Alectinib (NSCLC, adjuvant)

Addendum to Project A24-73 (dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
ALK	anaplastic lymphoma kinase
BICR	blinded independent central review
CTCAE	Common Terminology Criteria for Adverse Events
EMA	European Medicines Agency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
ILD	interstitial lung disease
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model with repeated measures
NSCLC	non-small cell lung cancer
PCS	Physical Component Summary
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SF-36v2	Short Form 36-version 2 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized MedDRA Query
SOC	System Organ Class
UICC	Union for International Cancer Control
VAS	visual analogue scale

1 Background

On 26 November 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A24-73 (Alectinib – Benefit assessment according to §35a Social Code Book V) [1].

The commission includes the re-assessment of the ALINA study for

- the total population,
- the population treated with vinorelbine + platinum, and
- the population treated with pemetrexed + platinum,

taking into account the information in the dossier [2] and the data subsequently submitted by the pharmaceutical company (hereinafter referred to as the “company”) in the commenting procedure [3].

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

Underlying data

In dossier assessment A24-73 [1], the randomized controlled trial (RCT) ALINA was not included in the assessment of alectinib for adjuvant treatment following complete tumour resection for adult patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) at high risk of recurrence. For research question 1 (patients for whom adjuvant platinum-based chemotherapy is suitable), this was due to the fact that, in the comparator arm of the study, the appropriate comparator therapy (ACT) specified by the G-BA was not implemented for the total population used by the company. The ALINA study was also not suitable for answering research question 2 (patients after prior platinum-based chemotherapy or patients for whom this therapy is not suitable), as no patients were included in the study who had previously received platinum-based chemotherapy or for whom this was not suitable, and who would therefore match the research question. For this reason, research question 2 is not considered further in this addendum and the conclusions relate to research question 1.

As part of the comments, the company presented further analyses for the ALINA study. These analyses refer to the comparison of all patients in the intervention arm (100%) with patients in the comparator arm who were treated with vinorelbine + cisplatin or carboplatin (18%) in accordance with the ACT for research question 1 (see below for the assessment of this population).

2.1 Assessment of the ALINA subpopulation treated with vinorelbine + cisplatin or carboplatin in accordance with the appropriate comparator therapy

In the comments, the company presented analyses on the comparison of all patients in the intervention arm (100%) with patients in the comparator arm who were treated with vinorelbine + cisplatin or carboplatin (18%).

As already explained in dossier assessment A24-73, this comparison is not appropriate. Since the choice of treatment in the comparator arm in the ALINA study was made after randomization, the analysis presented by the company broke randomization. By considering only part of the comparator arm (in this case the patients who received vinorelbine + cisplatin or carboplatin), the structural equality of the treatment arms is no longer guaranteed. There are no dramatic effects in this unadjusted comparison. The results of the population treated with vinorelbine + cisplatin or carboplatin are therefore not suitable for drawing conclusions about the added benefit of alectinib. The results of this comparison are therefore not presented.

The company also mentioned in the oral hearing on alectinib [4] that a propensity score analysis had been conducted. However, this propensity score analysis is not available, neither in the dossier nor in the comments submitted by the company.

2.2 Assessment of the ALINA population treated with pemetrexed + cisplatin or carboplatin

According to the commission, the population of the ALINA study treated with pemetrexed + cisplatin or carboplatin also has to be re-assessed. However, no data are available for this population.

2.3 Assessment of the total population of the ALINA study

Implementation of the appropriate comparator therapy in the ALINA study

For research question 1, the G-BA specified individualized treatment choosing from watchful waiting (only for patients in stage IB) and postoperative (adjuvant) systemic chemotherapy, taking into account the stage of the tumour. Adjuvant chemotherapy had to be chosen between cisplatin in combination with vinorelbine and cisplatin in combination with paclitaxel (only for patients in the advanced stage). In the ALINA study, treatment in the comparator arm could be chosen between treatment with cisplatin in combination with vinorelbine, gemcitabine or pemetrexed. In case of unacceptable toxicity, carboplatin could be used instead of cisplatin. The proportion of therapies used in the ALINA study can be found in Table 6 of the dossier assessment [1].

As already described in dossier assessment A24-73 [1], the ALINA study implemented the ACT specified by the G-BA only for the proportion of patients who received treatment with vinorelbine + cisplatin in the comparator arm (21 [17%] patients). The majority of patients (76%) in the study were treated with pemetrexed + cisplatin or carboplatin. This therapy is not comprised by the G-BA's ACT. The formation of a subpopulation that was treated in accordance with the ACT is not possible because therapy was chosen only after randomization (break in randomization, see also Section 2.1).

The ALINA study is not suitable for the benefit assessment because the ACT was not implemented in a large proportion of included patients. Below, the total population of the ALINA study is assessed in compliance with the commission.

2.3.1 Study characteristics

The characteristics of the ALINA study and of the study population can be found in dossier assessment A24-73 [1].

Data cut-off

Analyses on the data cut-off of 26 June 2023 are available for the ALINA study. This is the prespecified data cut-off for disease-free survival (planned after 59 recurrence events in the subpopulation of stage II to IIIA patients). The present analyses are based on this data cut-off.

Planned duration of follow-up observation

Table 1 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 1: Planned duration of follow-up observation – RCT, direct comparison: alectinib vs. platinum-based chemotherapy

Study **Outcome category** **Outcome**	**Planned follow-up observation**
ALINA	
Mortality	
Overall survival	Until death, lost to follow-up, withdrawal of consent, or end of study[a]
Morbidity	
Recurrence	Until recurrence, death, lost to follow-up, withdrawal of consent, or end of study[a]
Health status (EQ-5D VAS)	Until recurrence, death, withdrawal of consent, or Week 96
Health-related quality of life	
SF-36v2	Until recurrence, death, withdrawal of consent, or Week 96
Side effects	28 days after the last dose of the study treatment

a. About 5 years after inclusion of the last patient.

RCT: randomized controlled trial; SF-36v2: Short Form 36-version 2 Health Survey; VAS: visual analogue scale

In the ALINA study, the outcomes of overall survival and recurrence were recorded until study end.

The observation periods for the other relevant outcomes are shortened to varying degrees: The observation for the outcome of health status and for health-related quality of life ended at the onset of recurrence or Week 96. The observation periods for the outcomes of the category of side effects were also systematically shortened because they were recorded only for the period of treatment with the study medication (plus 28 days). However, drawing a reliable conclusion on the total study period or the time to patient death would require recording these outcomes for the total period, as was done for survival and recurrence.

Information on the course of the study

Table 2 shows the mean and median treatment durations of the patients and the median observation periods for individual outcomes.

Table 2: Information on the course of the study – RCT, direct comparison: alectinib vs. platinum-based chemotherapy

Study **Duration of the study phase** **Outcome category/outcome**	**Alectinib** **N = 130**	**Platinum-based chemotherapy** **N = 127**
ALINA		
Treatment duration [months]		
n	128	120
Median [min; max]	23.9 [0; 25]	2.1 [0; 4]
Mean (SD)	21.3 (6.3)	2.2 (0.5)
Observation period [months]		
Overall survival[a]		
n	130	127
Median [Q1; Q3]	27.8 [22.4; 38.9]	28.4 [22.1; 41.4]
Recurrence		
n	130	127
Median [Q1; Q3]	30.0 [ND]	23.5 [ND]
Health status EQ-5D VAS		
n	126	119
Median [Q1; Q3]	22.2 [ND]	22.1 [ND]
Health-related quality of life (SF-36v2)		
n	125	119
Median [Q1; Q3]	22.2 [ND]	22.1 [ND]
Side effects		
n	128	120
Median [Q1; Q3]	24.8 [22.0; 24.9]	3.7 [3.7; 3.8]

a. The observation period was calculated based on the observed time to event/censoring/end of study of all patients (deceased and non-deceased).

max: maximum; min: minimum; N: number of randomized patients; n: number of analysed patients; ND: no data; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation; SF-36v2: Short Form 36-version 2 Health Survey; VAS: visual analogue scale

In the ALINA study, the median treatment duration was notably longer in the intervention arm, at 23.9 months, than in the comparator arm, at 2.1 months. This is due to the fact that treatment with alectinib was planned for up to 2 years in the intervention arm, while treatment in the comparator arm was limited to 4 cycles of 21 days each.

The median observation period for overall survival is comparable between the arms. For the outcome of recurrence, the observation period was around 6.5 months longer in the intervention arm than in the comparator arm, which is due to the fact that overall more recurrences occurred at earlier time points in the comparator arm than in the intervention arm. The observation period for the outcome of recurrence is not sufficient overall to cover the high-risk period for recurrence in all patients (see also Section 2.3.2.1). For each of the outcomes of the outcome categories of morbidity and health-related quality of life, the median observation period between the arms is comparable and corresponds to the planned observation period of a maximum of 96 weeks.

For outcomes in the side effects category, the observation period linked to the treatment duration led to a notably longer median observation period in the intervention arm (24.8 months) than in the comparator arm (3.7 months). This difference in observation periods is taken into account when assessing the outcome-specific risk bias of the outcomes in the category of side effects (see Section 2.3.2.2).

Information on subsequent therapies

Table 3 shows the subsequent therapies patients with recurrence received after discontinuing the study medication.

Table 3: Information on subsequent antineoplastic therapies in patients with recurrence – RCT, direct comparison: alectinib vs. platinum-based chemotherapy

Study	**Patients with subsequent therapy, n (%)**	
Drug class **Drug**	**Alectinib** **N = 15**	**Platinum-based chemotherapy** **N = 49**
ALINA		
Total	13 (86.7)	43 (87.8)
Systemic therapy	13 (86.7)	38 (77.6)
ALK-TKI	7 (46.7)	37 (75.5)
Alectinib	4 (26.7)	29 (59.2)
Brigatinib	4 (26.7)	4 (8.2)
Crizotinib	0 (0)	4 (8.2)
Lorlatinib	0 (0)	2 (4.1)
Ceritinib	0 (0)	1 (2.0)
Chemotherapy	6 (40.0)	2 (4.1)
Immunotherapy	1 (6.7)	1 (2.0)
Other anticancer therapies	1 (6.7)	1 (2.0)
Radiotherapy	5 (33.3)	9 (18.4)
Surgical intervention	1 (6.7)	3 (6.1)

ALK: anaplastic lymphoma kinase; n: number of patients with subsequent therapy; N: number of patients with recurrence; RCT: randomized controlled trial TKI: tyrosine kinase inhibitor

The study documents of the ALINA study do not contain any information on restrictions regarding subsequent therapies.

Of the patients with recurrence, 86.7% in the intervention arm and 87.8% in the comparator arm received at least one subsequent therapy. Data on the first subsequent therapy of the patients are not available. 76% of patients with recurrence received an ALK tyrosine kinase inhibitor, predominantly alectinib. This basically corresponds to the guideline recommendation for the advanced stage of NSCLC [5,6]. However, it is unclear whether the patients received this therapy as a first subsequent therapy or in a later line of treatment.

It should also be noted that according to current guidelines, molecular pathological examinations should be initiated for patients in advanced stages of NSCLC for all therapeutically relevant molecular changes (according to the current status prior to first-line therapy, EGFR mutations in exons 18-21, BRAF V600 mutations, ALK fusions, ROS1 fusions, RET fusions and NTRK1-3 fusions as a minimum requirement) [5]. The ALINA study documents show that a biopsy to confirm the diagnosis of recurrence and to test for ALK mutations and other resistance mutations had to be performed within 30 days of recurrence if clinically feasible. No further information is available.

