Alectinib
(NSCLC, adjuvant)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ALK	anaplastic lymphoma kinase
CE	Conformité Européenne
DFS	disease-free survival
ECOG PS	Eastern Cooperative Oncology Group-Performance Status
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NSCLC	non-small cell lung cancer
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
UICC	Union for International Cancer Control

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug alectinib. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the “company”). The dossier was sent to IQWiG on 04 July 2024.

Research question

The aim of the present report was to assess the added benefit of alectinib in comparison with the appropriate comparator therapy (ACT) for the adjuvant treatment following complete tumour resection in adult patients with anaplastic lymphoma kinase(ALK)-positive non-small cell lung cancer NSCLC at high risk of recurrence.

The research questions presented in Table 2 result from the ACT specified by the G-BA.

Table 2: Research questions on the benefit assessment of alectinib

Research question	Therapeutic indication	ACT[a, b]
1	Adjuvant treatment following complete tumour resection for adult patients with anaplastic lymphoma kinase-positive NSCLC at high risk of recurrence[c] for whom adjuvant platinum-based chemotherapy is suitable	Individualized treatment[d] choosing from ▪ Watchful waiting (only for patients in stage IB[c]) and ▪ postoperative (adjuvant) systemic chemotherapy choosing from ▫ cisplatin in combination with vinorelbine and ▫ cisplatin in combination with paclitaxel (only for patients in the advanced stage) taking into account the stage of the tumour
2	Adjuvant treatment following complete tumour resection for adult patients with anaplastic lymphoma kinase-positive NSCLC at high risk of recurrence[c] after prior platinum-based chemotherapy or patients for whom this therapy is not suitable	Watchful waiting

a. Presented is the respective ACT specified by the G-BA.
b. For stages IB to IIIA, the ACT was determined according to UICC 8.
c. When defining the high risk of recurrence following complete tumour resection, the Summary of Product Characteristics (SPC) for alectinib is based on the patient population included in the ALINA study (stages IB T ≥ 4 cm to IIIA according to UICC 7). According to the stage classification in the 8th edition of the UICC, only patients with a tumour size of exactly 4 cm are included in stage IB.
d. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons).

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control

The appropriate comparator therapy was determined by the G-BA according to Table 2. According to the information provided by the company, a consultation with the G-BA took place on 13 June 2024, but the final result of this consultation was still pending at the time of dossier submission, so that the current ACT could not be considered in the present dossier. Consequently, the company deviated from the definition of the current ACT by naming a systemic antineoplastic treatment of physician's choice consisting of a cisplatin-based combination chemotherapy with vinorelbine, gemcitabine, pemetrexed, docetaxel or paclitaxel as comparator therapy with reference to a consultation with the G-BA from 2018. In case of cisplatin intolerance, this drug could be replaced with carboplatin. The company justified defining an off-label use for the comparator therapy on the grounds that the

preferred regimen is a combination of cisplatin and pemetrexed and that the only alternative is vinorelbine.

The present assessment is implemented in comparison with the current ACT specified by the G-BA (see Table 2). The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used to derive added benefit.

Since no usable data are available for either of the research questions identified by the G-BA, the 2 research questions are assessed together below.

Results

Concurring with the company, the check of the completeness of the study pool produced the ALINA RCT comparing alectinib with platinum-based chemotherapy. The company used the total population of this study to derive the added benefit.

However, the ALINA study presented by the company is unsuitable for the benefit assessment. For research question 1, this is due to the fact that the ACT defined by the G-BA for the total population used by the company was not implemented in the comparator arm of the study. Although the ACT has been implemented for a subpopulation of the ALINA study, it is not clear from the study documents that the allocation to the various treatment options in the comparator arm took place prior to randomization. Forming a subpopulation relevant to research question 1 is not possible in this case, as this would violate the randomization (for a detailed explanation, see the following sections). The ALINA study is also not suitable for answering research question 2, as no patients were included in the study who had previously received platinum-based chemotherapy or for whom this is not suitable, and would therefore match the research question.

