for the endpoint PRO CTCAE. The endpoint was not assessed in the cohort in China.

Other specific UEs

In the other specific UEs, the endpoint hypertonia shows a statistically significant difference between the treatment arms to the detriment of durvalumab in combination with chemotherapy compared to chemotherapy alone.

For the endpoint blood and lymphatic system disorders, the time-to-event analyses showed a statistically significant difference between the treatment arms to the advantage of durvalumab in combination with chemotherapy compared to chemotherapy alone. However, this endpoint presented a modification effect on the feature brain metastases at start of study.

There was no statistically significant difference between the study arms for patients without brain metastases at the start of the study. In contrast, there was a statistically significant difference to the advantage of durvalumab in combination with chemotherapy for patients with brain metastases at the start of the study. This effect modification was only shown in one further endpoint on AEs and in no benefit endpoint. The corresponding subgroup results are presented, but do not lead to any specific statements in this regard in the overall assessment.

In summary, despite differences in specific AEs with regard to side effects, overall neither an advantage nor a disadvantage can be determined for treatment with durvalumab in combination with chemotherapy.

Overall assessment

For the benefit assessment of durvalumab in combination with etoposide and either carboplatin or cisplatin for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC), results of the CASPIAN study on the endpoint categories of mortality, morbidity, health-related quality of life and side effects are available compared to cisplatin in combination with etoposide or carboplatin in combination with etoposide.

The assessment is based on the meta-analytical summary of the results of the two cohorts assessed in this study (global and Chinese cohort).

Durvalumab combined with chemotherapy results compared to chemotherapy alone in a statistically significant prolongation of overall survival, evaluating its extent as a small improvement.

There were no relevant differences for the endpoints in the category morbidity, measured using the measuring instruments EORTC-QLQ-LC13 and the visual analogue scale of the EQ-5D. In particular, no relevant differences are shown for disease-specific symptoms. In general, the symptoms in extensive-stage SCLC are pronounced and distressing for the patients; therefore, the effects on the symptomatology are significant for patients.

The data on health-related quality of life reported by patients and determined by the EORTC QLQ-C30 and QLQ-LC13 EORTC, overall show no relevant differences between the treatment groups.

In terms of side effects, neither an advantage nor a disadvantage can be determined for treatment with durvalumab combined with chemotherapy.

In the overall assessment, for durvalumab in combination with etoposide and either carboplatin or cisplatin in the first-line treatment of adult patients with advanced small cell lung cancer a minor additional benefit could be determined when compared to cisplatin in combination with etoposide or carboplatin in combination with etoposide.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the open, randomised phase III CASPIAN study.

The risk of bias is classified as low at study level.

Due to the open study design and the resulting lack of blinding in the case of subjective endpoint assessment, the patient-reported endpoints on morbidity and health-related quality of life are classified as highly biased.

Evaluation-relevant uncertainties also arise from the fact that the proportion of the patients with brain metastases in the study is low. Furthermore, no data are available on patients with symptomatic brain metastases. Since the incidence of brain metastases is particularly high initially in the extensive-stage small cell lung cancer and is particularly relevant for the course of the disease, meaningful data in this regard are of particular importance.

Another further valuation-relevant uncertainty results from the different number of chemotherapy cycles in the intervention and the comparator arms. It remains unclear whether the administration of more than 4 cycles of chemotherapy leads to a survival benefit. Especially for patients who were treated with 6 cycles of chemotherapy, a higher toxicity can not be excluded while the benefit is uncertain.

Thus, the present data basis has assessment-relevant uncertainties, which lead to a downgrading of the reliability of data for the overall assessment. Therefore, the reliability of data for the additional benefit determined is classified in the category "hint".

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient durvalumab. "Imfinzi in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC). "

Cisplatin and etoposide or carboplatin and etoposide and atezolizumab in combination with carboplatin and etoposide were determined as appropriate comparator therapy.

The pharmaceutical company is launching the open, randomised phase III CASPIAN study, in which durvalumab is compared with etoposide and either carboplatin or cisplatin versus etoposide in combination with carboplatin or cisplatin. The assessment is based on the meta-analytical summary of the results of the global and Chinese cohorts assessed in the study.

Durvalumab in combination with chemotherapy compared to chemotherapy alone leads to a small improvement in overall survival.

For the endpoint categories morbidity, health-related quality of life and side effects neither an advantage nor a disadvantage can be determined for the treatment with durvalumab in combination with chemotherapy.

Uncertainties exist due to the open study design, the low proportion of patients with brain metastases, lack of data on symptomatic brain metastases and different number of cycles of chemotherapy between treatment arms.

Overall, for durvalumab in combination with chemotherapy versus chemotherapy was identified a hint for a minor additional benefit.

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 data submitted by the pharmaceutical company in the dossier is subject to uncertainty. This is due to methodological weaknesses and underestimations. Uncertainties are particularly evident due to the deviating determination of patients with an SCLC diagnosis at an earlier stage and the delimitation of patients with platinum-based chemotherapy.

As part of the written statement procedure, the pharmaceutical company also submits a corrected derivation of the target population. This specified number of patients from 3207–6133 represents a more suitable approximation of the number of patients with ES-SCLC. However, the upper limit of the range described is underestimated, since basically all patients with ES-SCLC are eligible for first-line treatment with durvalumab in combination with etoposide and cisplatin or carboplatin.

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 Imfinzi (active ingredient: durvalumab) at the following publicly accessible link (last access: 4 February 2021:

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

Treatment with durvalumab may only be initiated and monitored by specialists in internal medicine, haematology and oncology who are experienced in the treatment of patients with small cell lung cancer, as well as specialists in internal medicine and pneumology or specialists in pulmonary medicine and doctors from other specialist groups participating in the Oncology Agreement.

Patients with symptomatic brain metastases were excluded from the CASPIAN study. No data are available for patients with symptomatic brain metastases.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 March 2021):

Treatment duration:

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

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:				
Induction therapy with cisplatin				
Durvalumab	1 x per 21 day cycle	4	1	4
Cisplatin	1 x per 21 day cycle	4	1	4
Etoposide	on day 1-3 of an 21 day cycle	4	3	12
Induction therapy with carboplatin				
Durvalumab	1 x per 21 day cycle	4	1	4
Carboplatin	1 x per 21 day cycle	4	1	4
Etoposide	on day 1-3 of an 21 day cycle	4	3	12
Maintenance treatment				
Durvalumab	1 x per 28 day cycle	10	1	10
Appropriate comparator therapy				
Cisplatin + etoposide				
Cisplatin	1 x per 21 day cycle	17.4	1	17.4
Etoposide	on day 1-3 of an 21 day cycle	17.4	3	52.2
Carboplatin + etoposide				
Carboplatin	1 x per 21 day cycle	17.4	1	17.4
Etoposide	on day 1-3 of an 21 day cycle	17.4	3	52.2

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Atezolizumab+ carboplatin + etoposide				
Induction therapy				
Atezolizumab	1 x per 21 day cycle	4	1	4
Carboplatin	1 x per 21 day cycle	4	1	4
Etoposide	on day 1-3 of an 21 day cycle	4	3	12
Maintenance treatment				
Atezolizumab	1 x per 21 day cycle	13.4	1	13.4

Consumption:

For dosages depending on body weight or body surface, 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).

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

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency / day of treatment	Days of treatment/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed:					
Induction therapy with cisplatin					
Durvalumab	1,500 mg	1,500 mg	3 x 500 mg	4	12 x 500 mg
Cisplatin	75 mg/m² = 142.5 mg-	142,5 mg	1 x 100 mg + 1 x 50 mg	4	4 x 100 mg + 4 x 50 mg
	80 mg/m² = 152 mg	152 mg	1 x 100 mg + 1 x 50 mg + 1 x 10 mg	4	4 x 100 mg + 4 x 50 mg + 4 x 10 mg
Etoposide	80 mg/m² = 152 mg- 100 mg/m² = 190 mg	152 mg 190 mg	1 x 200 mg	12	12 x 200 mg

