IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Alectinib (non-small cell lung cancer) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Alectinib (nicht kleinzelliges Lungenkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 July 2017). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[3] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AEs	adverse events
AJCC	American Joint Committee on Cancers
ALK	anaplastic lymphoma kinase
BSC	best supportive care
CI	confidence interval
CNS	central nervous system
CORR	objective response rate in the central nervous system
ECOG PS	Eastern Cooperative Oncology Group Performance Status
G-BA	Federal Joint Committee
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IRC	independent review committee
NSCLC	non-small cell lung cancer
ORR	objective response rate
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria In Solid Tumours
SGB	Social Code Book
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug alectinib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 2 May 2017.

Research question

The aim of this report was to assess the added benefit of alectinib in comparison with the appropriate comparator therapy (ACT) in adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib.

Three research questions derived from the specification of the ACT resulted for the assessment. Table 2 shows an overview of the research questions.

Table 2: Research questions on the benefit assessment of alectinib

Research question	Subindication	ACT[a]
1	Crizotinib-pretreated adult patients with ALK-positive advanced NSCLC who have not received prior chemotherapy	(ECOG PS) 0, 1 or 2: ▪ **cisplatin in combination with a third-generation cytostatic agent** (vinorelbine, gemcitabine, docetaxel, paclitaxel or pemetrexed) under consideration of the approval status or ▪ **carboplatin in combination with a third-generation cytostatic agent** (only for patients with increased risk of cisplatin-induced side effects within the framework of a combination therapy; see Appendix VI to Section K of the Pharmaceutical Directive) Patients with ECOG PS 2: ▪ as an alternative to the platinum-based combination therapy: monotherapy with gemcitabine or vinorelbine
2	Crizotinib-pretreated adult patients with ALK-positive advanced NSCLC who were eligible for treatment with docetaxel or pemetrexed after pretreatment with platinum-based chemotherapy	**Docetaxel** or **pemetrexed**
3	Crizotinib-pretreated adult patients with ALK-positive advanced NSCLC for whom treatment with docetaxel or pemetrexed is not an option after pretreatment with platinum-based chemotherapy	BSC[b]

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Best supportive care (BSC) refers to the therapy that provides the patient with the best possible individually optimized supportive treatment to alleviate symptoms and improve quality of life.
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer

For easier presentation and better readability, the present benefit assessment uses the following terms for the 3 patient populations:

- Research question 1: Patients who have not received prior chemotherapy
- Research question 2: Patients for whom treatment with docetaxel or pemetrexed is an option
- Research question 3: Patients for whom treatment with docetaxel or pemetrexed is not an option

The company expanded the ACT on research questions 1 and 2 with ceritinib. In research question 3, the company expanded the patient population with patients for whom treatment with ceritinib is not an option. The ACT specified by the G-BA was used for the present benefit assessment.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

Research questions 1 and 2: Patients who have not received prior chemotherapy or for whom treatment with docetaxel or pemetrexed is an option

For research questions 1 and 2, the company identified no directly comparative randomized controlled or non-randomized studies on the comparison of alectinib with the ACTs. The company therefore presented comparisons using individual arms from different studies.

For alectinib, the company included subpopulations from two single-arm prospective phase 2 studies (studies NP28673 and NP28761) for research questions 1 and 2. Both studies are single-arm, multicentre approval studies of alectinib. The studies included adult patients with locally advanced (stage IIIB according to American Joint Committee on Cancers, AJCC), non-curatively treatable or metastatic (AJCC stage IV) ALK-positive NSCLC who had progressed under treatment with crizotinib.

For the comparator therapy, the company used data from the US cancer database (Flatiron Health Database) on the outcome "overall survival" for research question 1 (patients who have not received prior chemotherapy). Due to the non-interventional design, the data from the Flatiron Health Database are a retrospective case series. Since the company identified no further relevant studies for research question 1 within the therapeutic indication of alectinib, it used the arm of the platinum-based combination chemotherapy from the randomized controlled trial (RCT) PROFILE 1014 as the best approximation for further outcomes. The study was not conducted within the therapeutic indication of alectinib because the included patients were treatment-naive and had not been pretreated with crizotinib.

