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 Brigatinib (New Therapeutic Indication: NSCLC, ALK+, ALK-inhibitor-naïve patients)

of 15 October 2020

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 proof 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 brigatinib (Alunbrig) was listed for the first time on 15 January 2019 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 1 April 2020, brigatinib received the marketing authorisation for a new therapeutic indication classified as a major variation of Type 2 according to Annex 2, number 2a to Regulation (EC) No. 1234/2008 of the Commission from 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 24 April 2020, the pharmaceutical company 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 brigatinib with the new therapeutic indication “Alunbrig is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor” in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication) “Alunbrig is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor”.

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 3 August 2020, 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 brigatinib compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has assessed 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 brigatinib.

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

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

2.1.1 Approved therapeutic indication of brigatinib (Alunbrig) in accordance with the product information

Alunbrig is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor.

Appropriate comparator therapy for brigatinib as monotherapy:

- Crizotinib

or

- Alectinib

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

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

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

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

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 applications or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

On 1. In addition to brigatinib, alectinib, bevacizumab, ceritinib, cisplatin, crizotinib, docetaxel, durvalumab, etoposide, gemcitabine, ifosfamide, mitomycin, nab-paclitaxel, Nintedanib, nivolumab, paclitaxel, pemetrexed, ramucirumab, vindesine and vinorelbine are approved in the present therapeutic indication; carboplatin can also be prescribed off-label.

Medicinal products with explicit marketing authorisation for the treatment of NSCLC with activating EGFR or BRAF V600 mutations and exclusively squamous histology were not included.

On 2. Non-medicinal treatment is not an appropriate comparator therapy for the present therapeutic indication.

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

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

Durvalumab:	Resolution of 4 April 2019
Alectinib:	Resolution of 21 June 2018
Ceritinib:	Resolution of 1 February 2018
Crizotinib:	Resolution of 16 March 2017
Crizotinib:	Resolution of 15 December 2016
Nivolumab:	Resolution of 20 October 2016
Ramucirumab:	Resolution of 1 September 2016
Crizotinib:	Resolution of 16 June 2016
Nintedanib:	Resolution of 18 June 2015

Guidelines:

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

On 4. The generally accepted state of medical knowledge for the indication was established by means of a search for guidelines as well as systematic reviews of clinical studies.

Because ALK-positive, non-small cell lung cancers are usually EGFR-negative and have non-squamous histology, EGFR-specific therapy options as well as therapies explicitly indicated for squamous histology were not considered.

National and international guidelines recommend treatment with ALK inhibitors for patients with ALK-positive, non-small cell lung cancer who have not yet received targeted therapy. In this respect, medicinal products containing the active ingredients crizotinib, alectinib, and ceritinib are currently available in Germany.

In the benefit assessment of the G-BA on crizotinib, there was a hint for a considerable additional benefit compared with platinum-based chemotherapy in the first-line treatment of patients with ALK-positive tumours (resolution of 16 June 2016). This assessment was based on the positive effects of crizotinib compared with platinum-based chemotherapy in terms of disease-specific symptomatology, health-related quality of life, and side effects.

By resolution of 21 June 2018, the benefit assessment on alectinib for the first-line treatment of ALK-positive advanced NSCLC identified a hint for a non-quantifiable additional benefit compared with crizotinib. This assessment was based on the fact that alectinib was shown to have a statistically significant positive effect compared with crizotinib in terms of time to disease progression in the central nervous system, which is associated with a significant deterioration in the prognosis of the patient. For ceritinib, on the other hand, no additional benefit was found in the benefit assessment by the G-BA compared with the appropriate comparator therapy (crizotinib). No valid data were available to assess the additional benefit (resolution of 1 February 2018)

In the overall review of the evidence available, the active ingredients crizotinib or alectinib are therefore identified as equally appropriate comparator therapies in the present therapeutic indication.

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

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of brigatinib as monotherapy is assessed as follows:

a) Adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) with brain metastases previously not treated with an ALK inhibitor:

For brigatinib for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor and who had brain metastases at the start of study, there is a hint for a considerable additional benefit.

b) Adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) without brain metastases previously not treated with an ALK inhibitor:

For brigatinib for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor and who did not have brain metastases at the start of study, there is a hint for a minor additional benefit.