The subsequent therapies used appear appropriate overall. Irrespective of this, this has no consequences for the present assessment, as only 6 deaths occurred overall at the present data cut-off without statistically significant difference between the treatment arms, and the observation of the other outcomes ended after recurrence (see Table 1). In this specific data constellation, potential deficiencies in the subsequent therapy would have no effect on the assessment of the risk of bias of the results presented.

Risk of bias across outcomes (study level)

Table 4 shows the risk of bias across outcomes (risk of bias at study level).

Table 4: Risk of bias across outcomes (study level) – RCT, direct comparison: alectinib vs. platinum-based chemotherapy

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
ALINA	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for the ALINA study.

Limitations resulting from the open-label study design are described under the outcome-specific risk of bias in Section 2.3.2.2.

Transferability of the study results to the German health care context

The company stated that the study population corresponded to the available evidence on the epidemiology of ALK-positive NSCLC with regard to sex distribution, age and smoking status, and that treatment in the comparator arm also corresponded to the recommendations of the S3-guideline *Prevention, Diagnosis, Treatment and Follow-up of Lung Cancer*. The company summarized that the patients in the approval population of the ALINA study corresponded to the German health care context both with regard to general patient characteristics and disease-specific criteria.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.3.2 Results

2.3.2.1 Presented outcomes

The following patient-relevant outcomes are presented in the present addendum:

- Mortality
  - overall survival
- Morbidity
  - recurrence
  - health status, surveyed using the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
  - measured using the Short Form 36-version 2 Health Survey (SF-36v2)
- Side effects
  - serious adverse events (SAEs)
  - severe adverse events (AEs) (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - myalgia (Preferred Term [PT], severe AEs)
  - interstitial lung disease (ILD)/pneumonitis (Standardized Medical Dictionary for Regulatory Activities [MedDRA] Query [SMQ] interstitial lung disease [narrow], SAEs)

- hepatotoxicity (SMQ drug related hepatic disorders – comprehensive search [narrow], severe AEs)
- other specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4 A).

Table 5 shows the outcomes for which data were available in the study.

Table 5: Matrix of outcomes – RCT, direct comparison: alectinib vs. platinum-based chemotherapy

Study	Outcomes										
	Overall survival	Recurrence[a]	Health status (EQ-5D VAS)	Health-related quality of life (SF-36v2)	SAEs	Severe AEs[b]	Discontinuation due to AEs[c]	Myalgia (PT, severe AEs[b])	ILD/pneumonitis[d] (SMQ, SAEs)	Hepatotoxicity[e] (SMQ, severe AEs[b])	Other specific AEs[f]
ALINA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Presented via the recurrence rate and disease-free survival (includes the events of death, local recurrence, regional recurrence, distant recurrence, new primary NSCLC) as assessed by the investigator.
b. Severe AEs are operationalized as CTCAE ≥ 3.
c. Discontinuation of both drug components in the comparator arm; data for discontinuation of any of the drug components are not available.
d. Operationalized via the SMQ interstitial lung disease (narrow).
e. Operationalized via the SMQ drug related hepatic disorders – comprehensive search (narrow).
f. The following events are considered (MedDRA coding): gastrointestinal disorders (SOC, AEs), malaise (PT, AEs), decreased appetite (PT, AEs), haematopoietic cytopenias (SMQ, severe AEs), and blood creatine phosphokinase increased (PT, severe AEs).

AE: adverse event; BICR: blinded independent central review; CTCAE: Common Terminology Criteria for Adverse Events; ILD: interstitial lung disease; MedDRA: Medical Dictionary for Regulatory Activities; NSCLC: non-small cell lung cancer; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form 36-version 2 Health Survey; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

Recurrence

The outcome of recurrence is a composite outcome, comprising the components of death, local recurrence, regional recurrence, distant recurrence and new primary NSCLC. The results

of the operationalizations “proportion of patients with recurrence” (hereinafter referred to as “recurrence rate”) and disease-free survival are presented for the outcome of recurrence.

Observation period does not fully cover the high-risk period for recurrence

The patients considered in the present stage of the disease are a group of patients who were treated with a curative treatment approach. The occurrence of a recurrence in this situation means that the attempt at cure by the curative treatment approach was not successful. At the time point of the analysed data cut-off of 26 June 2023, the median observation period was about 28 months (see Table 2). The probability of recurrence is highest in the first 2 years after resection [7]. Accordingly, the observation period to date fully covers this critical phase only for some of the patients. This results in uncertainties for the interpretation of the observed effects of alectinib on the outcome of recurrence (see Section 2.3.2.2).

Analyses according to investigator assessment and blinded independent central review

In Module 4 A, the company presented analyses based on investigator assessment and additionally based on the blinded independent central review (BICR) for the operationalization of the outcome.

The assessment by the investigator was based on radiological and (if available) pathological data and clinical status. For the BICR, Module 4 A only shows that the assessment was based on radiological and other data. No further data are available on the BICR. The European Public Assessment Report [8] describes that this is a retrospective BICR. It is therefore assumed that the investigator assessment was decisive for the decision to discontinue therapy (and thus determined the end of the imaging examinations) and that the BICR assessment was not taken into account for this decision. In the event that the BICR subsequently came to the different assessment that, in their view, there was no recurrence yet, it is thus assumed that the BICR did not have any further subsequent scans to determine a recurrence (as assessed by the BICR).

In the comparator arm in particular, there were differences between investigator assessment and BICR assessment as to whether recurrences occurred during the course of the study. According to the investigator assessment, 1 (6%) fewer recurrences were detected in the intervention arm and 11 (22%) more recurrences in the comparator arm. This is taken into account in the outcome-specific risk of bias.

The European Medicines Agency (EMA) guideline addresses the increased detection bias in investigator assessment if the treatment group a patient has been assigned to is known and that this influences the recording [9]. Methodologically, the BICR analysis is thus superior to the assessments by the investigator, but the implementation of this analysis in the ALINA study has weaknesses (see above): It is assumed, for example, that the recording of recurrences by imaging was terminated as soon as the investigators detected a recurrence.

The present benefit assessment presents the results for both operationalizations, with the BICR analyses as supplementary information.

Since the decision regarding treatment continuation was based on investigator assessment, it can be generally assumed in such cases that this also results in an increased risk of bias for all outcomes whose observation is linked to the end of treatment. However, this has no consequences in the present data situation (see Section 2.3.2.2).

Notes on patient-reported outcomes (recorded with EQ-5D VAS, SF-36v2)

In the ALINA study, patient-reported outcomes on health status and health-related quality of life were recorded using EQ-5D VAS and SF-36v2. According to the study protocol, these outcomes were to be recorded every 3 weeks until Week 12, and then every 12 weeks until recurrence, death, withdrawal of consent, or Week 96. The company presented responder analyses (deterioration at Week 12) and analyses using a mixed-effects model with repeated measures (MMRM) for each of these outcomes, which are assumed to be analyses of the change at Week 12 (and not the mean change until Week 12). Analyses over the entire recording period are not available; the Appendix to Module 4 A only contains descriptive information on mean values per recording time point over the entire recording period.

The company justified the analyses at Week 12 with the fact that the questionnaires were recorded with a difference of approx. 4 weeks between the treatment arms after this point in time.

This approach is not appropriate. While patients in the intervention arm received daily alectinib for up to 2 years, patients in the comparator arm were only treated for 4 cycles of 21 days each (see Table 7 in I Appendix B in dossier assessment A24-73 [1]). Subsequently, the patients in the comparator arm were treatment-free. In view of the continuous therapy in the intervention arm and freedom from therapy in the comparator arm after Week 12, it is assumed that the 4-week difference in recording between the arms has no relevant impact on the observed effects. Analyses at later time points of recording would therefore be interpretable and would provide additional information on the patients' symptoms and health-related quality of life. For the analyses for Week 12 presented by the company, it should be taken into account that they only allow conclusions to be drawn about a single early time point and, in particular in the comparator arm, represent a time point with high burden for the patients. The informative value of this analysis is therefore notably limited overall.

For the SF-36v2, the responder analyses for Week 12 are presented. For the EQ-5D VAS, the treatment arms differed by > 15 percentage points in the proportion of patients included in the analysis. The responder analyses for Week 12 are therefore not suitable. The MMRM analysis for Week 12 is therefore shown for the EQ-5D VAS.

2.3.2.2 Risk of bias

Table 6 describes the risk of bias for the results of the relevant outcomes.

Table 6: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: alectinib vs. platinum-based chemotherapy

Study	Study level	Outcomes										
		Overall survival	Recurrence[a]	Health status (EQ-5D VAS)	Health-related quality of life (SF-36v2)	SAEs	Severe AEs[b]	Discontinuation due to AEs[c]	Myalgia (PT, severe AEs[b])	ILD/pneumonitis[d] (SMQ, SAEs)	Hepatotoxicity[e] (SMQ, severe AEs[b])	Other specific AEs[f]
ALINA	L	L	H[g]	H[h, i]	H[h, j]	H[k]	H[k]	H[l]	H[k]	H[k]	H[k]	H[k, l]

a. Presented via the recurrence rate and disease-free survival (includes the events of death, local recurrence, regional recurrence, distant recurrence, new primary NSCLC) as assessed by the investigator.
b. Severe AEs are operationalized as CTCAE ≥ 3.
c. Discontinuation of both drug components in the comparator arm; data for discontinuation of any of the drug components are not available.
d. Operationalized via the SMQ interstitial lung disease (narrow).
e. Operationalized via the SMQ drug related hepatic disorders – comprehensive search (narrow).
f. The following events are considered (MedDRA coding): gastrointestinal disorders (SOC, AEs), malaise (PT, AEs), decreased appetite (PT, AEs), haematopoietic cytopenias (SMQ, severe AEs), and blood creatine phosphokinase increased (PT, severe AEs).
g. Subjective investigator assessment in the presence of an open-label study design; for the additionally presented analyses according to BICR, there are in each case incomplete observations for potentially informative reasons, leading to a high risk of bias of the results (see Section 2.3.2.1); despite the high risk of bias, the certainty of results for the outcome of recurrence is assumed to be high (see text below the table).
h. Lack of blinding in the presence of subjective recording of outcomes.
i. Decrease in questionnaire return rates in the course of the study, which differed between treatment arms.
j. Large difference between the treatment groups (> 5 percentage points) regarding the proportion of patients who were not considered in the analysis.
k. Incomplete observations for potentially informative reasons.
l. Lack of blinding in subjective recording of outcomes or subjective decision to discontinue; for the other specific side effects, this aspect only contributes to a high risk of bias of the results if they are not severe side effects of CTCAE grade ≥ 3.

AE: adverse event; BICR: blinded independent central review; CTCAE: Common Terminology Criteria for Adverse Events; ILD: interstitial lung disease; MedDRA: Medical Dictionary for Regulatory Activities; NSCLC: non-small cell lung cancer; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form 36-version 2 Health Survey; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

The outcome-specific risk of bias is rated as high for the results of all patient-relevant outcomes except the outcome of overall survival.

For the outcome of recurrence, there is a high risk of bias due to the subjective investigator assessment in the presence of an open-label study design. Due to the premature or delayed discontinuation of observation, the subjective assessment of recurrences is also a potentially biasing factor for other outcomes that are only observed until the occurrence of a recurrence or treatment discontinuation. In the present situation, the premature discontinuation of observation in the comparator arm (see Section 2.3.2.1) has no consequences for the assessment of the risk of bias of the other outcomes (patient-reported outcomes and side effects), as the analyses of the outcomes concerned represent early time points or periods when only a few recurrences had occurred.

The risk of bias of the results for the patient-reported outcomes on health status and health-related quality of life, recorded using EQ-5D VAS and SF-36v2, is high due to the lack of blinding in subjective recording of outcomes. Another potentially biasing factor for the EQ-5D VAS is the decreasing response rate of questionnaires over the course of the study and the discrepancy in response rate between the treatment arms. For the SF-36v2, the large difference between the treatment groups (> 5 percentage points) in the proportion of patients who were not considered in the analysis is another aspect for a high risk of bias.