The RCT ALINA presented by the company is described below, followed by the reasons for its unsuitability for the benefit assessment.

Evidence presented by the company – ALINA study

The ALINA study is an ongoing, open-label, multicentre RCT comparing alectinib and platinum-based chemotherapy in the adjuvant treatment of ALK-positive NSCLC following complete tumour resection.

The study included adult patients following complete resection of histologically confirmed stage IB (tumour size ≥ 4 cm) to IIIA NSCLC according to the 7th edition of the UICC staging criteria. In addition, ALK positivity had to be proven. Patients also had to be eligible for platinum-based chemotherapy according to local approval or guidelines and have an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of 0 or 1.

A total of 257 patients were randomly allocated to treatment with alectinib (N = 130) or platinum-based chemotherapy (N = 127).

Treatment with alectinib was in compliance with the recommendations of the SPC. In the comparator arm, the investigator could choose between treatment with cisplatin and vinorelbine or gemcitabine or pemetrexed. In the event of unacceptable toxicity, carboplatin could be used instead of cisplatin. There is no indication in the study documents that the therapy was selected prior to randomization.

The primary outcome of the ALINA study was disease-free survival (DFS). Further secondary outcomes were outcomes of the categories “mortality”, “morbidity” and “side effects”.

ALINA study unsuitable for the benefit assessment

The ALINA study presented by the company is unsuitable for deriving conclusions on the added benefit of alectinib in comparison with the ACT for the research questions of the present benefit assessment. This is explained below.

For research question 1, the G-BA specified an individualized treatment choosing from watchful waiting (only for patients in stage IB) and postoperative (adjuvant) systemic chemotherapy choosing from cisplatin in combination with vinorelbine and cisplatin in combination with paclitaxel (only for patients in advanced stages), taking into account the tumour stage. In the comparator arm of the ALINA study, patients could choose between treatment with cisplatin in combination with vinorelbine, gemcitabine or pemetrexed. In the event of unacceptable toxicity, carboplatin could be used instead of cisplatin. Watchful waiting and platinum-based chemotherapy with paclitaxel were not options in the ALINA study. This means that the ACT defined by the G-BA has been implemented only in the proportion of patients who received cisplatin + vinorelbine. The other combinations used in the ALINA study are not covered by the ACT.

21 (17%) patients received a combination of cisplatin and vinorelbine according to the ACT. These patients therefore would not fall under research question 1. However, an analysis that only includes these patients in the comparator arm is not available and would also not be appropriate, as the study documents do not show that the therapy was selected prior to randomization. A comparison based on all patients in the intervention arm versus only those patients in the comparator arm who were treated with the ACT specified by the G-BA is not appropriate, as this would violate the randomization. The ALINA study is therefore not suitable for drawing conclusions on the added benefit of alectinib for research question 1.

The ALINA study is also not suitable for answering research question 2, as no patients were included in the study who had previously received platinum-based chemotherapy or for whom this is not suitable, and would therefore match the research question.

Results on added benefit

Since no suitable data are available for the benefit assessment for either of the 2 research questions, there is no hint of an added benefit of alectinib in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 presents a summary of the probability and extent of the added benefit of alectinib.

[3] 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, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Alectinib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a, b]	Probability and extent of added benefit
1	Adjuvant treatment following complete tumour resection for adult patients with ALK-positive NSCLC at high risk of recurrence[c] for whom adjuvant platinum-based chemotherapy is suitable	Individualized treatment[d] choosing from ▪ Watchful waiting (only for patients in stage IB[c]) and ▪ postoperative (adjuvant) systemic chemotherapy choosing from ▫ cisplatin in combination with vinorelbine and ▫ cisplatin in combination with paclitaxel (only for patients in the advanced stage) taking into account the stage of the tumour	Added benefit not proven
2	Adjuvant treatment following complete tumour resection for adult patients with ALK-positive NSCLC at high risk of recurrence[c] after prior platinum-based chemotherapy or patients for whom this therapy is not suitable	▪ Watchful waiting	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. For stages IB to IIIA, the ACT was determined according to UICC 8.
c. When defining the high risk of recurrence following complete tumour resection, the SPC for alectinib is based on the patient population included in the ALINA study (stages IB T ≥ 4 cm to IIIA according to UICC 7). According to the stage classification in the 8th edition of the UICC, only patients with a tumour size of exactly 4 cm are included in stage IB.
d. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons).