Justification:

To demonstrate an additional benefit of brigatinib for the treatment of ALK-positive advanced non-small cell lung cancer (NSCLC), the pharmaceutical company has presented the results of the ALTA-1L study.

ALTA-1L is a multi-centre, open-label, randomised controlled study in which brigatinib is compared with crizotinib. The ongoing global study, which started in May 2016, included adult patients with ALK-positive, locally advanced, recurrent or metastatic NSCLC. For inclusion, patients were allowed a maximum of one systemic previous therapy for the advanced or metastatic stage. However, previous therapy with a tyrosine kinase inhibitor was not allowed. Furthermore, patients should have had an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of ≤ 2. While patients with symptomatic CNS metastases were excluded from the ALTA-1L study, patients with asymptomatic CNS metastases were allowed to participate.

The 275 patients included were randomised at a ratio of 1:1 to the intervention arm (brigatinib; N = 137) and the comparator arm (crizotinib; N = 138) and stratified by the presence of brain metastases at the start of study (yes vs no) and prior chemotherapy for the treatment of the advanced or metastatic disease (yes vs no).

Treatment with the study medication was to be continued until disease progression, the start of a new antineoplastic therapy, or discontinuation for other reasons (e.g. because of AE or patient decision).

In the intervention arm, even with disease progression, treatment with brigatinib was continued as long as patients had a clinical benefit according to the assessment of the study physician. After disease progression, patients in the control arm were able to receive brigatinib as follow-up therapy at the investigator's discretion.

ALTA-1L is being conducted in 92 study centres in North America, Asia, Australia, and Europe.

For the benefit assessment, the data cut-off of 28 June 2019 was submitted; this corresponds to the 2nd interim analysis planned after 149 events for the primary endpoint progression-free survival (PFS). The final data cut-off is planned after the occurrence of 198 PFS events. A further data cut-off (primary analysis for the overall survival endpoint) is planned after the occurrence of approx. 150 deaths.

Extent and probability of the additional benefit

Mortality

In the ALTA-1L study, overall survival was defined as the time between randomisation and death regardless of the underlying cause of death.

For the overall survival endpoint, there was no statistically significant difference between study arms in the overall study population.

However, the was an effect modification was shown by the characteristic "brain metastases at the start of study", which showed a statistically significant effect in favour of brigatinib compared with crizotinib for patients with brain metastases at the start of study. For patients without brain metastases at the start of study, there was no difference between the study arms. Median survival had not yet been achieved because of the low number of events in the ALTA-1L study; final analyses on the endpoint overall survival are pending.

In the present therapeutic indication CNS metastases have a high clinical relevance. Patients with ALK-positive non-small cell lung cancer are more likely to develop CNS metastases during the course of the disease than patients with other molecular biological entities of non-small cell lung cancer. The prognosis of patients is significantly worsened by the occurrence of brain metastases as well as because of the limited treatment options.

Against this background and the effect modifications, the G-BA considers it appropriate to divide the patient population with regard to the characteristic "with or without brain metastases

at the start of treatment" and to carry out a separate assessment of the additional benefit in each case.

For patients with brain metastases at the start of study, treatment with brigatinib shows to a prolongation of survival compared with treatment with crizotinib; this is considered a considerable improvement

For patients without brain metastases at the start of study, there was no statistically significant difference between the treatment arms.

Morbidity

Progression-free survival (PFS)

In the ALTA-1L study, progression-free survival was the primary endpoint and was defined as the time between randomisation and disease progression (determined using the RECIST criteria version 1.1) or death regardless of the underlying cause.

The PFS in the intervention arm was significantly longer than in the control arm.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. In the present study, the endpoint component "mortality" was surveyed as an independent endpoint using the endpoint overall survival. The morbidity component was not assessed on the basis of symptoms but rather exclusively using imaging procedures (radiologically determined disease progression according to the RECIST criteria). Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the PFS endpoint.
The overall statement on the extent of the additional benefit remains unaffected.

Time to CNS progress

In the ALTA-1L study, time to CNS progression was defined as the time from randomisation to the first radiological detection of progression of brain metastases already present at the start of study and/or newly developed brain metastases since the start of study (detected using RECIST criteria Version 1.1).

As already described, patients with ALK-positive non-small cell lung cancer are more likely to develop CNS metastases during the course of the disease than patients with other molecular biological entities of non-small cell lung cancer.