Due to incomplete observations for potentially informative reasons, the risk of bias is rated as high for the outcomes of SAEs, severe AEs, and specific AEs. For the outcome of discontinuation due to AEs and (as a further reason) for the other specific AEs that cannot be assigned to SAEs or severe AEs, the risk of bias is rated as high due to the lack of blinding in subjective recording of outcomes.

Summary assessment of the outcome-specific certainty of results

Due to the high risk of bias, the certainty of results is limited for all outcomes except overall survival. For the outcome of recurrence, there is also uncertainty due to the relatively short observation period to date (see Section 2.3.2.3). Nevertheless, due to the size of the effects (see Table 7), a high overall certainty of results is assumed for this outcome.

2.3.2.3 Results

Table 7, Table 8 and Table 9 summarize the results of the comparison of alectinib with platinum-based chemotherapy following complete tumour resection for adult patients with ALK-positive NSCLC at high risk of recurrence for whom adjuvant platinum-based chemotherapy is suitable.

The results on common AEs, SAEs, severe AEs, and discontinuations due to AEs are presented in Appendix A, and the Kaplan-Meier curves on the time-to-event analyses are presented in Appendix B.

Table 7: Results (mortality, morbidity, side effects, time to event) – RCT, direct comparison: alectinib vs. platinum-based chemotherapy (multipage table)

Study **Outcome category** **Outcome**	**Alectinib**		**Platinum-based chemotherapy**		**Alectinib vs. platinum-based chemotherapy**
	N	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value**
ALINA					
Mortality					
Overall survival	130	NA 2 (1.5)	127	NA 4 (3.1)	0.46 [0.08; 2.52]; 0.360[a]
Morbidity					
Recurrence					
Recurrence rate[b] (investigator)	130	15 (11.5)	127	50 (39.4)	RR: 0.29 [0.17; 0.49]; < 0.001[c]
Death	130	0 (0)	127	1 (0.8)	–
Local recurrence	130	8 (6.2)	127	20 (15.7)	–
Regional recurrence	130	5 (3.8)	127	12 (9.4)	–
Distant recurrence	130	5 (3.8)	127	27 (21.3)	–
New primary NSCLC	130	1 (0.8)	127	0 (0)	–
Disease-free survival[d] (investigator)	130	NA 15 (11.5)	127	41.3 [28.5; NC] 50 (39.4)	0.24 [0.13; 0.43]; < 0.001[a]
Recurrence rate (BICR; supplementary information)	*130*	*16 (12.3)*	*127*	*39 (30.7)*	*RR: 0.40 [0.24; 0.67];* *< 0.001*[c]
Disease-free survival[d] (BICR; supplementary information)	*130*	*NA* *16 (12.3)*	*127*	*NA [37.4; NC]* *39 (30.7)*	*0.30 [0.17; 0.54];* *< 0.001*[a]

Table 7: Results (mortality, morbidity, side effects, time to event) – RCT, direct comparison: alectinib vs. platinum-based chemotherapy (multipage table)

Study Outcome category Outcome	Alectinib		Platinum-based chemotherapy		Alectinib vs. platinum-based chemotherapy
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value
Side effects[e]					
AEs (supplementary information)	128	ND 126 (98.4)	120	ND 112 (93.3)	–
SAEs	128	ND 17 (13.3)	120	ND 10 (8.3)	0.32 [0.10; 1.04]; 0.048[f]
Severe AEs[g]	128	ND 38 (29.7)	120	ND 37 (30.8)	0.50 [0.29; 0.85]; 0.009[f]
Discontinuation due to AEs (of all drug components in the comparator arm)	128	ND 7 (5.5)	120	ND 15 (12.5)	0.24 [0.08; 0.71]; 0.005[f]
Myalgia (PT, severe AEs[g])	128	ND 1 (0.8)	120	ND 0 (0)	NC [0.00; NC]; 0.333[f]
ILD/pneumonitis[h] (SMQ, SAEs)	128	ND 1 (0.8)	120	ND 0 (0)	NC [0.00; NC]; 0.333[f]
Hepatotoxicity[i] (SMQ, severe AEs[g])	128	ND 6 (4.7)	120	ND 0 (0)	NC [0.00; NC]; 0.029[f]
Gastrointestinal disorders (SOC, AEs)	128	ND 87 (68.0)	120	ND 95 (79.2)	0.42 [0.31; 0.58]; < 0.001[f]
Malaise (PT, AEs)	128	ND 6 (4.7)	120	ND 16 (13.3)	0.27 [0.10; 0.74]; 0.007[f]
Decreased appetite (PT, AEs)	128	ND 7 (5.5)	120	ND 35 (29.2)	0.16 [0.07; 0.36]; < 0.001[f]
Haematopoietic cytopenias[j] (SMQ, severe AEs[g])	128	ND 1 (0.8)	120	ND 25 (20.8)	0.03 [0.00; 0.25]; < 0.001[f]
Blood creatine phosphokinase increased[k] (PT, severe AEs[g])	128	ND 8 (6.3)	120	ND 1 (0.8)	6.77 [0.83; 55.13]; 0.038[f]

Table 7: Results (mortality, morbidity, side effects, time to event) – RCT, direct comparison: alectinib vs. platinum-based chemotherapy (multipage table)

Study Outcome category Outcome	Alectinib		Platinum-based chemotherapy		Alectinib vs. platinum-based chemotherapy
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value

a. HR and CI from Cox regression model, stratified by disease stage (IB vs. II vs. IIIA) and family origin (Asian vs. non-Asian); p-value from log-rank test.
b. Proportion of patients, individual components are presented in the lines below. In accordance with the information provided by the company, the first qualifying event is shown in each case. However, the sum of the events of the individual components is greater than the number of events that are included in the recurrence rate.
c. Logistic regression model, stratified by disease stage (IB vs. II vs. IIIA) and family origin (Asian vs. non-Asian).
d. Operationalized as time from randomization to recurrence, new primary NSCLC or death from any cause, whichever occurs first.
e. The fixed treatment duration and the associated discontinuation of observation in the comparator arm mean that the hazard ratio only reflects approximately the first 4 months after randomization.
f. HR and CI from unstratified Cox regression model; p-value from log-rank test.
g. Operationalized as CTCAE grade ≥ 3.
h. Operationalized via the SMQ interstitial lung disease (narrow).
i. Operationalized via the SMQ drug related hepatic disorders – comprehensive search (narrow).
j. Operationalized via the SMQ haematopoietic cytopenias (wide).
k. In Weeks 2 and 4, different recordings were planned in the intervention and comparator arm: In the intervention arm, additional measurements of blood creatine phosphokinase took place at these time points (additional mandatory safety assessments), while the patients in the comparator arm were called at these time points (additional mandatory phone calls).

AE: adverse event; BICR: blinded independent central review; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; ILD: interstitial lung disease; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; NSCLC: non-small cell lung cancer; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SMQ: Standardized Medical Dictionary for Regulatory Activities Query: SOC: System Organ Class

Table 8: Results (morbidity, continuous) – RCT, direct comparison: alectinib vs. platinum-based chemotherapy

Study Outcome category Outcome	Alectinib			Platinum-based chemotherapy			Alectinib vs. platinum-based chemotherapy
	N[a]	Values at baseline mean (SD)	Change at Week 12 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at Week 12 mean[b] (SE)	MD [95% CI]; p-value[b]
ALINA							
Morbidity							
Health status (EQ-5D VAS)[c]	126	81.1 (16.4)	−0.5 (1.1)	119	76.1 (15.2)	−1.5 (1.2)	1.01 [−1.81; 3.83]; ND

a. Number of patients taken into account in the effect estimation; baseline values may rest on different patient numbers.
b. MMRM adjusted for disease stage (IB vs. II vs. IIIA) and family origin (Asian vs. non-Asian).
c. Higher (increasing) values indicate improved symptoms; positive effects (intervention minus comparison) indicate an advantage for the intervention (scale range: 0 to 100).

CI: confidence interval; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale

Table 9: Results (health-related quality of life, dichotomous) – RCT, direct comparison: alectinib vs. platinum-based chemotherapy

Study Outcome category Outcome	Alectinib		Platinum-based chemotherapy		Alectinib vs. platinum-based chemotherapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
ALINA					
Health-related quality of life					
SF-36v2 (deterioration at Week 12)[b]					
Physical Component Summary (PCS)	109	7 (6.4)	91	5 (5.5)	1.37 [0.45; 4.17]; 0.576
Mental Component Summary (MCS)	109	8 (7.3)	91	22 (24.2)	0.30 [0.14; 0.65]; 0.002
Physical functioning	117	27 (23.1)	96	20 (20.8)	1.14 [0.69; 1.91]
Physical role functioning	117	19 (16.2)	96	26 (27.1)	0.59 [0.35; 1.00]
Physical pain	116	14 (12.1)	96	18 (18.8)	0.65 [0.34; 1.24]
General health perception	110	20 (18.2)	91	28 (30.8)	0.62 [0.38; 1.03]
Vitality	116	17 (14.7)	96	25 (26.0)	0.58 [0.33; 1.01]
Social functioning	117	15 (12.8)	96	22 (22.9)	0.55 [0.30; 1.00]
Emotional role functioning	117	22 (18.8)	96	38 (39.6)	0.46 [0.29; 0.72]
Mental well-being	116	11 (9.5)	96	16 (16.7)	0.57 [0.28; 1.16]

a. Logistic regression model, stratified by disease stage (IB vs. II vs. IIIA) and family origin (Asian vs. non-Asian).
b. A decrease in PCS by ≥ 9.4 points or in MCS by ≥ 9.6 points from baseline is considered a clinically relevant deterioration (scale range: 7.3 to 70.1 for PCS and 5.8 to 69.9 for MCS; determined using the 2009 norm sample [10]). In Module 4 A, the company used rounded response criteria for the subscales. The response criteria of the 2 subscales of physical role functioning and mental well-being deviate slightly from 15% of the scale range.

CI: confidence interval; MCS: Mental Component Summary; n: number of patients with (at least one) event; N: number of analysed patients; PCS: Physical Component Summary; RCT: randomized controlled trial; RR: relative risk; SF-36v2: Short Form 36-version 2 Health Survey

Mortality

For the outcome of overall survival, no statistically significant difference between treatment groups was found.

Morbidity

Recurrence

For the outcome of recurrence (operationalized as recurrence rate and disease-free survival), a statistically significant difference in favour of alectinib in comparison with platinum-based chemotherapy was shown for both operationalizations. The operationalizations according to

BICR presented as supplementary information also show a statistically significant difference in favour of alectinib in comparison with platinum-based chemotherapy.

Health status (EQ-5D VAS)

For the outcome of health status (EQ-5D VAS), no statistically significant difference between treatment groups was found until Week 12. Analyses over the entire recording period are not available, although this outcome was recorded until Week 96.

Health-related quality of life

SF-36v2 – Physical and Mental Component Summary

Health-related quality of life was recorded using the SF-36v2. Although this questionnaire was recorded up to Week 96 (provided that the recording was not discontinued before, e.g. due to recurrences), only recordings at Week 12 were included in the analyses presented by the company. Analyses over the entire recording period are not available.

For the Physical Component Summary (PCS), no statistically significant difference between treatment groups was shown at Week 12 on the basis of the responder analyses on the response threshold of 15% of the scale range.

For the Mental Component Summary (MCS), a statistically significant difference in favour of alectinib compared with platinum-based chemotherapy was shown at Week 12 on the basis of the responder analyses on the response threshold of 15% of the scale range.