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control

The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report was to assess the added benefit of alectinib in comparison with the appropriate comparator therapy (ACT) for the adjuvant treatment following complete tumour resection in adult patients with anaplastic lymphoma kinase(ALK)-positive non-small cell lung cancer NSCLC at high risk of recurrence.

The research questions presented in Table 4 result from the ACT specified by the G-BA.

Table 4: Research questions on the benefit assessment of alectinib

Research question	Therapeutic indication	ACT[a, b]
1	Adjuvant treatment following complete tumour resection for adult patients with ALK-positive NSCLC at high risk of recurrence[c] for whom adjuvant platinum-based chemotherapy is suitable	Individualized treatment[d] choosing from ▪ Watchful waiting (only for patients in stage IB[c]) and ▪ postoperative (adjuvant) systemic chemotherapy choosing from ▫ cisplatin in combination with vinorelbine and ▫ cisplatin in combination with paclitaxel (only for patients in the advanced stage) taking into account the stage of the tumour
2	Adjuvant treatment following complete tumour resection for adult patients with ALK-positive NSCLC at high risk of recurrence[c] after prior platinum-based chemotherapy or patients for whom this therapy is not suitable	Watchful waiting

a. Presented is the respective ACT specified by the G-BA.
b. For stages IB to IIIA, the ACT was determined according to UICC 8.
c. When defining the high risk of recurrence following complete tumour resection, the SPC for alectinib [3] is based on the patient population included in the ALINA study (stages IB T ≥ 4 cm to IIIA according to UICC 7). According to the stage classification in the 8th edition of the UICC, only patients with a tumour size of exactly 4 cm are included in stage IB.
d. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons).

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control

The appropriate comparator therapy was determined by the G-BA according to Table 4. According to the information provided by the company, a consultation with the G-BA took place on 13 June 2024, but the final result of this consultation was still pending at the time of

dossier submission, so that the current ACT could not be considered in the present dossier. Consequently, the company deviated from the definition of the current ACT by naming a systemic antineoplastic treatment of physician's choice consisting of a cisplatin-based combination chemotherapy with vinorelbine, gemcitabine, pemetrexed, docetaxel or paclitaxel as ACT for the entire therapeutic indication with reference to a consultation with the G-BA from 2018 [4]. In case of cisplatin intolerance, this drug could be replaced with carboplatin. The company justified defining an off-label use for the comparator therapy on the grounds that the preferred regimen is a combination of cisplatin and pemetrexed and that the only alternative is vinorelbine (see Section I 3.2).

The present assessment is implemented in comparison with the current ACT specified by the G-BA (see Table 4). The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used to derive added benefit. This concurs with the company's inclusion criteria.

Since no usable data are available for either of the research questions identified by the G-BA, the 2 research questions are assessed together below.

I 3 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 list on alectinib (status: 6 May 2024)
- bibliographical literature search on alectinib (last search on 6 May 2024)
- search in trial registries / trial results databases for studies on alectinib (last search on 29 May 2024)
- searches on the G-BA website for alectinib (last search on 29 May 2024)

To check the completeness of the study pool:

- search in trial registries for studies on alectinib (last search on 9 July 2024); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check of the completeness of the study pool produced the ALINA RCT [5-8] comparing alectinib with platinum-based chemotherapy. The company used the total population of this study to derive the added benefit.