Because the prognosis of patients is significantly deteriorated, in particular by the first occurrence of CNS metastases or the progression of existing metastases in conjunction with newly occurring symptomatology, the endpoint "time to CNS progress" has particular clinical relevance for the present patient population. This is also due to the limited therapeutic options (surgery/radiosurgery/radiotherapy) for CNS metastases, which can also result in considerable morbidity in patients, partly because of cognitive limitations. The time to CNS progression is therefore considered a patient-relevant morbidity endpoint for the patient population studied here.

In the ALTA-1L study, CNS progression was assessed using the RECIST criteria Version 1.1. This means that the survey was carried out exclusively using imaging techniques and not additionally on the basis of disease symptoms. Thus, the operationalisation of the endpoint is not directly relevant to patients. The RANO criteria provide an option to assess the clinical-neurological status of patients and corticosteroid consumption in clinical studies. This was not used in the ALTA-1L study.

In the analyses in the dossier of the pharmaceutical company, patients with a progress outside the CNS were censored. Thus, only those CNS progression events that occurred outside the CNS before progression of the disease were included in the evaluation. In the written statement procedure, the pharmaceutical company later submitted evaluations that were not censored accordingly. However, according to the study protocol, the CNS progression was only monitored until the last administration of the study medication, until disease progression or the

start of a new systemic cancer therapy. The CNS progression could therefore not be fully recorded regardless of the evaluation. Thus, only for a selective proportion of the randomised patients was a CNS progression (even after progression outside the CNS) considered in the evaluation.

In summary, the endpoint in the present operationalisation is not suitable for assessing the patient-relevant therapeutic effects with regard to CNS progression. The results are presented additionally.

Symptomatology

In the ALTA-1L study, the symptomatology was measured using the symptom scales of the disease-specific questionnaire EORTC QLQ-C30. In the study, data were collected regularly (every 4 weeks) until 30 days after the end of treatment.

The symptomatology in the ALTA-1L study was also assessed in accordance with a protocol change using the additional lung cancer-specific module EORTC QLQ-LC13. However, this survey did not start until approx. 4 months after the inclusion of the first patient. In view of the low return rates in relation to the total population, a relevant part of the study population was not included in the survey. The pharmaceutical company therefore did not present any results for the EORTC QLQ-LC13 in the benefit assessment dossier. In the IQWiG benefit assessment, this procedure was assessed as inappropriate because a random and representative sub-population was to be assumed for the patients included after the introduction of the EORTC QLQ-LC13. Against this background, the pharmaceutical company submitted corresponding evaluations of the EORTC QLQ-LC13 within the framework of the written statement procedure on the present benefit assessment.

For EORTC QLQ-C30, the pharmaceutical company presented responder analyses for the time to first deterioration (defined as an increase of the score by at least 10 points compared with baseline) in the dossier for the benefit assessment.

For the endpoints nausea and vomiting, constipation, fatigue, and loss of appetite, there was a statistically significant difference to the advantage of brigatinib compared with crizotinib For the pain endpoint, there was no statistically significant difference between the study arms. However, for this endpoint, there was an effect modification using the characteristic “sex”. This showed a statistically significant effect in favour of brigatinib compared with crizotinib for women. For men, there was no difference between treatment groups. For all further endpoints presented, there was no statistically significant difference between the study arms.

For the EORTC QLQ-LC13, the pharmaceutical company submitted responder analyses for the time to first deterioration (defined as an increase of the score by at least 10 points compared with baseline) in the written statement procedure.

For the endpoints pain (arm / shoulder) and peripheral neuropathy, there was a statistically significant difference to the advantage of brigatinib compared with crizotinib.

Because of the delayed survey the EORTC QLQ-LC13, only 63 patients in the brigatinib arm and 78 patients in the crizotinib arm were included in the questionnaire survey. The results available are therefore subject to uncertainties because the return rate for the questionnaire in relation to the ITT population was already ≤ 70% at the beginning of the survey. Even though it remains unclear to what extent the patients with missing values are representative of the overall study population, it is assumed that the values are not systematically missing because of the direction of effect. In the present case, the G-BA considers it appropriate, despite the remaining uncertainties regarding the poor return rates, to take the data for the present benefit assessment into account, especially because the patients included are a random and representative sub-population.