For research question 2 (patients for whom treatment with docetaxel or pemetrexed is an option), the company also used data from the US Flatiron Health cancer database for the outcome "overall survival". For further outcomes, the company used the comparator arm from the RCT ASCEND-5. This ASCEND-5 study was within the therapeutic indication of alectinib and examined the patient population relevant for research question 2.

The data presented by the company were unsuitable to derive an added benefit of alectinib in comparison with the ACTs platinum-based combination chemotherapy (research question 1) and docetaxel or pemetrexed (research question 2).

Comparison of single-arm studies on alectinib with data of the Flatiron Health Database (research questions 1 and 2) on the outcome "overall survival"

For the comparison of results on the outcome "overall survival" with the ACTs platinum-based combination chemotherapy (research question 1) and pemetrexed or docetaxel (research question 2), the company used propensity score matching to compare the respective relevant subpopulations from the single-arm alectinib studies with the data of a US cancer database (Flatiron Health Database) on adult patients with locally advanced or metastatic ALK-positive NSCLC who had progressed under treatment with crizotinib.

The company based the derivation of the added benefit on the results of the "adjusted central analysis". Within the framework of the adjusted analysis the patient groups were weighted using "inverse probability of treatment weighting", which produced artificially increased sample sizes on both sides of the comparison. Therefore, the calculation of the respective confidence interval (CI) for the hazard ratio yielded CIs that were too narrow and suggested an inadequately high accuracy and were thus unsuitable for the derivation of conclusions on the added benefit. This could not be inferred from the information on the analyses provided by the company.

Moreover, the data on the survival times of patients who had been treated with docetaxel or pemetrexed differed notably between the ASCEND-5 study used by the company for research question 2 and the Flatiron Health Database. The patients of the ASCEND-5 study survived more than twice as long as the patients included in the Flatiron Health Database (median: 20.1 vs. 8.7 months), which additionally raised doubts about the relevance of the effects from the "adjusted central analysis" presented by the company.

Apart from the fact that the effects on overall survival presented by the company were weak enough to be caused by systematic bias alone, their reliable assessment was impossible due to the described major uncertainties. An added benefit for the outcome "overall survival" could therefore neither be derived for research question 1 nor for research question 2.

Comparison of single-arm studies on alectinib with the PROFILE 1014 study on the comparator therapy platinum-based combination chemotherapy (research question 1)

For research question 1, the company conducted a descriptive comparison on further outcomes using individual arms from different studies in addition to the comparison with the data of the Flatiron Health Database on the outcome "overall survival". For this purpose, the company compared results of the subpopulation of the alectinib studies NP28761 and NP28673 relevant for this research question with results of the ACT platinum-based combination chemotherapy from the chemotherapy arm of the PROFILE 1014 study. However, the company did not present effect estimates with CIs and p-values.

However, the differences between the treatment groups were small enough to be based on systematic bias alone. Thus, no added benefit of alectinib in comparison with the ACT

platinum-based combination chemotherapy could be derived from the data presented by the company.

Comparison of single-arm studies on alectinib with the ASCEND-5 study on the comparator therapy docetaxel or pemetrexed (research question 2)

For research question 2, the company conducted a descriptive comparison on further outcomes using individual arms from different studies in addition to the comparison with the data of the Flatiron Health Database on the outcome "overall survival". For this purpose, the company compared results of the subpopulations of the alectinib studies NP28761 and NP28673 relevant for this research question with results of the ACT docetaxel or pemetrexed from the chemotherapy arm of the ASCEND-5 study. However, the company did not present effect estimates with CIs and p-values.

For research question 2, the differences between the treatment groups were also small enough to be based on systematic bias alone. Thus, no added benefit of alectinib in comparison with the ACT could be derived from the data presented by the company.

RCT ALUR

In its search, the company identified an ongoing RCT on the direct comparison of alectinib versus docetaxel or pemetrexed in patients with ALK-positive advanced NSCLC previously treated with both crizotinib and a platinum-based combination chemotherapy (ALUR study). According to the company, the results of this study were not yet available at the time point of the submission of the dossier on the benefit assessment of alectinib to the G-BA on 27 April 2017, and were to be submitted later as far as they became available during the procedure. The ClinicalTrials.gov trial registry indicates 26 January 2017 as the date of the primary data analysis. However, the company's dossier does not indicate why the data of the RCT ALUR were not available at the time of the dossier submission. Against the background that with its dossier submission the company announced data of a directly comparative study that was potentially relevant for research question 2 (patients for whom treatment with docetaxel or pemetrexed is an option), it was not comprehensible why the company presented an elaborate comparison of individual arms from different studies based on extremely uncertain data. The present assessment of research question 2 on the basis of the presented comparisons using individual arms from different studies is therefore presumably irrelevant.