However, the ALINA study presented by the company is unsuitable for the benefit assessment. For research question 1, this is due to the fact that the ACT defined by the G-BA for the total population used by the company was not implemented in the comparator arm of the study. Although the ACT has been implemented for a subpopulation of the ALINA study, it is not clear from the study documents that the allocation to the various treatment options in the comparator arm took place prior to randomization. Forming a subpopulation relevant to research question 1 is not possible in this case, as this would violate the randomization (for a detailed explanation, see the following sections). The ALINA study is also not suitable for answering research question 2, as no patients were included in the study who had previously received platinum-based chemotherapy or for whom this is not suitable, and would therefore match the research question.

The RCT ALINA presented by the company is described below, followed by the reasons for its unsuitability for the benefit assessment. The characteristics of the ALINA study presented by the company plus the patient characteristics are presented in Table 6 to Table 8 in Appendix A.

I 3.1 Evidence presented by the company – ALINA study

The ALINA study is an ongoing, open-label, multicentre RCT comparing alectinib and platinum-based chemotherapy in the adjuvant treatment of ALK-positive NSCLC following complete tumour resection.

The study included adult patients 4 to 12 weeks following complete resection of histologically confirmed stage IB (tumour size ≥ 4 cm) to IIIA NSCLC according to the 7th edition of the UICC staging criteria. In addition, the ALK positivity had to be demonstrated using a test bearing the Food and Drug Administration (FDA) and Conformité Européenne (CE) marks. Patients also had to be eligible for platinum-based chemotherapy according to local approval or guidelines and have an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of 0 or 1. Previous radiotherapy was only allowed if it was neoadjuvant radiotherapy and had been completed at least 4 weeks prior to the first administration of the study medication. Previous systemic tumour therapies were disallowed with the exception of therapies for early stages of the disease, whereby the last dose had to have been administered more than 5 years prior to study inclusion.

A total of 257 patients were randomly allocated to treatment with alectinib (N = 130) or platinum-based chemotherapy (N = 127). Randomization was stratified according to tumour stage (IB [T ≥ 4 cm] vs. II vs. IIIA) and family origin (Asian vs. non-Asian).

Treatment with alectinib was in compliance with the specifications of the SPC [3]. In the comparator arm, the investigator could choose between treatment with cisplatin and vinorelbine or gemcitabine or pemetrexed. However, no information is available on selection criteria for the various treatment options. In the event of unacceptable toxicity, carboplatin could be used instead of cisplatin. There is no indication in the study documents that the therapy was selected prior to randomization. A regular switch of the patients from the comparator arm to a treatment with alectinib was not provided for in the ALINA study. The study materials do not contain any information on restrictions regarding subsequent therapies.

The primary outcome of the ALINA study was disease-free survival (DFS). Further secondary outcomes were outcomes of the categories “mortality”, “morbidity” and “side effects”.

I 3.2 Assessment of the evidence presented by the company

ALINA study unsuitable for the benefit assessment for either of the 2 research questions

The ALINA study presented by the company is unsuitable for deriving conclusions on the added benefit of alectinib in comparison with the ACT for the research questions of the present benefit assessment. This is explained below.

For research question 1, the G-BA specified an individualized treatment choosing from watchful waiting (only for patients in stage IB) and postoperative (adjuvant) systemic chemotherapy choosing from cisplatin in combination with vinorelbine and cisplatin in combination with paclitaxel (only for patients in advanced stages), taking into account the tumour stage. In the comparator arm of the ALINA study, patients could choose between

treatment with cisplatin in combination with vinorelbine, gemcitabine or pemetrexed. In the event of unacceptable toxicity, carboplatin could be used instead of cisplatin. Watchful waiting and platinum-based chemotherapy with paclitaxel were not options in the ALINA study. This means that the ACT defined by the G-BA has been implemented only in the proportion of patients who received cisplatin + vinorelbine. The other combinations used in the ALINA study are not covered by the ACT.