Overall, both patients with and without brain metastases at the start of study showed a relevant improvement in symptomatology through positive effects on individual endpoints when treated with brigatinib compared with treatment with crizotinib.

Quality of life

In the ALTA-1L study, the functional scales of the disease-specific questionnaire EORTC QLQ-C30 were used to assess the health-related quality of life. In the study, data were collected regularly (every 4 weeks) until 30 days after the end of treatment.

For the benefit assessment, the pharmaceutical company presented in the dossier responder analyses for the time to first deterioration (defined as a decrease of the score by at least 10 points compared with baseline).

For the endpoints global health status and emotional functioning, there was a statistically significant difference to the advantage of brigatinib compared with crizotinib. For the role functioning endpoints, there was no statistically significant difference between the study arms. For the endpoint social functioning, there was a statistically significant difference to the advantage of brigatinib. However, an effect modification according to the characteristic “sex” occurred for these two endpoints. This showed a statistically significant effect in favour of brigatinib compared with crizotinib for women. For men, there was no difference between treatment groups.

Overall, treatment with brigatinib shows an advantage in health-related quality of life compared with treatment with crizotinib for both patient population a) and patient population b).

Side effects

Adverse events (AE)

All endpoints on adverse events were surveyed up to 30 days after the end of treatment.

In ALTA-1L, an adverse event occurred in almost every patient in both study arms.

Serious adverse events (SAE)

For the serious adverse events, there was no statistically significant difference between the study arms.

Severe AE (CTCAE grade ≥ 3)

With regard to severe adverse events with CTCAE grade ≥ 3, there was no statistically significant difference between the study arms.

Discontinuation because of AE

For the endpoint “therapy discontinuation because of an AE”, there was no statistically significant difference between the study arms.

Specific AE

With regard to specific AE eye disorders (SOC), peripheral oedema (PT), and gastrointestinal disorders (SOC), there was a statistically significant difference to the advantage of brigatinib compared with crizotinib.

For the specific AE skin and subcutaneous tissue disorders (SOC), there was a statistically significant difference to the disadvantage of brigatinib. However, there was an effect modification for this endpoint by the characteristic “age”, according to which there was a statistically significant difference to the disadvantage of brigatinib in patients ≥ 65 years. There was no statistically significant difference for patients < 65 years.

With respect to the specific severe AE (CTCAE grade ≥ 3) creatine phosphokinase increased (PT) and hypertension (PT), there was a statistically significant difference to the disadvantage of brigatinib compared with crizotinib.

In the overall view, for the side effects, there is no statistically significant difference between the study arms with regard to the endpoints serious AE, severe adverse events (CTCAE grade ≥ 3), and discontinuation because of AE. In detail, for the specific AE, there are both positive and negative effects of brigatinib compared with crizotinib.

Overall assessment

To assess the additional benefit of brigatinib compared with crizotinib, results on mortality (overall survival), morbidity (symptomatology), health-related quality of life, and side effects are available from the open-label, randomised, controlled ALTA-1L study.

For the overall survival endpoint, an effect modification was shown by the characteristic “brain metastases at the start of study: yes/no”, which showed a statistically significant effect in favour of brigatinib compared with crizotinib for patients with brain metastases at the start of study. For patients without brain metastases at the start of study, there was no statistically significant difference between the study arms.

In the present therapeutic indication CNS metastases have a high clinical relevance. Patients with ALK-positive non-small cell lung cancer are more likely to develop CNS metastases during the course of the disease than patients with other molecular biological entities of non-small cell lung cancer. The prognosis of patients is significantly worsened by the occurrence of brain metastases as well as because of the limited treatment options. Based on the results of the ALTA-1L study, in particular because of the existing effect modification in overall survival, the G-BA considers a subdivision of the patient population according to the characteristic “with or without brain metastases” to be appropriate.

a) Adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) with brain metastases previously not treated with an ALK inhibitor:

In the endpoint category mortality, the results for the endpoint overall survival for the sub-group of patients with brain metastases at the start of study show a statistically significant prolongation in survival time compared with treatment with crizotinib. This is assessed as a considerable improvement. Median survival had not yet been achieved because of the low number of events; final analyses on the endpoint overall survival are pending.