Patients for whom treatment with docetaxel or pemetrexed is not an option (research question 3)

In its dossier, the company presented no data on the comparison of alectinib with best supportive care (BSC) for research question 3. Hence, there was no hint of an added benefit of alectinib in comparison with BSC. An added benefit of alectinib is not proven for patients with ALK-positive advanced NSCLC after pretreatment with crizotinib and a platinum-based combination chemotherapy, for whom treatment with docetaxel or pemetrexed is not an option.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the probability and the extent of the added benefit of the drug alectinib compared with the ACT is assessed as follows:

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit). For further details see [1,2].

Table 3: Alectinib – probability and extent of added benefit

Research question	Subindication	ACT[a]	Extent and probability of added benefit
1	Crizotinib-pretreated adult patients with ALK-positive advanced NSCLC who have not received prior chemotherapy	Patients with ECOG PS 0, 1 or 2: ▪ **cisplatin in combination with a third-generation cytostatic agent** (vinorelbine, gemcitabine, docetaxel, paclitaxel or pemetrexed) under consideration of the approval status or ▪ **carboplatin in combination with a third-generation cytostatic agent** (only for patients with increased risk of cisplatin-induced side effects within the framework of a combination therapy; see Appendix VI to Section K of the Pharmaceutical Directive) Patients with ECOG PS 2: ▪ as an alternative to the platinum-based combination therapy: monotherapy with gemcitabine or vinorelbine	Added benefit not proven
2	Crizotinib-pretreated adult patients with ALK-positive advanced NSCLC who were eligible for treatment with docetaxel or pemetrexed after pretreatment with platinum-based chemotherapy	**Docetaxel** or **pemetrexed**	Added benefit not proven
3	Crizotinib-pretreated adult patients with ALK-positive advanced NSCLC for whom treatment with docetaxel or pemetrexed is not an option after pretreatment with platinum-based chemotherapy	BSC[b]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: BSC refers to the therapy that provides the patient with the best possible individually optimized supportive treatment to alleviate symptoms and improve quality of life.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of alectinib in comparison with the ACT in adult patients with ALK-positive advanced NSCLC previously treated with crizotinib.

In its specification of the ACT, the G-BA differentiated between crizotinib-pretreated patients who had not received prior chemotherapy and patients who had been pretreated with a platinum-based chemotherapy. The G-BA further differentiated the latter patients into patients for whom treatment with docetaxel or pemetrexed is an option and those patients for whom such treatment is not an option.

Therefore, 3 research questions derived from the specification of the ACT resulted for the assessment. Table 4 shows an overview of the research questions.

Table 4: Research questions on the benefit assessment of alectinib

Research question	Subindication	ACT[a]
1	Crizotinib-pretreated adult patients with ALK-positive advanced NSCLC who have not received prior chemotherapy	Patients with ECOG PS 0, 1 or 2: ▪ **cisplatin in combination with a third-generation cytostatic agent** (vinorelbine, gemcitabine, docetaxel, paclitaxel or pemetrexed) under consideration of the approval status or ▪ **carboplatin in combination with a third-generation cytostatic agent** (only for patients with increased risk of cisplatin-induced side effects within the framework of a combination therapy; see Appendix VI to Section K of the Pharmaceutical Directive) Patients with ECOG PS 2: ▪ as an alternative to the platinum-based combination therapy: monotherapy with gemcitabine or vinorelbine
2	Crizotinib-pretreated adult patients with ALK-positive advanced NSCLC who were eligible for treatment with docetaxel or pemetrexed after pretreatment with platinum-based chemotherapy	**Docetaxel** or **pemetrexed**
3	Crizotinib-pretreated adult patients with ALK-positive advanced NSCLC for whom treatment with docetaxel or pemetrexed is not an option after pretreatment with platinum-based chemotherapy	BSC[b]

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: BSC refers to the therapy that provides the patient with the best possible individually optimized supportive treatment to alleviate symptoms and improve quality of life.
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer

For easier presentation and better readability, the present benefit assessment uses the following terms for the 3 patient populations:

- Research question 1: Patients who have not received prior chemotherapy
- Research question 2: patients for whom treatment with docetaxel or pemetrexed is an option
- Research question 3: patients for whom treatment with docetaxel or pemetrexed is not an option

The company expanded the ACT of the G-BA on research questions 1 and 2 with ceritinib. In research question 3, the company expanded the patient population with patients for whom treatment with ceritinib is not an option. This approach was not followed (see Section 2.6.1 of the full dossier assessment). The ACT specified by the G-BA was used for the present benefit assessment.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 Research questions 1 and 2: Patients who have not received prior chemotherapy or for whom treatment with docetaxel or pemetrexed is an option

2.3.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study lists on alectinib (status: 24 February 2017)
- bibliographical search on alectinib (last search on 15 February 2017)
- search in trial registries for studies on alectinib (last search on 8 February 2017)
- bibliographical search on ACTs (last search on 15 February 2017)
- search in trial registries for studies on ACTs (last search on 23 February 2017)

To check the completeness of the study pool:

- bibliographical search on alectinib (last search on 6 June 2017)
- search in trial registries for studies on alectinib (last search on 12 May 2017)

The check identified no further directly comparative study on alectinib in comparison with the ACT.

With its information retrieval, the company identified no directly comparative randomized controlled or non-randomized studies on the comparison of alectinib with the ACTs apart from the ALUR study. The company did not use the identified RCT ALUR for the benefit assessment because data were not available at the time point of the dossier submission (see further below in this section).

Since data of directly comparative studies were not available to the company, it presented comparisons of individual arms from different studies for research questions 1 and 2.

The data presented by the company were unsuitable to derive an added benefit of alectinib. This is justified below for research questions 1 (patients who have not received prior chemotherapy) and 2 (patients for whom treatment with docetaxel or pemetrexed is an

option). Because the company partly presented data from the same studies for both questions, the evidence provided by the company is first summarized.

Data presented by the company

Table 5 shows an overview of the studies included by the company for research questions 1 and 2.

Table 5: Study pool of the company – further investigations: studies on alectinib and on the ACT

Research question	Subindication	Data presented by the company
Crizotinib-pretreated adult patients with ALK-positive advanced NSCLC		
1	Patients who have not received prior chemotherapy	Studies on alectinib: ▪ NP28673 [NCT01801111] ▪ NP28761 [NCT01871805]
		Studies on the comparator therapy platinum-based combination chemotherapy: ▪ Flatiron Health Database ▪ PROFILE 1014 [NCT01154140][a]
2	Patients for whom treatment with docetaxel or pemetrexed is an option	Studies on alectinib: ▪ NP28673 [NCT01801111] ▪ NP28761 [NCT01871805]
		Studies on the comparator therapy pemetrexed or docetaxel: ▪ Flatiron Health Database ▪ ASCEND-5 [NCT01828112]
a: Inclusion of the study by the company irrespective of the pretreatment with crizotinib. ALK: anaplastic lymphoma kinase, NSCLC: non-small cell lung cancer		

For alectinib, the company included subpopulations from two single-arm prospective phase 2 studies (studies NP28673 [3-14] and NP28761 [8,12-21]) for research questions 1 and 2 which were conducted within the investigated therapeutic indication (crizotinib-pretreated patients with ALK-positive advanced NSCLC). The check of the completeness of the company's study pool identified no additional potentially relevant studies on alectinib.

For the comparator therapy, the company used data from the US cancer database (Flatiron Health Database, [22]) for research question 1 (patients who have not received prior chemotherapy). Due to the non-interventional design, these data constitute a retrospective case series. The company compared the data from the Flatiron Health Database with the 2 single-arm alectinib studies using propensity score matching. However, this comparison only yielded results on the outcome "overall survival".

Besides the data from the Flatiron Health Database on the outcome "overall survival", the company identified no relevant studies for research question 1 within the therapeutic

indication of alectinib. According to the company, it therefore used the arm of the platinum-based combination chemotherapy of RCT PROFILE 1014 [23-25] for further outcomes as the best approximation to the therapeutic indication to conduct a descriptive comparison using individual arms from different studies. The study was not conducted within the therapeutic indication of alectinib because the included patients were treatment-naive and had not been pretreated with crizotinib.