21 (17%) patients received a combination of cisplatin and vinorelbine according to the ACT (see Table 6). These patients therefore would not fall under research question 1. However, an analysis that only includes these patients in the comparator arm is not available and would also not be appropriate, as the study documents do not show that the therapy was selected prior to randomization. Allocation to the therapy before randomization would have been possible if, for instance, all patients had been assigned a therapy before randomization for the event that they were later allocated to the comparator arm. A comparison based on all patients in the intervention arm versus only those patients in the comparator arm who were treated with the ACT specified by the G-BA is not appropriate, as this would violate the randomization.

The ALINA study is therefore not suitable for drawing conclusions on the added benefit of alectinib for adjuvant treatment following complete tumour resection in adult patients with ALK-positive NSCLC at high risk of recurrence for whom adjuvant platinum-based chemotherapy is suitable (research question 1).

The ALINA study is also not suitable for answering research question 2, as no patients were included in the study who had previously received platinum-based chemotherapy or for whom this is not suitable, and would therefore match the research question.

Tumour staging was conducted based the 7th edition of the UICC classification

It should be noted that the staging of NSCLC in the ALINA study was based on the 7th edition of the UICC classification. In the dossier, the company also stated the staging according to the 8th edition of the UICC classification. There are differences between UICC 7 and UICC 8, which may lead to a change in the tumour classification of some patients [9]. The staging changes are no problem for patients with a tumour size > 4 cm who were assigned to stage IB according to UICC 7. These are now classified as stage II according to UICC 8. They are therefore still covered by the research questions of the present benefit assessment. However, it is a problem that patients with a tumour size of T3-4 and a lymph node status of N2 are assigned to stage IIIA based on UICC 7, but to stage IIIB according to UICC 8. They are therefore no longer covered by the research questions of the present benefit assessment. In the ALINA study, however, only 5% of patients have stage IIIB NSCLC according to UICC 8 and are therefore no longer included in the research questions of this benefit assessment. This is of no consequence for the present benefit assessment.

I 4 Results on added benefit

For the assessment of the added benefit of alectinib for adjuvant treatment following complete tumour resection in adult patients with ALK-positive NSCLC at high risk of recurrence, no suitable data are available for comparison with the ACT for both research questions. For both research questions, there was no hint of added benefit of alectinib in comparison with the ACT; an added benefit is therefore not proven for either of the 2 research questions.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of alectinib in comparison with the ACT is summarized in Table 5.

Table 5: Alectinib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a, b]	Probability and extent of added benefit
1	Adjuvant treatment following complete tumour resection for adult patients with ALK-positive NSCLC at high risk of recurrence[c] for whom adjuvant platinum-based chemotherapy is suitable	Individualized treatment[d] choosing from ▪ Watchful waiting (only for patients in stage IB[c]) and ▪ postoperative (adjuvant) systemic chemotherapy choosing from ▫ cisplatin in combination with vinorelbine and ▫ cisplatin in combination with paclitaxel (only for patients in the advanced stage) taking into account the stage of the tumour	Added benefit not proven
2	Adjuvant treatment following complete tumour resection for adult patients with ALK-positive NSCLC at high risk of recurrence[c] after prior platinum-based chemotherapy or patients for whom this therapy is not suitable	Watchful waiting	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. For stages IB to IIIA, the ACT was determined according to UICC 8.
c. When defining the high risk of recurrence following complete tumour resection, the SPC for alectinib [3] is based on the patient population included in the ALINA study (stages IB T ≥ 4 cm to IIIA according to UICC 7). According to the stage classification in the 8th edition of the UICC, only patients with a tumour size of exactly 4 cm are included in stage IB.
d. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons).

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control

The assessment described above departs from that by the company, which, based on the results of the ALINA study, derived an indication of major added benefit of alectinib in comparison with the ACT.

The G-BA decides on the added benefit.

I 6 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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