Side effects

With regard to the results on side effects, it should be noted that the clear differences in observation periods between the treatment arms mean that the hazard ratio only reflects approximately the first 4 months after randomization.

SAEs and severe AEs

For each of the outcomes of SAEs and severe AEs, a statistically significant difference was shown in favour of alectinib in comparison with platinum-based chemotherapy.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs (of all drug components in the comparator arm), a statistically significant difference was found in favour of alectinib versus platinum-based chemotherapy. No data are available for the discontinuation of at least one drug component.

However, there is an effect modification by age. For patients < 65 years of age, a statistically significant difference was shown in favour of alectinib versus platinum-based chemotherapy.

No statistically significant difference between treatment groups was found for patients ≥ 65 years, however.

Specific AEs

Malaise (AEs), decreased appetite (AEs) and haematopoietic cytopenias (severe AEs)

For each of the outcomes of malaise (AEs), decreased appetite (AEs) and haematopoietic cytopenias (severe AEs), a statistically significant difference was shown in favour of alectinib in comparison with platinum-based chemotherapy.

Gastrointestinal disorders (AEs)

For the outcome of gastrointestinal disorders (AEs), a statistically significant difference was shown in favour of alectinib in comparison with platinum-based chemotherapy.

However, there is an effect modification by age. For patients < 65 years of age, a statistically significant difference was shown in favour of alectinib versus platinum-based chemotherapy. No statistically significant difference between treatment groups was found for patients ≥ 65 years, however.

Myalgia (severe AEs) and ILD/pneumonitis (SAEs)

For each of the outcomes of myalgia (severe AEs) and ILD/pneumonitis (SAEs), only one event occurred in the intervention arm. In each case, there was no statistically significant difference between the treatment groups.

Hepatotoxicity (severe AEs) and blood creatine phosphokinase increased (severe AEs)

For each of the outcomes of hepatotoxicity (severe AEs) and blood creatine phosphokinase increased (severe AEs), a statistically significant difference was shown to the disadvantage of alectinib in comparison with platinum-based chemotherapy.

2.3.2.4 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account in the present benefit assessment:

- age (< 65 years versus ≥ 65 years)
- sex (male versus female)
- disease stage (IB vs. II vs. IIIA)

Subgroup analyses of the characteristic of disease stage are available only based on the Union for International Cancer Control (UICC) 7 and not based on the currently valid version 8. The subgroup characteristics selected in the present benefit assessment had been defined a priori, but only for the outcomes of disease-free survival and side effects. Nevertheless, no subgroup

analyses on the characteristic of disease stage are available for the side effect outcomes. There are also no subgroup analyses on health status (EQ-5D VAS, MMRM analysis) in the company's dossier.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

The results are presented in Table 10. The Kaplan-Meier curves for the subgroup results for the outcome of discontinuation due to AEs are shown in Appendix B.3.3. No Kaplan-Meier curves are available for the subgroup results for the outcome of gastrointestinal disorders (AEs) presented in the present assessment.

Table 10: Subgroups (side effects) – RCT, direct comparison: alectinib vs. platinum-based chemotherapy

Study Outcome	Alectinib		Platinum-based chemotherapy		Alectinib vs. platinum-based chemotherapy	
Characteristic Subgroup	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]	p-value[a]
ALINA						
Side effects[b]						
Discontinuation due to AEs (of all drug components in the comparator arm)						
Age						
< 65 years	101	ND 2 (2.0)	87	ND 10 (11.5)	0.00 [0.00; NC]	< 0.001
≥ 65 years	27	ND 5 (18.5)	33	ND 5 (15.2)	0.95 [0.26; 3.55]	0.942
Total					Interaction[c]:	0.028
Gastrointestinal disorders (SOC, AEs)						
Age						
< 65 years	101	ND 67 (66.3)	87	ND 73 (83.9)	0.34 [0.23; 0.49]	< 0.001
≥ 65 years	27	ND 20 (74.1)	33	ND 22 (66.7)	0.82 [0.44; 1.54]	0.543
Total					Interaction[c]:	0.022

a. HR and CI from unstratified Cox regression model; p-value from log-rank test.
b. The fixed treatment duration and the associated discontinuation of observation in the comparator arm mean that the hazard ratio only reflects approximately the first 4 months after randomization.
c. Likelihood ratio test.

AE: adverse event; CI: confidence interval; HR: hazard ratio; n: number of patients with at least one event; N: number of analysed patients; NC: not calculable; ND: no data; RCT: randomized controlled trial; SOC: System Organ Class

Side effects

With regard to the results on side effects, it should be noted that the clear differences in observation periods between the treatment arms mean that the hazard ratio only reflects approximately the first 4 months after randomization.

Discontinuation due to AEs and specific AE gastrointestinal disorders (AEs)

For each of the outcomes of discontinuation due to AEs (of all drug components in the comparator arm) and gastrointestinal disorders (AEs), there is a statistically significant effect modification by the characteristic of age. For patients < 65 years of age, a statistically

significant difference was shown in favour of alectinib versus platinum-based chemotherapy. However, no statistically significant difference between treatment groups was shown for patients ≥ 65 years.

2.3.2.5 Summary of the results

The following advantages and disadvantages at outcome level result from the ALINA study for research question 1 (adjuvant treatment following complete tumour resection for adult patients with ALK-positive NSCLC at high risk of recurrence for whom adjuvant platinum-based chemotherapy is suitable):

- Advantages of alectinib compared with platinum-based chemotherapy for the outcomes of recurrence, the MCS of the SF-36v2 at Week 12 (health-related quality of life), and for the outcomes of SAEs, severe AEs, malaise (AEs), decreased appetite (AEs), and haematopoietic cytopenias (severe AEs)
- Advantages of alectinib compared with platinum-based chemotherapy for the outcomes of discontinuation due to AEs and gastrointestinal disorders (AEs) in patients < 65 years of age
- Disadvantages of alectinib compared with platinum-based chemotherapy for the outcomes of hepatotoxicity (severe AEs) and blood creatine phosphokinase increased (severe AEs)

Only for the outcome of recurrence are the observed effects based on the entire observation period. For the MCS of the SF-36v2, the observed effects relate to the time point at Week 12 (see Section 2.3.2.1), and for the outcomes in the side effects category to the median period of around 4 months (see Section 2.3.1). Therefore, no conclusions regarding the entire recording period can be drawn for these outcomes.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure do not change the conclusion on the added benefit of alectinib drawn in dossier assessment A24-73.

Table 11 below shows the result of the benefit assessment of alectinib taking into account dossier assessment A24-73 [1] and the present addendum.

Table 11: 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. In the definition of high risk of recurrence following complete tumour resection, the SPC of alectinib [11] refers to the patient population included in the ALINA study (stages IB T ≥ 4 cm to IIIA according to UICC 7). According to the staging 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; SPC: Summary of Product Characteristics; UICC: Union for International Cancer Control

The G-BA decides on the added benefit.

3 References

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

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Alectinib (NSCLC, adjuvant); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2024 [Accessed: 05.12.2024]. URL: https://www.iqwig.de/download/a24-73_alectinib_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Roche Pharma. Alectinib (Alecensa); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2024 [Accessed: 03.12.2024]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1100/#dossier.

3. Roche Pharma. Stellungnahme zum IQWiG-Bericht Nr. 1868: Alectinib (NSCLC); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1100/#beschluesse in the document "Zusammenfassende Dokumentation"].

4. Gemeinsamer Bundesausschuss. Alectinib: mündliche Anhörung gemäß § 35 a Abs. 2 SGB V - stenografisches Wortprotokoll [online]. 2024 [Accessed: 03.12.2024]. URL: https://www.g-ba.de/downloads/91-1031-1100/2024-11-25_Wortprotokoll_Alectinib_D-1079.pdf.

5. Leitlinienprogramm Onkologie. S3-Leitlinie: Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms, Version 3.0. AWMF-Registernummer: 020/007OL [online]. 2024. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Lungenkarzinom/Version_3/LL_Lungenkarzinom_Langversion_3.0.pdf.

6. Deutsche Gesellschaft für Hämatologie und medizinische Onkologie. Leitlinie Lungenkarzinom, nicht-kleinzellig (NSCLC) [online]. 2022. URL: https://www.onkopedia.com/de/onkopedia/guidelines/lungenkarzinom-nicht-kleinzellig-nsclc.

7. Ng C, Schmid T, Augustin F. Optimale Strategie für die onkologische Nachsorge nach Lungenresektion. Wiener klinisches Magazin 2016; 19(5): 180-184. https://doi.org/10.1007/s00740-016-0140-3.

8. European Medicines Agency. Alecensa; Assessment report [online]. 2024 [Accessed: 03.12.2024]. URL: https://www.ema.europa.eu/en/documents/variation-report/alecensa-h-c-004164-ii-0047-epar-assessment-report-variation_en.pdf.

9. European Medicines Agency. Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man - methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials [online]. 2013 [Accessed: 03.12.2024]. URL: https://www.ema.europa.eu/en/appendix-1-guideline-evaluation-anticancer-medicinal-products-man-methodological-consideration-using.

10. Maruish ME. User's manual for the SF-36v2 Health Survey. Lincoln: QualityMetric; 2011.

11. Roche Registration. Alecensa [online]. 2024 [Accessed: 19.08.2024]. URL: https://www.fachinfo.de.

Appendix A Results on side effects

For the overall rates of AEs, SAEs, and severe AEs (CTCAE grade ≥ 3), the following tables present events for System Organ Classes (SOCs) and Preferred Terms (PTs) according to the MedDRA, each on the basis of the following criteria:

- Overall rate of AEs (irrespective of severity grade): events that occurred in at least 10% of patients in one study arm
- Overall rate of severe AEs (e.g. CTCAE grade ≥ 3) and SAEs: events that occurred in at least 5% of patients in one study arm
- In addition, for all events irrespective of severity grade: events that occurred in at least 10 patients and in at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs, a complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided.

Table 12: Common AEs[a] – RCT, direct comparison: alectinib vs. platinum-based chemotherapy (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	Alectinib N = 128	Platinum-based chemotherapy N = 120
ALINA		
Overall AE rate	126 (98.4)	112 (93.3)
Blood and lymphatic system disorders	36 (28.1)	46 (38.3)
Anaemia	30 (23.4)	31 (25.8)
Neutropenia	2 (1.6)	19 (15.8)
Cardiac disorders	20 (15.6)	3 (2.5)
Bradycardia	10 (7.8)	0 (0)
Eye disorders	12 (9.4)	3 (2.5)
Gastrointestinal disorders	87 (68.0)	95 (79.2)
Constipation	54 (42.2)	30 (25.0)
Diarrhoea	16 (12.5)	10 (8.3)
Nausea	10 (7.8)	87 (72.5)
Vomiting	9 (7.0)	30 (25.0)
General disorders and administration site conditions	56 (43.8)	54 (45.0)
Asthenia	14 (10.9)	19 (15.8)
Fatigue	18 (14.1)	16 (13.3)
Malaise	6 (4.7)	16 (13.3)
Oedema peripheral	13 (10.2)	1 (0.8)
Infections and infestations	74 (57.8)	13 (10.8)
COVID-19	37 (28.9)	1 (0.8)
Urinary tract infection	11 (8.6)	2 (1.7)
Injury, poisoning and procedural complications	49 (38.3)	3 (2.5)
Product dose omission in error	16 (12.5)	0 (0)
Product dose omission issue	21 (16.4)	0 (0)
Investigations	97 (75.8)	45 (37.5)
Alanine aminotransferase increased	43 (33.6)	11 (9.2)
Aspartate aminotransferase increased	53 (41.4)	6 (5.0)
Bilirubin conjugated increased	11 (8.6)	0 (0)
Blood alkaline phosphatase increased	32 (25.0)	4 (3.3)
Blood bilirubin increased	43 (33.6)	1 (0.8)
Blood creatine phosphokinase increased	55 (43.0)	1 (0.8)
Blood creatinine increased	19 (14.8)	6 (5.0)
Neutrophil count decreased	3 (2.3)	21 (17.5)
Weight increased	17 (13.3)	1 (0.8)