For research question 2 (patients for whom treatment with docetaxel or pemetrexed is an option), the company also used data from the US cancer database (Flatiron Health Database, [22]). The company compared the data from the Flatiron Health Database with the two single-arm alectinib studies using propensity score matching. However, this comparison only yielded results on the outcome "overall survival".

Besides the data from the Flatiron Health Database on the outcome "overall survival", the company additionally identified the chemotherapy arm of RCT ASCEND-5 [26,27] for research question 2 for the implementation of a descriptive comparison using individual arms from different studies for further outcomes.

Studies on alectinib (NP28673 and NP28761)

Both studies are single-arm, multicentre approval studies of alectinib. The studies included adult patients with locally advanced (AJCC stage IIIB) non-curatively treatable or metastatic (AJCC stage IV) ALK-positive NSCLC who had progressed under treatment with crizotinib.

The patients had to have a general condition corresponding to Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 to 2. There were no limitations in the study regarding the number of previous lines of treatment, however, the patients had to be pretreated at least with crizotinib and were not allowed to have undergone prior therapy with another ALK inhibitor.

Study NP28673 included 138 patients, and study NP28761 included 87 patients. Depending on the pretreatment, relevant subpopulations from the two studies were included in the benefit assessment for research questions 1 and 2. Patients who had exclusively received crizotinib as prior therapy were considered for research question 1 (NP28673: n = 28; NP28761: n = 23). Multiply pretreated patients who had been treated with a platinum-based combination chemotherapy prior to crizotinib and for whom treatment with docetaxel and pemetrexed was an option were considered for research question 2 (these are patients with an ECOG PS $\leq$ 2; NP28673: n = 103; NP28761: n = 46).

The primary outcome of the two alectinib studies was the objective response rate (ORR) recorded by an independent review committee (IRC). Relevant secondary outcomes were overall survival, symptoms, health-related quality of life, and adverse events (AEs).

Tables on the further characteristics of the studies NP28673 and NP28761 can be found in Appendix A of the full dossier assessment.

Overall, the patient populations relevant for research questions 1 and 2 were investigated in the studies NP28673 and NP28761. Alectinib was administered in compliance with the requirements of the Summary of Product Characteristics (SPC) [28].

Flatiron Health Database

The Flatiron Health Database comprises treatment data from more than 200 medical practices and from an academic network of 725.000 patients with cancer diseases. According to the company, the database comprised 17% of the cancers newly diagnosed in the USA in 2016. Data on the overall survival of adult patients with locally advanced (AJCC stage IIIB), non-curatively treatable or metastatic (AJCC stage IV) ALK-positive NSCLC were used for the comparison with alectinib. The disease had been diagnosed between 1 January 2011 and 21 December 2014, and the patients were observed until 28 February 2016. The patients should have progressed under treatment with crizotinib. Detailed information on the treatment of the patients who were included in the analyses were not available. The outcome of the study was overall survival.

Tables on the characteristics of the retrospective case series from the Flatiron Health Database can be found in Appendix A of the full dossier assessment.

Study PROFILE 1014 on the comparator therapy platinum-based combination chemotherapy

The PROFILE 1014 study was an open-label, multicentre, randomized controlled phase III study that compared crizotinib with the platinum-based combination chemotherapy in treatment-naive patients with ALK-positive NSCLC in the locally advanced or metastatic stage. The study was thus not conducted within the therapeutic indication of alectinib because the included patients were treatment-naive and had not been pretreated with crizotinib.

The primary outcome of the study was progression-free survival. Relevant secondary outcomes were overall survival, symptoms, health-related quality of life, and AEs.

Tables on the characteristics of the PROFILE 1014 study can be found in Appendix A of the full dossier assessment.

Study ASCEND-5 on the comparator therapy docetaxel or pemetrexed

The ASCEND-5 study was an open-label, multicentre, randomized controlled phase III study that compared ceritinib with docetaxel or pemetrexed in patients with advanced ALK-positive NSCLC (stage IIIB or IV). The patients had been pretreated with both crizotinib and 1 or 2 chemotherapy regimens (including a platinum-based combination chemotherapy). The ASCEND-5 study included by the company was thus conducted within the therapeutic indication of alectinib and investigates the patient population relevant for research question 2.