In the morbidity category, there is a relevant improvement in symptomatology (measured by EORTC QLQ-C30 and EORTC QLQ-LC13) because of positive effects on individual endpoints under brigatinib compared with crizotinib. These can be seen in the patient reported symptoms of nausea and vomiting, constipation, fatigue, and loss of appetite (EORTC QLQ-C30) as well as pain (arm/shoulder) and peripheral neuropathy (EORTC QLQ-LC13).

For health-related quality of life, there were also positive effects of treatment with brigatinib. These were observed for the patient-reported endpoints global health status, emotional functioning, and social functioning. In the health-related quality of life category, brigatinib has an advantage compared with crizotinib.

For the side effects, there is no statistically significant difference between the study arms with regard to the endpoint serious AE. There is no statistically significant difference between the study arms for the severe adverse events (CTCAE grade ≥ 3) and discontinuation because of AE. In detail, for the specific AE, there are both positive and negative effects of brigatinib compared with crizotinib.

Overall, for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer with brain metastases previously not treated with an ALK inhibitor, the G-BA found a considerable additional benefit for brigatinib compared with crizotinib.

b) Adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) without brain metastases previously not treated with an ALK inhibitor:

In the endpoint category mortality, the results for the overall survival endpoint show no statistically significant difference in survival time for the subgroup of patients without brain metastases at the start of study compared with treatment with crizotinib. Median survival had not yet been achieved because of the low number of events; final analyses on the endpoint overall survival are pending.

In the morbidity category, there is a relevant improvement in symptomatology (measured by EORTC QLQ-C30 and EORTC QLQ-LC13) because of positive effects on individual endpoints under brigatinib compared with crizotinib. These can be seen in the patient reported symptoms of nausea and vomiting, constipation, fatigue, and loss of appetite (EORTC QLQ-C30) as well as pain (arm/shoulder) and peripheral neuropathy (EORTC QLQ-LC13).

For health-related quality of life, there were also positive effects of treatment with brigatinib. These were observed for the patient-reported endpoints global health status, emotional functioning, and social functioning. In the health-related quality of life category, brigatinib has an advantage compared with crizotinib.

For the side effects, there is no statistically significant difference between the study arms with regard to the endpoint serious AE. There is no statistically significant difference between the study arms for the severe adverse events (CTCAE grade ≥ 3) and discontinuation because of AE. In detail, for the specific AE, there are both positive and negative effects of brigatinib compared with crizotinib.

Overall, for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer without brain metastases previously not treated with an ALK inhibitor, the G-BA found a minor additional benefit for brigatinib compared with crizotinib.

Reliability of data (probability of additional benefit)

a) Adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) with brain metastases previously not treated with an ALK inhibitor:

The present assessment is based on the results of an open, randomised controlled study. The cross-endpoint risk of bias is considered low for the study.

The endpoint specific risk of bias for the overall survival endpoint is also considered low. Because of the broad 95% confidence interval for the effect estimator on the hazard ratio for the corresponding sub-group, there is an uncertainty regarding the precision of the effect estimate.

In the endpoint categories morbidity and health-related quality of life, the results for EORTC QLQ-C30 and EORTC QLQ-LC13 are expected to have a high risk of bias. This is due to the lack of blinding in subjective endpoint surveys as well as the return rate of the questionnaires, which decreased sharply during the course of the study and differed between the study arms. Moreover, for the EORTC QLQ-LC13 only the evaluations of one sub-population are available. This is because the survey of the questionnaire was started only about 4 months after the inclusion of the first patient. At this time, 134 of the total 275 patients had already been randomised.

In the side effects endpoint category, the open study design contributes to a high risk of bias for the non-serious or non-severe endpoints.

For these reasons, the reliability of data for the additional benefit determined is considered as a hint.

b) Adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) without brain metastases previously not treated with an ALK inhibitor:

The present assessment is based on the results of an open, randomised controlled study. The cross-endpoint risk of bias is considered low for the study.

The endpoint specific risk of bias for the overall survival endpoint is also considered low. For the assessment of the reliability of data, it is also taken into account that for patients without brain metastases at the start of study, there is a clear reversal in the direction of the effect on overall survival (in the absence of statistical significance of the effect estimate).