Table 12: Common AEs[a] – RCT, direct comparison: alectinib vs. platinum-based chemotherapy (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Alectinib** **N = 128**	**Platinum-based chemotherapy** **N = 120**
White blood cell count decreased	2 (1.6)	23 (19.2)
Metabolism and nutrition disorders	39 (30.5)	48 (40.0)
Decreased appetite	7 (5.5)	35 (29.2)
Hyperuricaemia	12 (9.4)	2 (1.7)
Musculoskeletal and connective tissue disorders	65 (50.8)	9 (7.5)
Arthralgia	10 (7.8)	2 (1.7)
Myalgia	36 (28.1)	2 (1.7)
Nervous system disorders	40 (31.3)	24 (20.0)
Dizziness	9 (7.0)	11 (9.2)
Dysgeusia	13 (10.2)	3 (2.5)
Headache	14 (10.9)	8 (6.7)
Renal and urinary disorders	12 (9.4)	8 (6.7)
Respiratory, thoracic and mediastinal disorders	39 (30.5)	19 (15.8)
Cough	19 (14.8)	4 (3.3)
Dyspnoea	13 (10.2)	3 (2.5)
Skin and subcutaneous tissue disorders	50 (39.1)	22 (18.3)
Rash	18 (14.1)	7 (5.8)
Vascular disorders	11 (8.6)	17 (14.2)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 26.0; SOC and PT notation taken without adaptation from Module 4.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 13: Common SAEs[a] – RCT, direct comparison: alectinib vs. platinum-based chemotherapy

Study	Patients with event n (%)	
SOC[b] PT[b]	Alectinib N = 128	Platinum-based chemotherapy N = 120
ALINA		
Overall SAE rate	17 (13.3)	10 (8.3)
Infections and infestations	11 (8.6)	2 (1.7)

a. Events that occurred in ≥ 5% of the patients in at least one study arm.
b. MedDRA version 26.0; SOC and PT notation taken without adaptation from Module 4.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 14: Common severe AEs (CTCAE grade ≥ 3)[a] – RCT, direct comparison: alectinib vs. platinum-based chemotherapy

Study	Patients with event n (%)	
SOC[b] PT[b]	Alectinib N = 128	Platinum-based chemotherapy N = 120
ALINA		
Overall rate of severe AEs	38 (29.7)	37 (30.8)
Blood and lymphatic system disorders	0 (0)	12 (10.0)
Neutropenia	0 (0)	10 (8.3)
Gastrointestinal disorders	4 (3.1)	9 (7.5)
Infections and infestations	11 (8.6)	2 (1.7)
Investigations	15 (11.7)	15 (12.5)
Blood creatine phosphokinase increased	8 (6.3)	1 (0.8)
Neutrophil count decreased	0 (0)	12 (10.0)

a. Events that occurred in ≥ 5% of the patients in at least one study arm.
b. MedDRA version 26.0; SOC and PT notation taken without adaptation from Module 4.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 15: Discontinuations due to AEs (of all drug components in the comparator arm) – RCT, direct comparison: alectinib vs. platinum-based chemotherapy (multipage table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Alectinib** **N = 128**	**Platinum-based chemotherapy** **N = 120**
ALINA		
Overall rate of discontinuations due to AEs (of all drug components in the comparator arm)	7 (5.5)	15 (12.5)
Blood and lymphatic system disorders	0 (0)	2 (1.7)
Anaemia	0 (0)	1 (0.8)
Neutropenia	0 (0)	1 (0.8)
Ear and labyrinth disorders	0 (0)	3 (2.5)
Deafness	0 (0)	1 (0.8)
Tinnitus	0 (0)	2 (1.7)
Gastrointestinal disorders	0 (0)	4 (3.3)
Abdominal pain	0 (0)	1 (0.8)
Nausea	0 (0)	4 (3.3)
Regurgitation	0 (0)	1 (0.8)
Vomiting	0 (0)	2 (1.7)
General disorders and administration site conditions	0 (0)	5 (4.2)
Asthenia	0 (0)	3 (2.5)
Fatigue	0 (0)	2 (1.7)
Infections and infestations	0 (0)	1 (0.8)
Pneumonia	0 (0)	1 (0.8)
Investigations	3 (2.3)	3 (2.5)
Alanine aminotransferase increased	1 (0.8)	0 (0)
Aspartate aminotransferase increased	1 (0.8)	0 (0)
Blood creatinine increased	1 (0.8)	2 (1.7)
Creatinine renal clearance decreased	0 (0)	1 (0.8)
Liver function test increased	1 (0.8)	0 (0)
Metabolism and nutrition disorders	1 (0.8)	0 (0)
Hypertriglyceridaemia	1 (0.8)	0 (0)
Nervous system disorders	0 (0)	1 (0.8)
Neuropathy peripheral	0 (0)	1 (0.8)
Renal and urinary disorders	0 (0)	2 (1.7)
Renal failure	0 (0)	1 (0.8)
Renal impairment	0 (0)	1 (0.8)
Respiratory, thoracic and mediastinal disorders	3 (2.3)	1 (0.8)
Pneumonitis	3 (2.3)	0 (0)
Pulmonary embolism	0 (0)	1 (0.8)

Table 15: Discontinuations due to AEs (of all drug components in the comparator arm) – RCT, direct comparison: alectinib vs. platinum-based chemotherapy (multipage table)

Study	**Patients with event n (%)**	
SOC[a] PT[a]	**Alectinib**	**Platinum-based chemotherapy**
	N = 128	**N = 120**

a. MedDRA version 26.0; SOC and PT notation taken without adaptation from Module 4.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Appendix B Kaplan-Meier curves

B.1 Overall survival

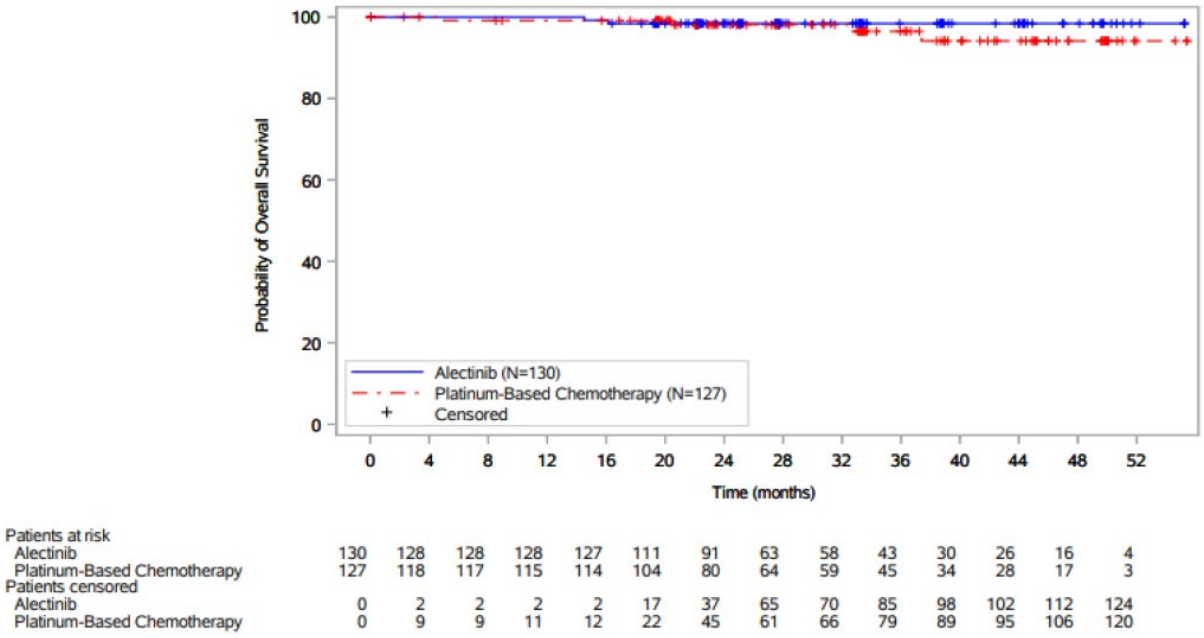


Figure 1: Kaplan-Meier curves for the outcome of overall survival of the ALINA study, total population

B.2 Recurrence

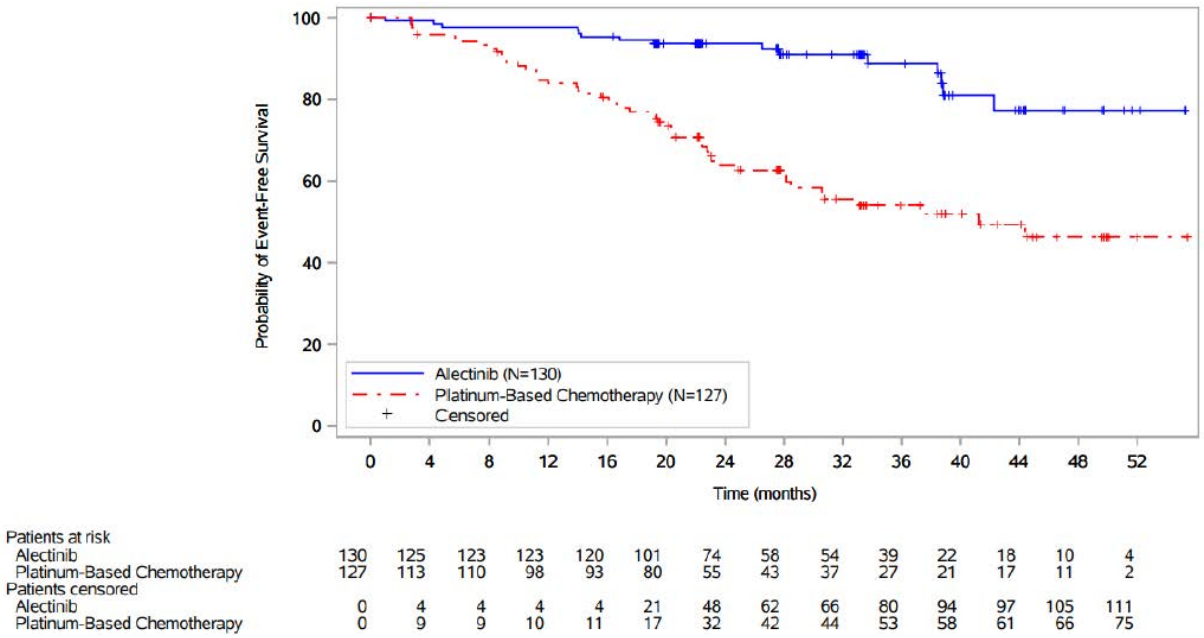
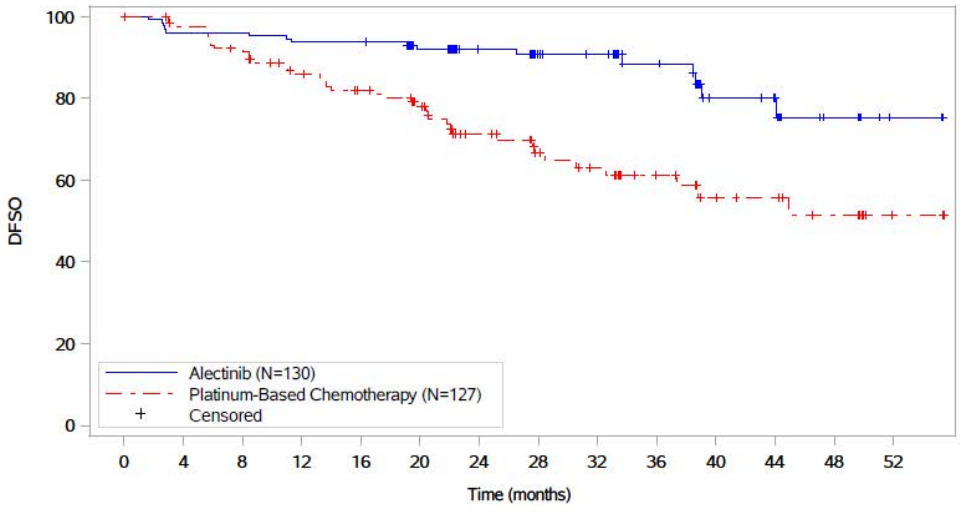