The primary outcome of the study was progression-free survival. Relevant secondary outcomes were overall survival, symptoms, health-related quality of life, and AEs.

Tables on the characteristics of the ASCEND-5 study can be found in Appendix A of the full dossier assessment.

Comparison of single-arm studies on alectinib with data of the Flatiron Health Database (research questions 1 and 2) on the outcome "overall survival"

For the comparison of results on the outcome "overall survival" with the ACTs platinum-based combination chemotherapy (research question 1) and pemetrexed or docetaxel (research question 2), the company compared the respective relevant subpopulations from the single-arm alectinib studies with the data of a US cancer database (Flatiron Health Database) on adult patients with locally advanced or metastatic ALK-positive NSCLC who had progressed under treatment with crizotinib. The company stated that the comparison had only been conducted on the outcome "overall survival", because the database did not provide information on other outcomes or other operationalizations.

Although the relevant subpopulations and interventions were in principle examined for research questions 1 and 2, the data of the Flatiron Health Database are not very robust with regard to their quality, source and choice, which is partially due to lacking information on the patients and the exact treatment regimens. Information on the ECOG PS, for instance, were lacking for 65.5% of the patients included for research question 1 (see Appendix A of the full dossier assessment, Table 12) and for 41.2% of the patients included for research question 2 (see Appendix A of the full dossier assessment, Table 14). Exact data on the treatment regimens of the platinum-based combination chemotherapy were missing, and it was unknown how many of the patients had been treated with carboplatin or cisplatin. Information on whether the reasons for the administration of carboplatin were in compliance with the criteria of Appendix VI to Section K of the Pharmaceutical Directive was also missing.

Apart from the uncertainties regarding the patient populations of the data from the Flatiron Health Database, it can be assumed that there were clear differences between the populations of the individual studies when comparing individual arms from different studies. Due to the missing randomization of the patients, the distribution of the relevant patient characteristics can be unequal. The company therefore tried to adjust for confounding variables using patient characteristics selected post hoc by means of propensity score matching and presented both the data of an "adjusted central analysis" according to the company and the data from an unbalanced sensitivity analysis on the outcome "overall survival" in the dossier. Propensity score matching permits to balance a missing structural equality only with regard to those possible influencing factors that are known and were actually measured in all studies. Since some confounding variables were unequally distributed among the studies and it was unclear whether and which further confounding variables were unequally distributed, the results are still subject to high uncertainty. This applied all the more for the analysis presented by the company that had not considered any influencing factors (described as a sensitivity analysis

by the company). Both analyses presented by the company were subject to high uncertainty, and it remained unclear whether the adjustment by the company increased of even reduced the certainty of results.

The company based the derivation of the added benefit on the results of the "adjusted central analysis". Within the framework of the adjusted analysis the patient groups were weighted using "inverse probability of treatment weighting", which produced artificially increased sample sizes on both sides of the comparison. Therefore, the calculation of the respective CI for the hazard ratio yielded CIs that were too narrow and suggested an inadequately high accuracy and were thus unsuitable for the derivation of conclusions on the added benefit. This could not be inferred from the information on the analyses provided by the company.

In addition, the company's approach of exclusively using data from the Flatiron Health Database on the outcome "overall survival" of the comparator therapy is inadequate. The comparator arm of the ASCEND-5 study, which was provided by the company only as additional information and solely presented descriptively, would have been just as relevant for research question 2. Moreover, the survival times of patients treated with docetaxel or pemetrexed clearly differed between patients included in the ASCEND-5 study and patients included in the Flatiron Health Database. The patients of the ASCEND-5 study survived twice as long as the patients included in the Flatiron Health Database (median: 20.1 vs. 8.7 months), which additionally raised doubts about the relevance of the effect from the "adjusted central analysis" presented by the company.

Apart from the fact that the effects on overall survival presented by the company were small enough to be caused by systematic bias alone (see further below in this section), their reliable assessment was impossible due to the described major uncertainties. An added benefit for the outcome "overall survival" could therefore neither be derived for research question 1 nor for research question 2.