In the endpoint categories morbidity and health-related quality of life, the results for EORTC QLQ-C30 and EORTC QLQ-LC13 are expected to have a high risk of bias. This is due to the lack of blinding in subjective endpoint surveys as well as the return rate of the questionnaires, which decreased sharply during the course of the study and differed between the study arms. Moreover, for the EORTC QLQ-LC13 only the evaluations of one sub-population are available. This is because the survey of the questionnaire was started only about 4 months after the inclusion of the first patient. At this time, 134 of the total 275 patients had already been randomised.

In the side effects endpoint category, the open study design contributes to a high risk of bias for the non-serious or non-severe endpoints.

For these reasons, the reliability of data for the additional benefit determined is considered as a hint.

2.1.4 Summary of the assessment

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

> "Alunbrig is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor".

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

> Crizotinib or alectinib

The pharmaceutical company presents the results on mortality, morbidity, health-related quality of life, and side effects from the open-label, randomised, controlled ALTA-1L study in which brigatinib is compared with crizotinib. The ALTA-1L study included patients with ALK-positive, locally advanced, recurrent or metastatic NSCLC who had previously received at most a systemic previous therapy for the advanced or metastatic stage but no previous therapy with a tyrosine kinase inhibitor.

For the overall survival endpoint, an effect modification was shown by the characteristic "brain metastases at the start of study: yes/no", which showed a statistically significant effect in favour of brigatinib compared with crizotinib for patients with brain metastases at the start of study. For patients without brain metastases at the start of study, there was no statistically significant difference between the study arms.

Based on this effect modification and the high clinical relevance of CNS metastases in the present therapeutic indication, the G-BA considers a sub-division of the patient population according to the characteristic "with or without brain metastases" to be appropriate. The following patient populations result:

a) adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) with brain metastases previously not treated with an ALK inhibitor

b) adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) without brain metastases previously not treated with an ALK inhibitor

Patient population a)

In the mortality category, there is a statistically significant effect in favour of brigatinib; this is assessed as a significant improvement.

Similarly, for some patient-reported morbidity and quality of life endpoints, brigatinib has clear advantages compared with crizotinib.

There are no advantages or disadvantages for brigatinib in the side effects endpoint category.

As a result, the G-BA found a considerable additional benefit for brigatinib as monotherapy compared with crizotinib.

In view of the open study design and the existing uncertainties in the endpoint overall survival with regard to the broad 95% confidence interval for the effect estimator on the hazard ratio and taking into account further uncertainties, only a hint for an additional benefit can be derived with regard to the reliability of data.

Patient population b)

In the mortality category, there was no statistically significant effect in favour of brigatinib.

In several patient-reported morbidity and quality of life endpoints, brigatinib shows clear advantages compared with crizotinib.

There are no advantages or disadvantages for brigatinib in the side effects endpoint category.

As a result, the G-BA found a minor additional benefit for brigatinib as monotherapy compared with crizotinib.

In view of the open study design and further uncertainties, only a hint for an additional benefit can be derived with regard to the reliability of data.

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).

In order to enable a consistent consideration of patient numbers, taking into account the most recent resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in therapeutic indication first-line treatment of metastatic non-small cell lung cancer (NSCLC) (ramucirumab, resolution of 20 August 2020; atezolizumab (combination with nab-paclitaxel and carboplatin), resolution of 2 April 2020; atezolizumab (combination with bevacizumab, paclitaxel and carboplatin), resolution of 2 April 2020; and others), the G-BA uses the following derivation of patient numbers:

For the number of patients in Germany with lung cancer, only the incidence for the year 2020 is used as the basis for the calculations because these are patients in first-line treatment. This patient population is narrowed down to the target population by further calculation steps as follows:

1. Incidence of lung cancer: 62,380 patients for 2020.[2]

[2] Resolution on ramucirumab (NSCLC, 1st EGFR mutation, combination with erlotinib) of 20 August 2020; references in the dossier assessment of the IQWiG (A20-13; ramucirumab (NSCLC, combination with erlotinib) of 13 May 2020.

2. The proportion of lung cancer patients with NSCLC is 80.3–82.0%.[3]
3. Of these, 61.6–66.1% are stage IIIB/IV patients.[4]
4. First-line treatment is performed in 76.9 to 78.5% of cases.
5. 2.0 to 3.9% of the patients have ALK-positive tumours.',[5]
6. 87.5% of patients are currently covered by statutory health insurance.

This results in a calculated number of 415 to 906 patients for the lower and upper limits.