Figure 2: Kaplan-Meier curves for the outcome of disease-free survival (according to investigator assessment) of the ALINA study, total population

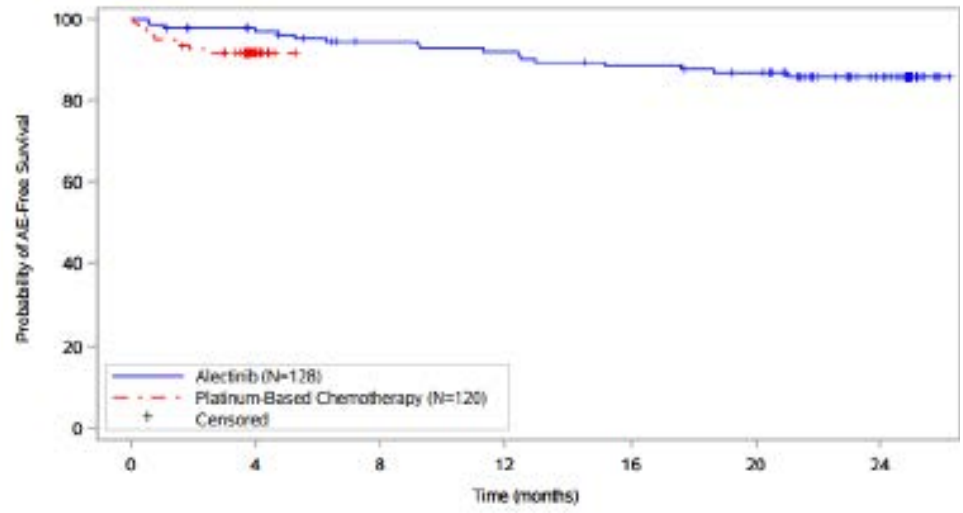


Patients at risk													
Alectinib	130	122	122	119	119	101	72	55	52	38	21	18	9	3
Platinum-Based Chemotherapy	127	111	104	92	85	74	51	39	34	24	17	15	11	2
Patients censored														
Alectinib	0	3	3	3	3	19	48	64	67	80	94	97	105	111
Platinum-Based Chemotherapy	0	13	14	19	22	29	46	55	58	67	72	74	77	86

Figure 3: Kaplan-Meier curves for the outcome of disease-free survival (according to BICR, supplementary presentation) of the ALINA study, total population

B.3 Side effects

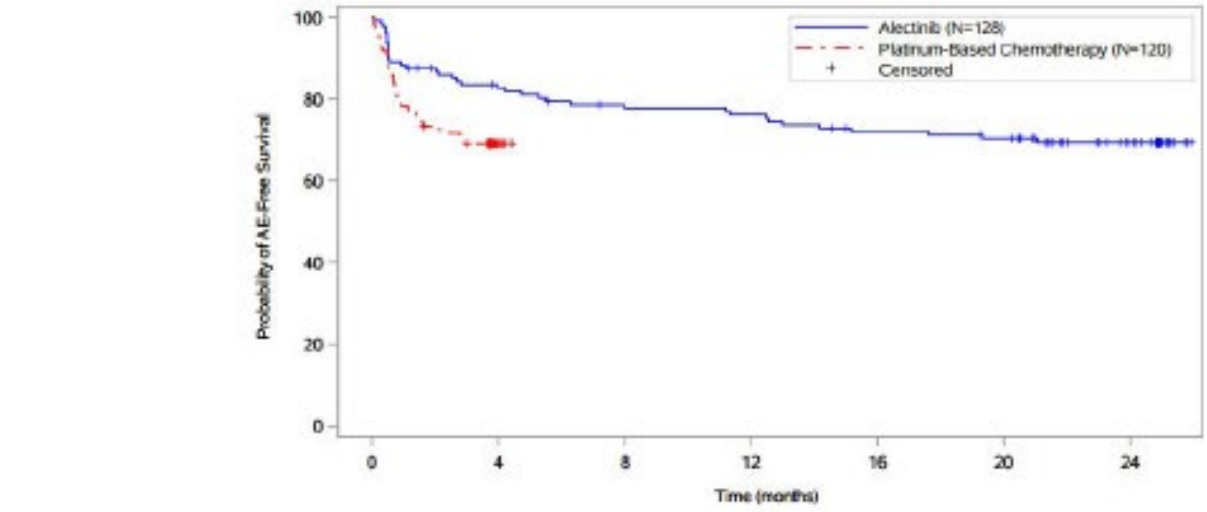
B.3.1 SAEs



Patients at risk							
Alectinib	128	119	111	108	103	99	74
Platinum-Based Chemotherapy	120	17	NE	NE	NE	NE	NE
Patients censored							
Alectinib	0	5	10	10	11	13	37
Platinum-Based Chemotherapy	0	93	NE	NE	NE	NE	NE

Figure 4: Kaplan-Meier curves for the outcome of SAEs of the ALINA study, total population

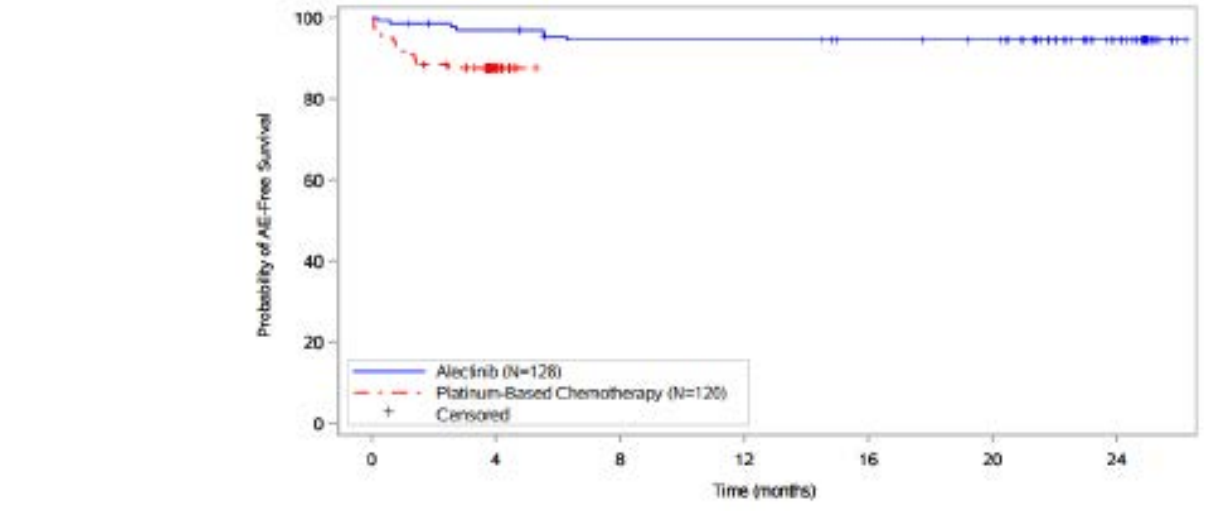
B.3.2 Severe AEs



Patients at risk							
Alectinib	128	102	94	92	85	82	61
Platinum-Based Chemotherapy	120	9	NE	NE	NE	NE	NE
Patients censored							
Alectinib	0	4	6	6	8	9	29
Platinum-Based Chemotherapy	0	74	NE	NE	NE	NE	NE

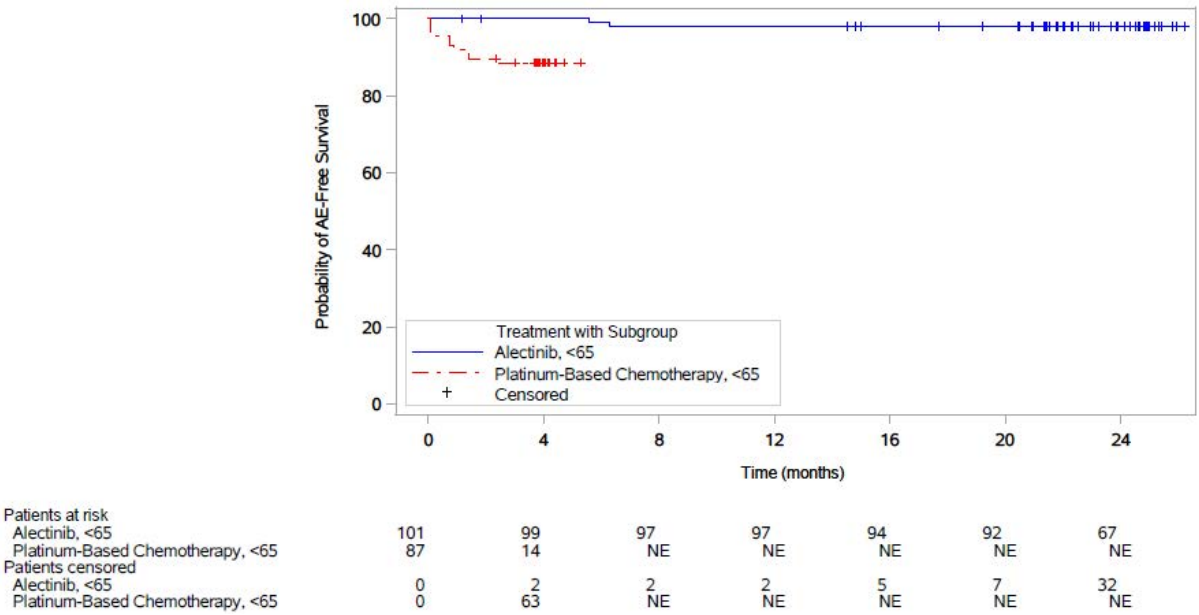
Figure 5: Kaplan-Meier curves for the outcome of severe AEs of the ALINA study, total population