Comparison of single-arm studies on alectinib with the PROFILE 1014 study on the comparator therapy platinum-based combination chemotherapy (research question 1)

For research question 1, the company conducted a descriptive comparison on further outcomes using individual arms from different studies in addition to the comparison with the data of the Flatiron Health Database on the outcome "overall survival". For this purpose, the company compared results of the subpopulations of the alectinib studies NP28761 and NP28673 relevant for this research question with results for the ACT platinum-based combination chemotherapy from the chemotherapy arm of the PROFILE 1014 study. However, the company did not present effect estimates with CIs and p-values.

No added benefit of alectinib in comparison with the ACT platinum-based combination chemotherapy could be derived from the data presented by the company.

Prerequisite for the derivation of an added benefit on the basis of comparisons of individual arms from different studies

Conclusions on the added benefit based on the comparison of individual arms from different studies were only possible in the presence of very large effects. The simulation results of Glasziou 2007 [29] cited in the IQWiG methods paper serve as an orientation for the classification of such effects. In an approach, an effect is regarded as sufficiently large if it is statistically significant at the level of 1% and, expressed as the estimated relative risk (RR), has a value of about 10 or higher (or about1/10 or lower) [1]. Moreover, the risk of the examined event should be at least 5% in at least 1 of the groups compared.

To derive such an effect, the studies for the drug under assessment and for the ACT would at first have to be generally suitable to provide information for the research questions of the benefit assessment. Finally, the effect estimated on the basis of the available data must be strong enough to ensure that it was not caused by systematic bias caused by the type of comparison alone.

There were no effects for any of the outcomes that could be considered dramatic in the comparisons presented by the company based on the two alectinib studies and the PROFILE 1014 study. An added benefit for research question 1 can therefore not be derived from these data.

Comparison of single-arm studies on alectinib with the ASCEND-5 study on the comparator therapy docetaxel or pemetrexed (research question 2)

For research question 2, the company conducted a descriptive comparison on further outcomes using individual arms from different studies in addition to the comparison with the data of the Flatiron Health Database on the outcome “overall survival”. For this purpose, the company compared results of the subpopulations of the alectinib studies NP28761 and NP28673 relevant for this research question with results for the ACT docetaxel or pemetrexed from the chemotherapy arm of the ASCEND-5 study. However, the company did not present effect estimates with CIs and p-values.

No added benefit of alectinib in comparison with the ACT could be derived from the data presented by the company.

The ASCEND-5 study was conducted in the same therapeutic indication of alectinib (crizotinib-pretreated patients). None of the differences between treatment groups observed in the comparison of individual arms from different studies achieved a magnitude that could not be explained by systematic bias alone (see above in this section).

Only the objective response rate in the central nervous system (CNS response rate, CORR) showed an observed group difference in a magnitude that could probably not be explained by systematic bias alone. However, the literature presented by the company was not suitable to show that the outcomes on the CNS response, which were recorded with the help of imaging

techniques according to RECIST (Response Evaluation Criteria In Solid Tumours), were directly patient-relevant or presented a valid surrogate for a patient-relevant outcome [30-32]. The patient relevance of the outcomes on the CNS response including the objective response rate thus remained unclear.

Overall, no added benefit can be derived from the descriptive comparison of alectinib with the comparator therapy pemetrexed or docetaxel conducted by the company using individual arms from different studies.

Ongoing RCT ALUR

In its search, the company identified an ongoing RCT on the direct comparison of alectinib versus docetaxel or pemetrexed in patients with ALK-positive advanced NSCLC previously treated with both crizotinib and a platinum-based combination chemotherapy (ALUR study) [NCT02604342] [33]). According to the company, the results of this study were not yet available at the time point of the submission of the dossier on the benefit assessment of alectinib to the G-BA on 27 April 2017, and were to be submitted later as far as they became available during the procedure. The ClinicalTrials.gov trial registry indicates 26 January 2017 as the date of the primary data analysis. However, the company's dossier does not explain why the data of the RCT ALUR were not available at the time of submission of the dossier. Against the background that with its dossier submission the company announced data of a directly comparative study that was potentially relevant for research question 2 (patients for whom treatment with docetaxel or pemetrexed is an option), it was not comprehensible why the company presented an elaborate comparison of individual arms from different studies based on extremely uncertain data. The present assessment of research question 2 on the basis of the presented comparisons using individual arms from different studies is therefore presumably irrelevant.

2.3.2 Results on added benefit

Based on the comparisons presented by the company using individual arms from different studies no added benefit of alectinib versus the ACTs could be derived both for research question 1 (patients who have not received prior chemotherapy) and for research question 2 (patients for whom treatment with docetaxel or pemetrexed is an option). There was no hint of an added benefit of alectinib in comparison with the ACTs platinum-based combination chemotherapy (research question 1) and docetaxel or pemetrexed (research question 2). An added benefit is therefore not proven.

2.3.3 Extent and probability of added benefit

The present data do not provide any hint of an added benefit of alectinib versus the respective ACT, both for patients who have not received prior chemotherapy (research question 1) and for patients for whom treatment with docetaxel or pemetrexed is an option (research question 2). Hence, there were no patient groups for whom a therapeutically important added benefit could be derived.

This assessment deviates from the approach of the company that derived a hint of a considerable added benefit of alectinib both for patients who have not received prior chemotherapy (research question 1) and for patients for whom treatment with docetaxel or pemetrexed is an option (research question 2).

2.3.4 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

2.4 Research question 3: patients for whom treatment with docetaxel or pemetrexed is not an option

In its dossier, the company presented no data on the comparison of alectinib with BSC for research question 3. It justified this by claiming that no data from the studies on alectinib were available for the patient populations for whom BSC was the ACT (patients pretreated with a platinum-based chemotherapy and for whom treatment with docetaxel or pemetrexed is not an option) and that conclusions on the added benefit versus BSC could thus not be derived. The company did not therefore consider BSC in its research on the ACTs.

2.4.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study lists on alectinib (status: 24 February 2017)
- bibliographical search on alectinib (last search on 15 February 2017)
- search in trial registries for studies on alectinib (last search on 8 February 2017)

To check the completeness of the study pool:

- bibliographical search on alectinib (last search on 6 June 2017)
- search in trial registries for studies on alectinib (last search on 12 May 2017)

No additional relevant study was identified from the check.

2.4.2 Results on added benefit

In its dossier, the company presented no data on the comparison of alectinib with BSC for research question 3. Hence, there was no hint of an added benefit of alectinib in comparison with BSC. An added benefit of alectinib is not proven for patients with ALK-positive advanced NSCLC after pretreatment with crizotinib and a platinum-based combination chemotherapy for whom treatment with docetaxel or pemetrexed is not an option.

2.4.3 Extent and probability of added benefit

The company did not present data for the assessment of the added benefit of alectinib in adult patients with ALK-positive advanced NSCLC after pretreatment with crizotinib and a platinum-based combination chemotherapy for whom treatment with docetaxel or pemetrexed is not an option. An added benefit of alectinib is not proven for this group of patients.

This assessment corresponds to the company's approach that does not claim an added benefit for this patient population.

2.4.4 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

2.5 Extent and probability of added benefit

The result of the assessment of the added benefit of alectinib in comparison with the ACT is summarized in Table 6.

Table 6: Alectinib – probability and extent of added benefit

Research question	Subindication	ACT[a]	Extent and probability of added benefit
1	Crizotinib-pretreated adult patients with ALK-positive advanced NSCLC who have not received previous chemotherapy	Patients with ECOG PS 0, 1 or 2: ▪ **cisplatin in combination with a third-generation cytostatic agent** (vinorelbine, gemcitabine, docetaxel, paclitaxel or pemetrexed) under consideration of the approval status or ▪ **carboplatin in combination with a third-generation cytostatic agent** (only for patients with increased risk of cisplatin-induced side effects within the framework of a combination therapy; see Appendix VI to Section K of the Pharmaceutical Directive) Patients with ECOG PS 2: ▪ as an alternative to the platinum-based combination therapy: monotherapy with gemcitabine or vinorelbine	Added benefit not proven
2	Crizotinib-pretreated adult patients with ALK-positive advanced NSCLC who were eligible for treatment with docetaxel or pemetrexed after pretreatment with platinum-based chemotherapy	**Docetaxel** or **pemetrexed**	Added benefit not proven
3	Crizotinib-pretreated adult patients with ALK-positive advanced NSCLC for whom treatment with docetaxel or pemetrexed is not an option after pretreatment with platinum-based chemotherapy	BSC[b]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: BSC refers to the therapy that provides the patient with the best possible individually optimized supportive treatment to alleviate symptoms and improve quality of life.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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