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency / day of treatment	Days of treatment/ patient/ year	Average annual consumption by potency
Induction therapy with carboplatin					
Durvalumab	1,500 mg	1,500 mg	3 x 500 mg	4	12 x 500 mg
Carboplatin	400 mg/m² = 760 mg	760 mg	1 x 50 mg + 1 x 150 mg + 1 x 600 mg	4	4 x 50 mg + 4 x 150 mg + 4 x 600 mg
	500 mg/m² = 950 mg	950 mg	1 x 50 mg + 2 x 150 mg + 1 x 600 mg	4	4 x 50 mg + 8 x 150 mg + 4 x 600 mg
Etoposide	80 mg/m² = 152 mg- 100 mg/m² = 190 mg	152 mg 190 mg	1 x 200 mg	12	12 x 200 mg
Maintenance treatment					
Durvalumab	1,500 mg	1,500 mg	3 x 500 mg	10	30 x 500 mg
Appropriate comparator therapy					
Cisplatin + Etoposide[2]					
Cisplatin	75 mg/m² = 142.5 mg	142.5 mg	1 x 100 mg + 1 x 50 mg	17.4	17.4 x 100 mg + 17.4 x 50 mg
Etoposide	100 mg/m² = 190 mg	190 mg	1 x 200 mg	52.2	52.2 x 200 mg
Carboplatin + Etoposide[3]					
Carboplatin	400 mg/m² = 760 mg	760 mg	1 x 50 mg + 1 x 150 mg + 1 x 600 mg	17.4	17.4 x 50 mg + 17.4 x 150 mg + 17.4 x 600 mg
Etoposide	100 mg/m² = 190 mg	190 mg	1 x 200 mg	52.2	52.2 x 200 mg
Atezolizumab + carboplatin + etoposide[4]					

[2] Belani CP et al., Randomized phase III trial comparing cisplatin-etoposide to carboplatin-paclitaxel in advanced or metastatic non-small-cell lung cancer. Ann Oncol 2005; 16(7): 1069-1075

[3] Socinski,M et al., Phase III Study of Pemetrexed Plus Carboplatin Compared With Etoposide Plus Carboplatin in Chemotherapy-Naive Patients With Extensive-Stage Small-Cell Lung Cancer. Journal of clinical oncology:official journal of the American Society of Clinical Oncology. 27. 4787-92. 10.1200/JCO.2009.23.1548.

[4] Liu SV. et al. Updated Overall Survival and PD-L1 Subgroup Analysis of Patients With Extensive-Stage Small-Cell Lung Cancer Treated With Atezolizumab, Carboplatin, and Etoposide (IMpower133). J Clin Oncol. 2021 Feb 20;39(6):619-630.

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency / day of treatment	Days of treatment/ patient/ year	Average annual consumption by potency
Induction therapy					
Atezolizumab	1,200 mg	1,200 mg	1 x 1,200 mg	4	4 x 1,200 mg
Carboplatin Etoposide	400 mg/m² = 760 mg 100 mg/m² = 190 mg	760 mg 190 mg	1 x 50 mg + 1 x 150 mg + 1 x 600 mg 1 x 200 mg	4 12	4 x 50 mg + 4 x 150 mg 4 x 600 mg 12 x 200 mg
Maintenance treatment					
Atezolizumab	1,200 mg	1,200 mg	1 x 1,200 mg	13.4	13.4 x 1,200 mg

Costs:

Costs of the medicinal product:

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:					
Durvalumab 500 mg	1 IFC	€ 2,470.63	€ 1.77	€ 137.82	€ 2,331.04
Cisplatin 100 mg	1 IFC	€ 83.86	€ 1.77	€ 9.22	€ 72.87
Cisplatin 50 mg	1 IFC	€ 47.46	€ 1.77	€ 4.61	€ 41.08
Carboplatin 50 mg	1 IFC	€ 34.38	€ 1.77	€ 1.11	€ 31.50
Carboplatin 150 mg	1 IFC	€ 82.79	€ 1.77	€ 3.40	€ 77.62
Carboplatin 600 mg	1 IFC	€ 300.57	€ 1.77	€ 13.74	€ 285.06
Etoposide 200 mg	1 IFC	€ 81.62	€ 1.77	€ 3.35	€ 76.50
Appropriate comparator therapy					
Atezolizumab 1,200 mg	1 IFC	€ 4,128.95	€ 1.77	€ 232.53	€ 3,894.65

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
Cisplatin 100 mg	1 IFC	€ 83.86	€ 1.77	€ 9.22	€ 72.87
Cisplatin 50 mg	1 IFC	€ 47.46	€ 1.77	€ 4.61	€ 41.08
Carboplatin 50 mg	1 IFC	€ 34.38	€ 1.77	€ 1.11	€ 31.50
Carboplatin 150 mg	1 IFC	€ 82.79	€ 1.77	€ 3.40	€ 77.62
Carboplatin 600 mg	1 IFC	€ 300.57	€ 1.77	€ 13.74	€ 285.06
Etoposide 200 mg	1 IFC	€ 81.62	€ 1.77	€ 3.35	€ 76.50
Abbreviations: IFC = Concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 15 March 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 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.

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I of the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

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	Days of treatment/ year	Costs/ patient/ year
Medicinal product to be assessed:							
Cisplatin							
Antiemetic treatment							
In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin. The product information for cisplatin does not provide any specific information on this, which is why the necessary costs cannot be quantified.							
Hydrogenation							
Mannitol 10% inf.	10 x 250 ml	€ 87.05	€ 4.35	€ 7.94	€ 74.76	4	€ 74.76

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	Days of treatment/ year	Costs/ patient/ year
solution, 37.5 g/day							
Sodium chloride 0.9 % inf. solution, 3 - 4,4 l/ day	10 x 1,000 ml	€ 37.66	€ 1.88	€ 3.22	€ 32.56	4	€ 48.72 -
	6 x 1,000 ml	€ 30.23	€ 1.51	€ 2.47	€ 26.25		
	1 x 1,000 ml	€ 9.21	€ 0.46	€ 0.67	€ 8.08		
	1 x 500 ml	€ 6.96	€ 0.35	€ 0.48	€ 6.13		€ 83.33
Appropriate comparator therapy							
Cisplatin							
Antiemetic treatment							
In clinical practice, an appropriate antiemetic treatment is established before and / or after administration of cisplatin. The product information for cisplatin does not provide any specific information on this, which is why the necessary costs cannot be quantified.							
Hydrogenation							
Mannitol 10% inf. solution, 37.5 g / day	10 x 500 ml	€ 106.22	€ 5.31	€ 9.81	€ 91.10	17.4	€ 158.51
Sodium chloride 0.9 % inf. solution, 3 - 4,4 l/ day	10 x 1,000 ml	€ 35.47	€ 1.77	€ 1.12	€ 32.58	17.4	€ 170.07
	10 x 500 ml	€ 22.72	€ 1.14	€ 0.69	€ 20.89		€ 263.11

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 special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) all surcharges for the production of parenteral preparations containing cytostatic drugs a maximum 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 special agreement on contractual unit costs of retail pharmacist services (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 special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

3. Bureaucratic costs

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

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 26 January 2016 .

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. Working group 35a determined the appropriate comparator therapy at its session on 15. September 2020.

On 23 September 2020, the pharmaceutical company submitted a dossier for the benefit assessment of durvalumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 24. September 2020 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 durvalumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 30 December 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 4 January 2021. The deadline for submitting written statements was 25 January 2021.

The oral hearing was held on 8 February 2021.

By letter dated 9 February 2021, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 12 March 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 were discussed at the session of the subcommittee on 23 March 2021, and the draft resolution was approved.

At its session on 1 April 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	26 January 2016	Determination of the appropriate comparator therapy
Working group Section 35a	15 September 2020	New determination of the appropriate comparator therapy
Working group Section 35a	2 February 2021	Information on written statements received; preparation of the oral hearing

Subcommittee Medicinal products	8 February 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	16 February 2021 16 February 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	23 March 2021	Concluding consultation of the draft resolution
Plenum	1 April 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 1 April 2021

Federal Joint Committee in accordance with Section 91 SGB V

The chair

Prof. Hecken