B.3.3 Discontinuation due to AEs



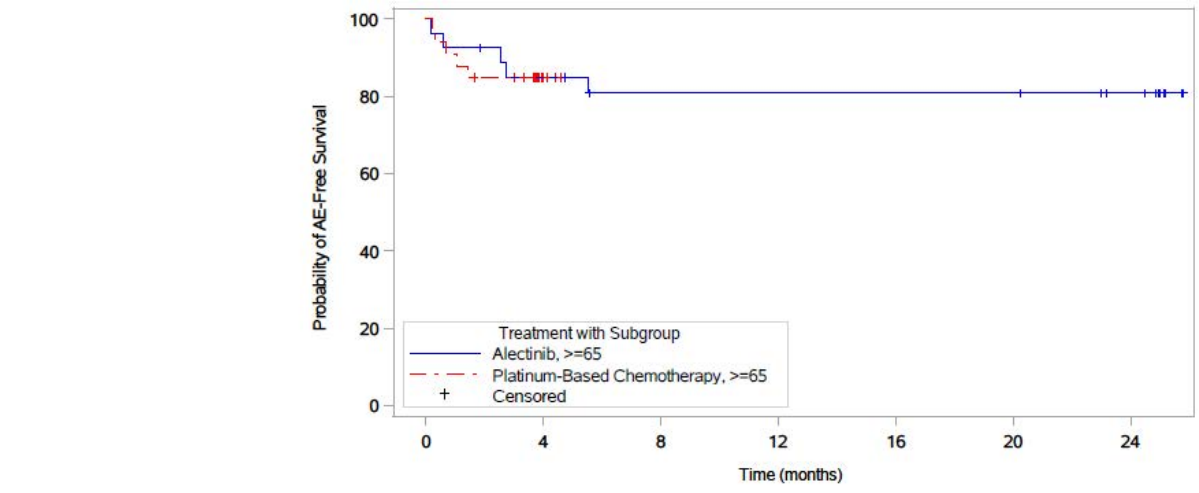
Patients at risk							
Alectinib	128	121	116	116	113	111	83
Platinum-Based Chemotherapy	120	17	NE	NE	NE	NE	NE
Patients censored							
Alectinib	0	3	5	5	8	10	38
Platinum-Based Chemotherapy	0	88	NE	NE	NE	NE	NE

Figure 6: Kaplan-Meier curves for the outcome of discontinuation due to AEs of the ALINA study, total population



Patients at risk							
Alectinib, <65	101	99	97	97	94	92	67
Platinum-Based Chemotherapy, <65	87	14	NE	NE	NE	NE	NE
Patients censored							
Alectinib, <65	0	2	2	2	5	7	32
Platinum-Based Chemotherapy, <65	0	63	NE	NE	NE	NE	NE

Figure 7: Kaplan-Meier curves for the outcome of discontinuation due to AEs of the ALINA study, subgroup < 65 years

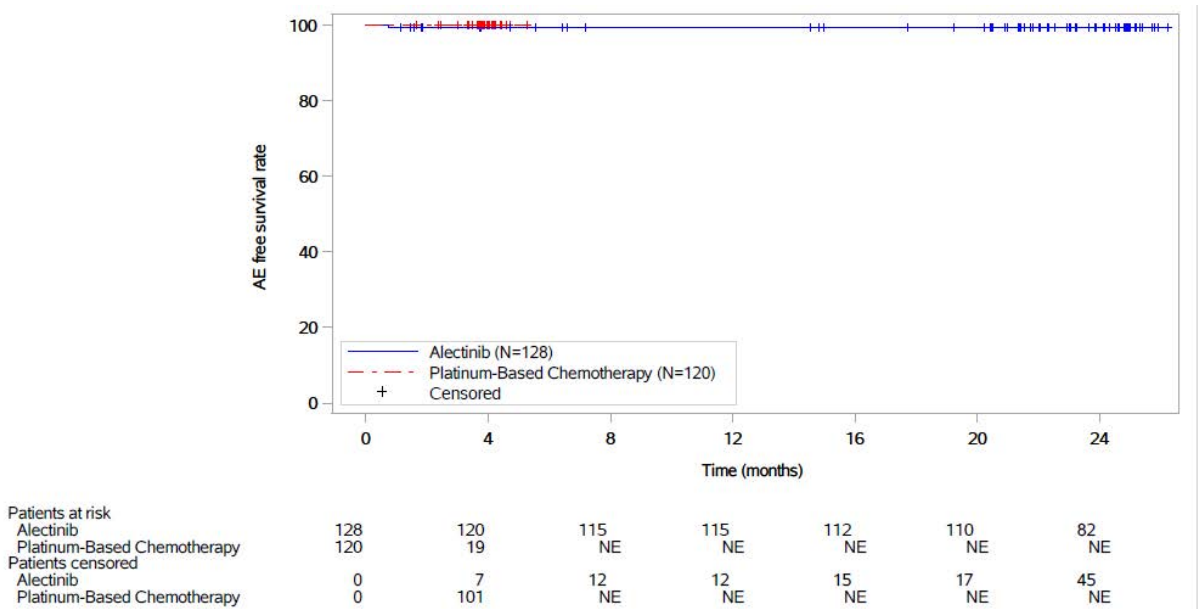


Patients at risk							
Alectinib, >=65	27	22	19	19	19	19	16
Platinum-Based Chemotherapy, >=65	33	3	NE	NE	NE	NE	NE
Patients censored							
Alectinib, >=65	0	1	3	3	3	3	6
Platinum-Based Chemotherapy, >=65	0	25	NE	NE	NE	NE	NE

Clinical cut-off: 26JUN2023

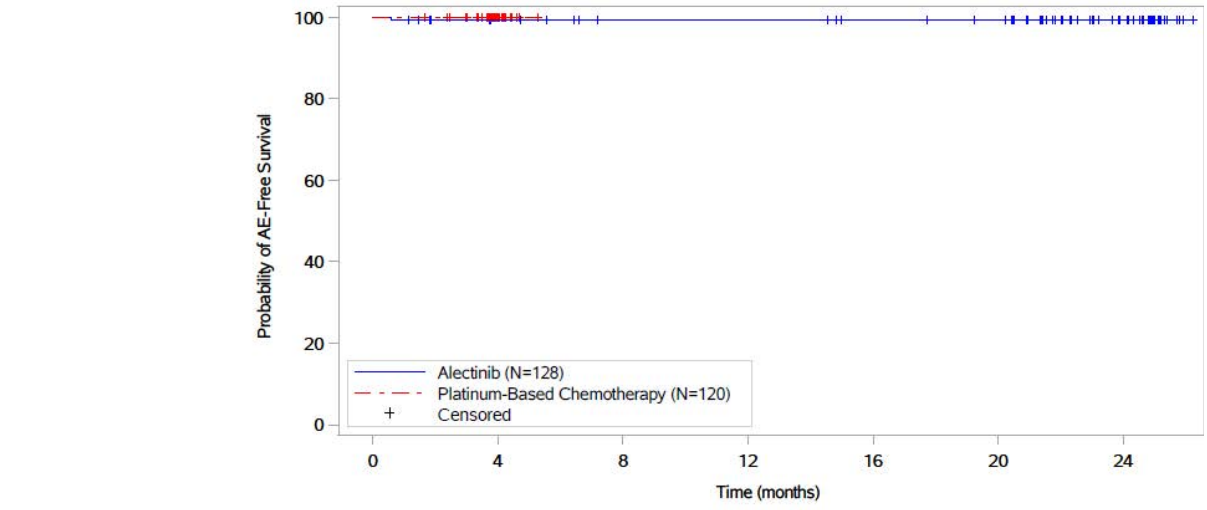
Figure 8: Kaplan-Meier curves for the outcome of discontinuation due to AEs of the ALINA study, subgroup ≥ 65 years

B.3.4 Specific AEs



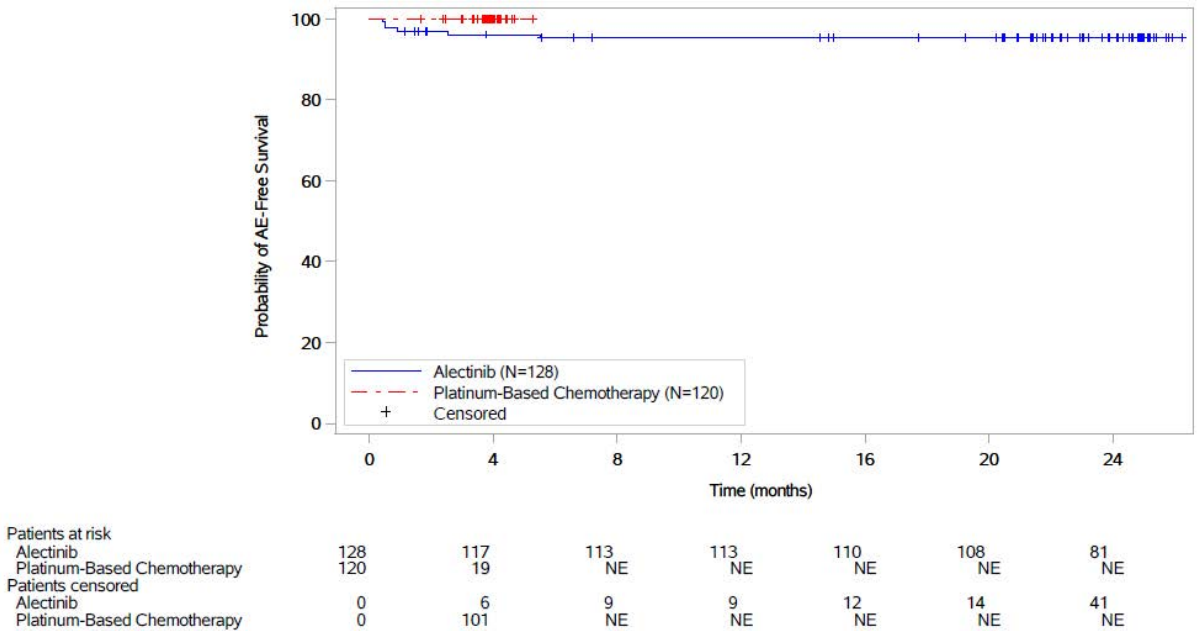
Patients at risk							
Alectinib	128	120	115	115	112	110	82
Platinum-Based Chemotherapy	120	19	NE	NE	NE	NE	NE
Patients censored							
Alectinib	0	7	12	12	15	17	45
Platinum-Based Chemotherapy	0	101	NE	NE	NE	NE	NE

Figure 9: Kaplan-Meier curves for the outcome of myalgia (PT, severe AEs) of the ALINA study, total population



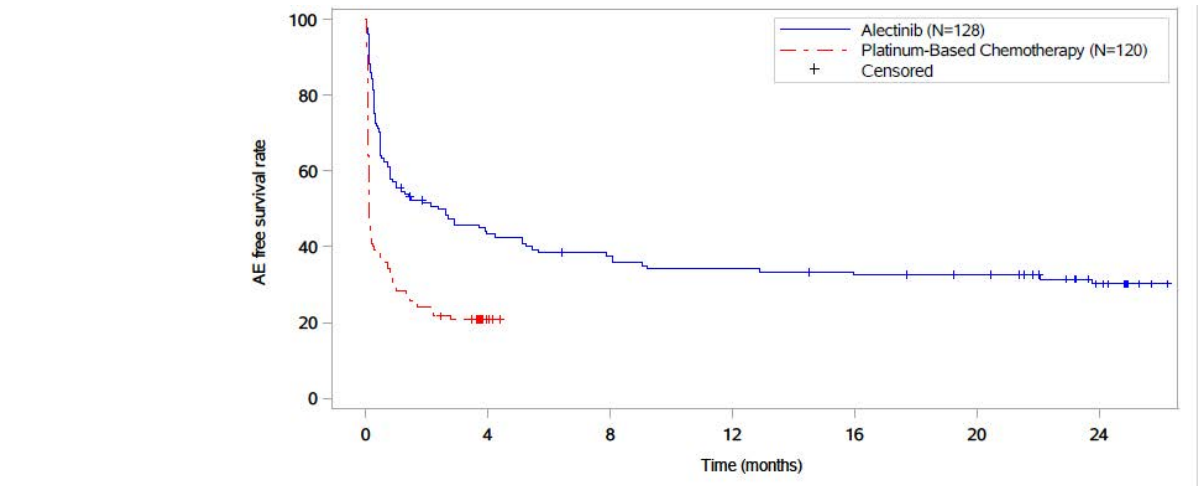
Patients at risk							
Alectinib	128	121	116	116	113	111	83
Platinum-Based Chemotherapy	120	19	NE	NE	NE	NE	NE
Patients censored							
Alectinib	0	6	11	11	14	16	44
Platinum-Based Chemotherapy	0	101	NE	NE	NE	NE	NE

Figure 10: Kaplan-Meier curves for the outcome of ILD/pneumonitis (SMQ, SAEs) of the ALINA study, total population



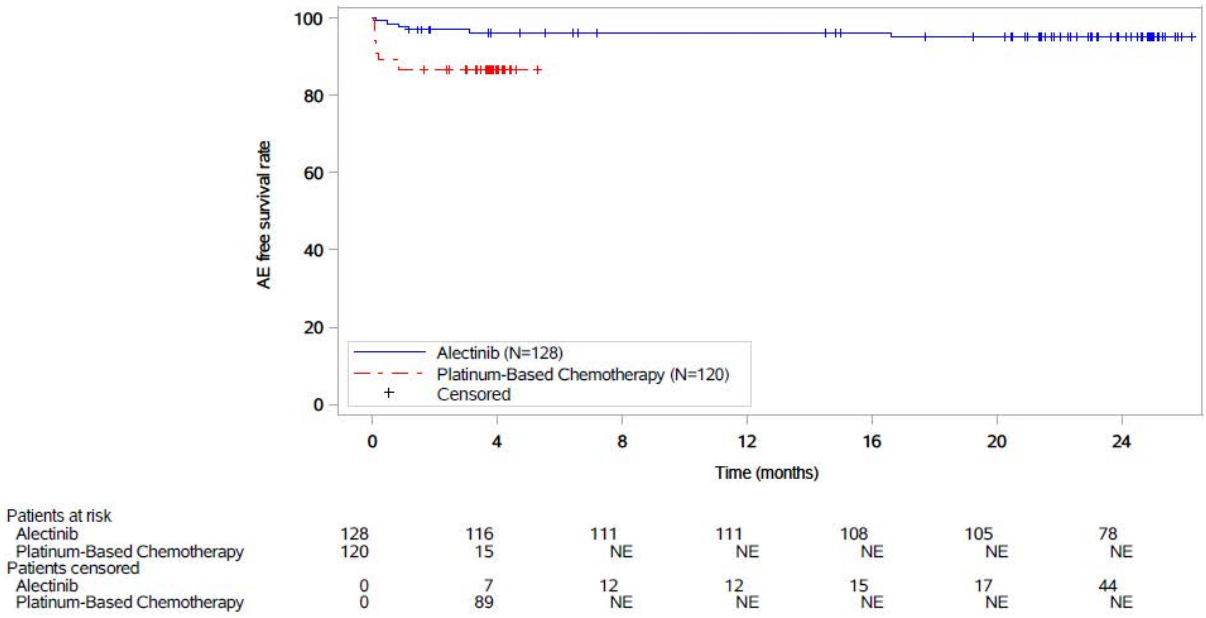
Patients at risk							
Alectinib	128	117	113	113	110	108	81
Platinum-Based Chemotherapy	120	19	NE	NE	NE	NE	NE
Patients censored							
Alectinib	0	6	9	9	12	14	41
Platinum-Based Chemotherapy	0	101	NE	NE	NE	NE	NE

Figure 11: Kaplan-Meier curves for the outcome of hepatotoxicity (SMQ, severe AEs) of the ALINA study, total population



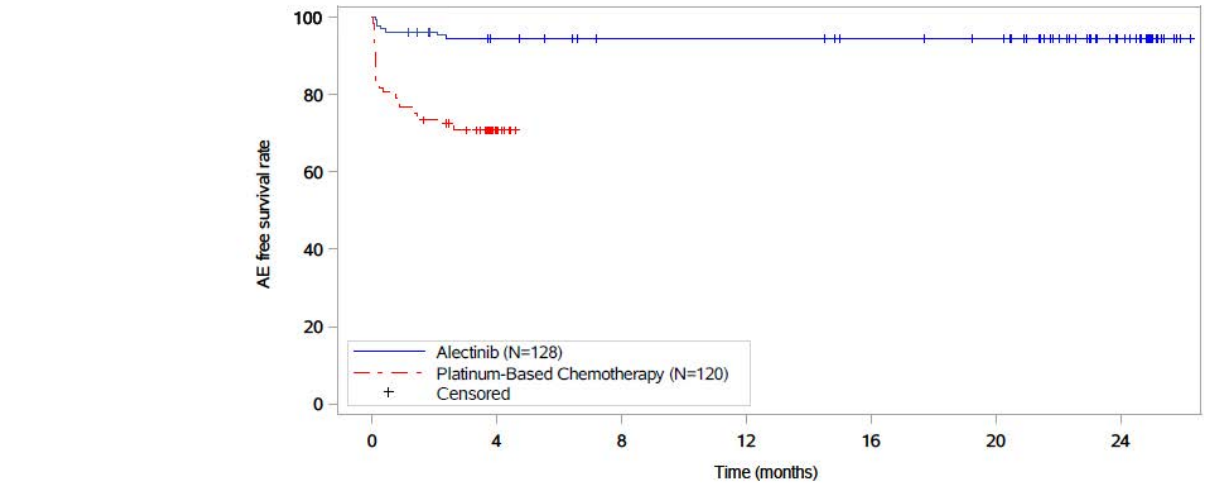
Patients at risk							
Alectinib	128	53	45	41	38	36	23
Platinum-Based Chemotherapy	120	4	NE	NE	NE	NE	NE
Patients censored							
Alectinib	0	3	4	4	5	7	18
Platinum-Based Chemotherapy	0	21	NE	NE	NE	NE	NE

Figure 12: Kaplan-Meier curves for the outcome of gastrointestinal disorders (SOC, AEs) of the ALINA study, total population



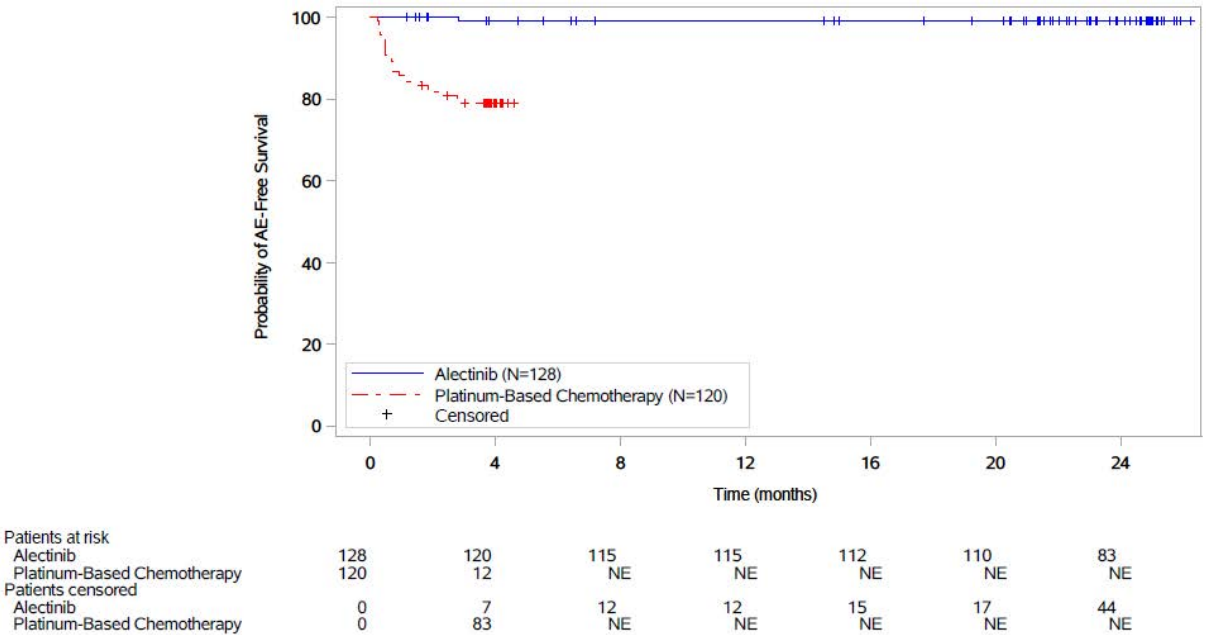
Patients at risk							
Alectinib	128	116	111	111	108	105	78
Platinum-Based Chemotherapy	120	15	NE	NE	NE	NE	NE
Patients censored							
Alectinib	0	7	12	12	15	17	44
Platinum-Based Chemotherapy	0	89	NE	NE	NE	NE	NE

Figure 13: Kaplan-Meier curves for the outcome of malaise (PT, AEs) of the ALINA study, total population



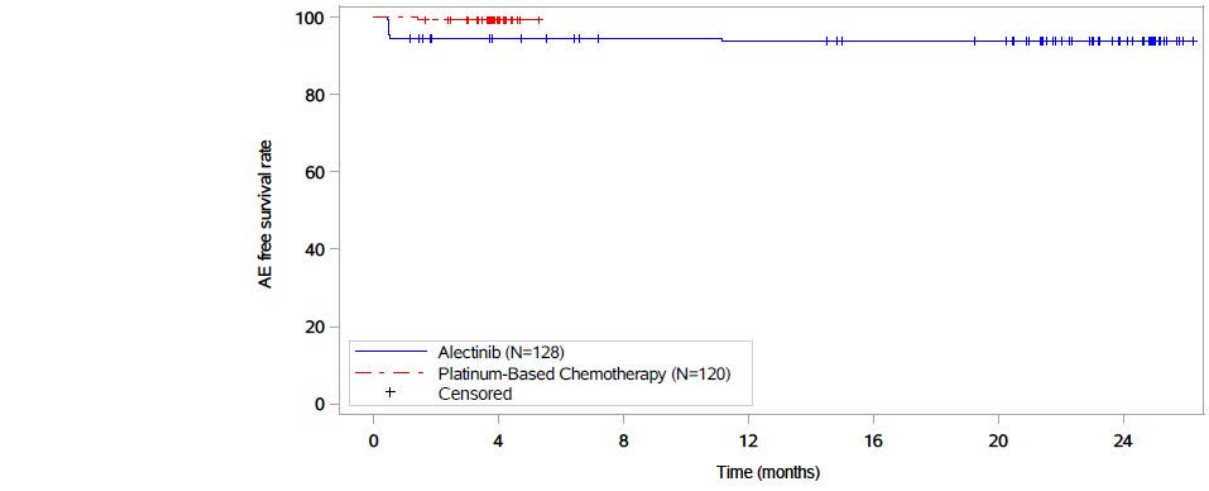
Patients at risk							
Alectinib	128	115	110	110	107	105	79
Platinum-Based Chemotherapy	120	11	NE	NE	NE	NE	NE
Patients censored							
Alectinib	0	6	11	11	14	16	42
Platinum-Based Chemotherapy	0	74	NE	NE	NE	NE	NE

Figure 14: Kaplan-Meier curves for the outcome of decreased appetite (PT, AEs) of the ALINA study, total population



Patients at risk							
Alectinib	128	120	115	115	112	110	83
Platinum-Based Chemotherapy	120	12	NE	NE	NE	NE	NE
Patients censored							
Alectinib	0	7	12	12	15	17	44
Platinum-Based Chemotherapy	0	83	NE	NE	NE	NE	NE

Figure 15: Kaplan-Meier curves for the outcome of haematopoietic cytopenias (SMQ, severe AEs) of the ALINA study, total population



Patients at risk							
Alectinib	128	114	109	108	105	104	77
Platinum-Based Chemotherapy	120	19	NE	NE	NE	NE	NE
Patients censored							
Alectinib	0	7	12	12	15	16	43
Platinum-Based Chemotherapy	0	100	NE	NE	NE	NE	NE

Figure 16: Kaplan-Meier curves for the outcome of blood creatine phosphokinase increased (PT, severe AEs) of the ALINA study, total population