Because of uncertainties regarding the data basis, both over- and underestimation of the patient numbers are possible.

With regard to a division of the number of patients in the target population into patients with and without brain metastases, no information was provided by the pharmaceutical company.

In accordance with the information in the dossier, between 15% and 35% of patients already had brain metastasis at the time of diagnosis, and this proportion can increase to 70% in the course of the disease. In the study presented, this was 30%.

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 Alunbrig® (active ingredient: brigatinib) at the following publicly accessible link (last access: 28 July 2020):

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

Treatment with brigatinib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in internal medicine and pneumology, specialists in pulmonary medicine, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with advanced bronchial carcinoma.

ALK verification

The ALK-positive NSCLC status should be known before initiating treatment with Alunbrig.

A validated ALK test is necessary to identify patients with ALK-positive NSCLC (see Section 5.1). The ALK-positive NSCLC status should be determined by laboratories with proven experience in the specific technique required.

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 September 2020).

[3] Resolution on ramucirumab (NSCLC, 1st line, EGFR mutation, combination with erlotinib) of 20 August 2020; references in the dossier assessment of the IQWiG (A16-11; ramucirumab (lung cancer)) of 30 May 2016
[4] Resolution on lorlatinib of 22 November 2019; references in the dossier assessment of the IQWiG (A16-11; ramucirumab (lung cancer)) of 30 May 2016.
[5] Resolution on atezolizumab (NSCLC, non-squamous, 1st line, combination with nab-paclitaxel and carboplatin) of 2 April 2020; references in the dossier assessment of the IQWiG (A15-59; crizotinib) of 30 March 2016.

In accordance with the product information of brigatinib (last revised 04/ 2020), the dosage is 90 mg once a day in Week 1, and 180 mg once a day from week 2 onwards.

According to the product information of crizotinib (last revised: 10/2019), the dosage is 500 mg/day divided into 2 doses of 250 mg each.

According to the product information (as of 04/ 2020), alectinib is administered at a maximum daily dose of 1200 mg – divided into 2 doses of 4 capsules of 150 mg each.

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 different for each individual patient and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, the time between individual treatments, and the maximum treatment duration if specified in the product information.

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Brigatinib	continuously, 1 × daily	365	1	365
Appropriate comparator therapy				
Patient population a) and b)				
Crizotinib	continuously, 2 × daily	365	1	365
Alectinib	continuously, 2 × daily	365	1	365

Usage and 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					
Brigatinib	Day 1–7: 90 mg from Day 8: 180 mg	90 – 180 mg	1 × 90 mg – 1 × 180 mg	365	7 × 90 mg + 358 × 180 mg
Appropriate comparator therapy					
Patient population a) and b)					
Crizotinib	250 mg	500 mg	2 × 250 mg	365	730 × 250 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
Alectinib	600 mg	1200 mg	8 × 150 mg	365	2920 × 150 mg

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 Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the 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 product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Brigatinib starter pack 90 mg + 180	28 FCT	€ 5,321.26	€ 1.77	€ 308.48	€ 5,011.01
Brigatinib 180 mg	28 FCT	€ 5,321.26	€ 1.77	€ 308.48	€ 5,011.01
Appropriate comparator therapy					
Patient population a) and b)					
Crizotinib 250 mg	60 HC	€ 5,289.16	€ 1.77	not applicable	€ 5,287.39
Alectinib 150 mg	224 HC	€ 5,825.96	€ 1.77	€ 338.05	€ 5,486.14

FCT = film-coated tablets, HC = hard capsules

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 September 2020

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 assessed and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations

(e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the appropriate comparator therapy according to the product information, no costs for additionally required SHI services had to be taken into account.

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

At its session on 12 June 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 24 April 2020, the pharmaceutical company submitted a dossier for the benefit assessment of brigatinib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 29 April 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 brigatinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 30 July 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 3 August 2020. The deadline for submitting written statements was 24 August 2020.

The oral hearing was held on 8 September 2020.

By letter dated 8 September 2020, 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 25 September 2020.

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 6 October 2020, and the proposed resolution was approved.

At its session on 15 July 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	12 June 2019	Determination of the appropriate comparator therapy
Working group Section 35a	1 September 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	8 September 2020	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	15 September 2020 29 September 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	6 October 2020	Concluding discussion of the draft resolution
Plenum	15 October 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 15 October 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken