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Alectinib (non-small cell lung cancer) –

Addendum to Commission A17-19[1]

Addendum

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[2] Due to legal data protection regulations, employees have the right not to be named.

Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
AE	adverse event
ALK	anaplastic lymphoma kinase
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
FISH	fluorescence in situ hybridization
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
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-LC13	Quality of Life Questionnaire-Lung Cancer 13
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 4 September 2017, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A17-19 (Alectinib – Benefit assessment according to §35a Social Code Book V [1]).

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") had identified with its literature search the ongoing randomized controlled trial (RCT) ALUR (NCT02604342) [3-6] sponsored by the company. The ALUR study was a study of direct comparison of alectinib versus docetaxel or pemetrexed in patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with both crizotinib and a platinum-based combination chemotherapy (research question 2). According to the company, the results of this study had not yet been available by the time the dossier for the benefit assessment of alectinib was submitted to the G-BA on 27 April 2017. As announced in the dossier, the company subsequently submitted the results of the ALUR study [3,8] with its comment [7]. The G-BA commissioned IQWiG with the assessment of the ALUR study.

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

In accordance with the commission, the ALUR study listed in the following table is assessed in the sections below.

Table 1: Study pool – RCT, direct comparison: alectinib vs. chemotherapy (pemetrexed or docetaxel)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
ALUR[b] (NCT02604342)	No	Yes	No
a: Study for which the company was sponsor. b: In the following tables, the study is referred to with this abbreviated form. RCT: randomized controlled trial; vs.: versus			

2.1 Study design and study characteristics

Study design

Table 2 and Table 3 describe the ALUR study.

Table 2: Characteristics of the ALUR study – RCT, direct comparison: alectinib vs. chemotherapy (pemetrexed or docetaxel)

Study	Study design	Population	Interventions (numbers of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ALUR	RCT, open-label, parallel	Adults with ALK-positive, advanced or recurrent (stage IIIB) or metastatic (stage IV) NSCLC with or without CNS metastases, after platinum-based chemotherapy and crizotinib, with ECOG PS of 0 to 2	Alectinib (N = 72) chemotherapy[b] (N = 35) thereof treated with pemetrexed: n = 9 docetaxel: n = 25	Screening: 28 days Treatment: until progression[c], unacceptable toxicity, withdrawal of consent, or death Follow-up: survival: every 3 months; side effects: until 4 weeks after the last dose of study drug End of study: when each patient is followed up for overall survival for up to 24 months or when 50% of randomized patients have died, whichever occurs first	40 centres in Belgium, France, Germany, Hong Kong, Hungary, Italy, Norway, Poland, Portugal, Republic of Korea, Russia, Spain, Turkey 11/2015–ongoing Data cut-offs: 26 Jan 2017 primary analysis (after 50 PFS events) final analysis planned after the end of study	Primary: PFS (assessed by the investigator) Secondary: overall survival, symptoms, health-related quality of life, adverse events

a: Primary outcomes include information without consideration of its relevance for this benefit assessment. Secondary outcomes exclusively include information on the relevant available outcomes for this benefit assessment.
b: The study documents contained no information on the criteria according to which docetaxel or pemetrexed was chosen in the comparator arm.
c: At the investigator's discretion, patients on the alectinib arm who showed progression were allowed to continue receiving alectinib beyond disease progression if he or she was benefitting from the drug. Patients on the chemotherapy arm who showed progression were allowed to cross over to receive alectinib treatment. Upon progression on cross-over treatment with alectinib, patients were allowed to continue receiving alectinib beyond disease progression if he or she was benefitting from the drug.

ALK: anaplastic lymphoma kinase; ECOG PS: Eastern Cooperative Oncology Group Performance Status; n: relevant subpopulation; N: number of randomized patients; NSCLC: non-small cell lung cancer; PFS: progression-free survival; RCT: randomized controlled trial; vs.: versus

Table 3: Characteristics of the intervention – RCT, direct comparison: alectinib vs. chemotherapy (pemetrexed or docetaxel)

Study	Intervention	Comparison
ALUR	Alectinib 600 mg BID, orally, in the morning and evening with a meal Dose adjustments and treatment discontinuations due to intolerance allowed; dose reductions in steps of 150 mg BID. Treatment discontinuation if a dose of 300 mg BID is not tolerated or in case of treatment interruptions for longer than 21 days	Chemotherapy, each every 3 weeks: ▪ pemetrexed 500 mg/m² IV, or ▪ docetaxel 75 mg/m² IV Application, dose adjustments and treatment interruptions in compliance with the approval <u>Additional medication in the pemetrexed arm:</u> ▪ folic acid (0.35 to 1 mg, orally), daily for 1 week before the first dose of the study medication until 3 weeks after the last dose of the study medication ▪ vitamin B12 (1 mg, IM or equivalent dose SC), first dose 1 week before the first dose of pemetrexed, then every 9 weeks ▪ dexamethasone (4 mg BID, orally) or equivalent, on the day of treatment, 1 day before and 1 day after <u>Additional medication in the docetaxel arm:</u> ▪ corticosteroids according to local practice (e.g. dexamethasone 8 mg, orally, BID, on the day of treatment, 1 day before and 1 day after) ▪ antiemetic prophylaxis
	Pretreatment and concomitant treatment	
	Pretreatment platinum-based chemotherapy and crizotinib **Non-permitted pretreatment** ▪ strong CYP3A inhibitors or inducers within 14 days before initiation of treatment ▪ other ALK inhibitors	
	Concomitant treatment Treatments to be used with precaution ▪ substrates of the BCRP or P-gp transporter and those with a narrow therapeutic index (e.g. digoxin, methotrexate) ▪ paracetamol up to 2 g daily ▪ local treatment (stereotactic radiotherapy, surgery) in patients with progression under alectinib requiring treatment interruption, before treatment continuation	<u>For pemetrexed</u> ▪ concomitant treatment in compliance with the SPC <u>For docetaxel</u> ▪ treatment with granulocyte-stimulating factor; patients ≥ 60 years and/or comorbidities should receive primary prophylaxis ▪ antiemetics, antiallergics and other concomitant treatments for docetaxel-induced toxicities ▪ other concomitant treatment in compliance with the SPC

(continued)

Table 3: Characteristics of the intervention – RCT, direct comparison: alectinib vs. chemotherapy (pemetrexed or docetaxel) (continued)

Study	Intervention	Comparison
	Non-permitted concomitant treatment ▪ strong CYP3A inducers (e.g. rifampicin, rifabutin, phenobarbital, phenytoin, carbamazepine and St. John's Wort, grapefruit or grapefruit juice) or inhibitors (e.g. ketoconazole) within 2 weeks or 5 half-lives of the prior therapy before initiation of the study medication ▪ systemic immunosuppressants, cytotoxic or chemotherapeutic treatments, ergot derivatives, probenecid and bile acid sequestrants ▪ systemic chemotherapy ▪ radiotherapy, except palliative treatment of bone lesions for pain control ▪ additional/other experimental study medications (except during follow-up observation)	For pemetrexed ▪ non-permitted concomitant treatment according to the SPC For docetaxel ▪ strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole, as well as grapefruit and grapefruit juice) and CYP3A4 inducers ▪ non-permitted concomitant treatment according to the SPC

ALK: anaplastic lymphoma kinase; BCRP: breast cancer resistance protein; BID: twice daily; CYP3A: cytochrome P450 3A; IM: intramuscular; IV: intravenous; NSCLC: non-small cell lung cancer; P-gp: P-glycoprotein; RCT: randomized controlled trial; SC: subcutaneous; SPC: Summary of Product Characteristics; vs.: versus

The ALUR study was an open-label, randomized controlled trial (RCT) on the comparison of alectinib versus docetaxel or pemetrexed. The study included patients with ALK-positive advanced or recurrent or metastatic NSCLC. The patients had been pretreated with platinum-based chemotherapy and crizotinib.

ALK translocation must have been determined by a validated fluorescence in situ hybridization (FISH) test (Vysis ALK Break-Apart Probe) or a validated immunohisto-chemistry test (recommended antibody: D5F3).

The patients were randomly allocated in a 2:1 ratio to treatment with alectinib or chemotherapy (docetaxel or pemetrexed), stratified by Eastern Cooperative Oncology Group Performance Status (ECOG PS) and presence of CNS metastases.

Treatment with alectinib and chemotherapy was until disease progression (diagnosed using Response Evaluation Criteria in Solid Tumours [RECIST]), in accordance with the respective approval [9-11]. Deviating from the Summary of Product Characteristics (SPC), patients in the alectinib arm could continue treatment with alectinib on occurrence of disease progression if the investigator considered this treatment to have a clinical advantage. At the investigator's discretion, patients in the chemotherapy arm could switch to treatment with alectinib on occurrence of disease progression. At the time point of the data cut-off for the primary

analysis (26 January 2017), 68.6% of the randomized patients had already switched from the chemotherapy arm to treatment with alectinib.

Table 4 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 4: Planned duration of follow-up observation – RCT, direct comparison: alectinib vs. chemotherapy (pemetrexed or docetaxel)

Study **Outcome category** **Outcome**	**Planned follow-up**
ALUR	
Mortality	
Overall survival	Every 3 months after the last dose of the study medication, at most until completion of the 24-month follow-up observation of all patients or after the death of 50% of the randomized patients
Morbidity	
Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13)	Week 3, week 6 and week 12 after initiation of treatment, then every 6 weeks, until disease progression 3 months after treatment discontinuation for patients without alectinib treatment after disease progression, or at the end of the randomized treatment for patients with continued alectinib treatment after disease progression
Health-related quality of life (EORTC QLQ-C30)	Week 3, week 6 and week 12 after initiation of treatment, then every 6 weeks, until disease progression 3 months after treatment discontinuation for patients without alectinib treatment after disease progression, or at the end of the randomized treatment for patients with continued alectinib treatment after disease progression
Side effects	
All outcomes in the category “side effects”	Until 4 weeks after the last dose of the study medication; patients with continued alectinib treatment after disease progression are observed until 4 weeks after the last dose of alectinib
AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus	

Characteristics of the study population

Table 5 shows the characteristics of the patients in the ALUR study.

Table 5: Characteristics of the study population – RCT, direct comparison: alectinib vs. chemotherapy (pemetrexed or docetaxel)

Study Characteristics Category	**Alectinib**	**Chemotherapy**
ALUR	N[a] = 72	N[a] = 35
Age [years], mean (SD)	54.5 (12.6)	58.8 (10.4)
Sex [F/M], %	43/57	51/49
Ethnicity, n (%)		
White	61 (84.7)	28 (80.0)
Asian	5 (6.9)	7 (20.0)
Other	6 (8.3)	0 (0)
Region, n (%)		
Western Europe	50 (69.4)	21 (60.0)
Asia	4 (5.6)	7 (20.0)
Other	18 (25.0)	7 (20.0)
Smoking status, n (%)		
Current smoker	2 (2.8)	2 (5.7)
Previous smoker	35 (48.6)	17 (48.6)
Never smoker	35 (48.6)	16 (45.7)
ECOG PS at baseline, n (%)		
0	29 (40.3)	11 (31.4)
1	37 (51.4)	19 (54.3)
2	6 (8.3)	5 (14.3)
Disease duration[b] [weeks]		
Median [first quartile; third quartile]	93.6 [58.0; 114.3]	98.2 [60.1; 129.5]
Mean (SD)	105.5 (60.0)	106.6 (68.6)
Disease stage at baseline, n (%)		
IIIB	3 (4.2)	1 (2.9)
IV	69 (95.8)	34 (97.1)
Histology, n (%)		
Adenocarcinoma	72 (100.0)	35 (100.0)
CNS metastases at baseline (according to the IRC), n (%)		
Yes	50 (69.4)	26 (74.3)
No	22 (30.6)	9 (25.7)
Number of prior lines of therapy, n (%)		
1	0 (0)	0 (0)
2	68 (94.4)	34 (97.1)
≥ 3	4 (5.6)	1 (2.9)
Treatment discontinuation, n (%)[c, d]	26 (37.1)	29 (85.3)
Study discontinuation, n (%)[d]	19 (26.4[e])	10 (28.6[e])

(continued)

Table 5: Characteristics of the study population – RCT, direct comparison: alectinib vs. chemotherapy (pemetrexed or docetaxel) (continued)

a: Number of randomized patients. Data that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Time from first diagnosis to randomization.
c: The most common reason for treatment discontinuation in both treatment arms was disease progression (alectinib: n = 20; chemotherapy: n = 23).
d: Including deaths; for study discontinuation these were n = 16 patients under alectinib and n = 7 patients under chemotherapy.
e: Institute's calculation.
ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; IRC: independent review committee; M: male; n: number of patients in the category; N: number of randomized (or included) patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The distribution of the patient characteristics was largely balanced between the study arms. The mean age of the patients included in the ALUR study was between 55 and 60 years; they mostly had stage IV disease and had received 2 other prior therapies. There were minor differences, which could be expected due to the small size of the study, regarding the distribution of the sexes, origin and general condition at the start of the study. There were more women and more Asians in the chemotherapy arm than in the alectinib arm, and more patients had an ECOG PS of 2.

Table 6 shows the median treatment duration and the median observation period for individual outcomes.

Table 6: Information on the course of the study – RCT, direct comparison: alectinib vs. chemotherapy (pemetrexed or docetaxel)

Study **Duration of the study phase** **Outcome category**	**Alectinib**	**Chemotherapy**
ALUR	N = 72	N = 35
Treatment duration[a] [months]		
Median [first quartile; third quartile]	9.9[b] [5.6; 12.5]	1.4[b] [1.2; 3.3]
Mean (SD)	ND	ND
Observation period [months]		
Overall survival[c]		
Median [first quartile; third quartile]	6.5 [3.5; 10.9]	5.8 [3.8; 10.0]
Mean (SD)	ND	ND
Morbidity, health-related quality of life, side effects	ND	ND

a: First treatment phase, before progression and possible treatment switch.
b: Kaplan-Meier estimator. In this analysis, patients who are still under treatment at the date of analysis are censored. In a different analysis, the time until the date of analysis was used as uncensored treatment period for these patients. According to this analysis, the medians are 20 vs. 6 weeks.
c: Presentation of the follow-up observation period from the end of the first treatment phase, after progression and possible treatment switch.
max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The study documents contained different information on the median treatment duration. On the one hand, the median treatment duration estimated by Kaplan-Meier curves was indicated as 9.9 versus 1.4 months. On the other, the respective numbers provided were 20 versus 6 weeks, for which only the observed, uncensored data were used. Irrespective of the type of estimation, the median treatment duration was notably longer in the alectinib arm than in the chemotherapy arm. The difference was due to early disease progression and corresponding discontinuation of chemotherapy. Overall, 23 of the 35 patients (66%) in the chemotherapy arm discontinued treatment due to disease progression, and 24 patients switched to alectinib treatment.

Risk of bias

Table 7 shows the risk of bias at study level.

Table 7: Risk of bias at study level – RCT, direct comparison: alectinib vs. chemotherapy (pemetrexed or docetaxel)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
ALUR	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias of the ALUR study was rated as low.

Limitations resulting from the open-label study design are described in Section 2.2.2 with the outcome-specific risk of bias.

2.2 Results

2.2.1 Outcomes included

The following patient-relevant outcomes were considered in the assessment:

- Mortality
  - overall survival
- Morbidity
  - symptoms recorded with the symptom scales of the instruments European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13)
- Health-related quality of life
  - recorded with the EORTC QLQ-C30 functional scales
- Side effects
  - serious adverse events (SAEs)
  - severe adverse events (AEs) (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - if applicable, further specific AEs

A choice of specific AEs was not possible because the company presented suitable survival time analyses only for selective AEs and therefore usable data were not available for all specific AEs.

Table 8 shows for which outcomes results were available in the ALUR study.

Table 8: Matrix of outcomes – RCT, direct comparison: alectinib vs. chemotherapy (pemetrexed or docetaxel)

Study	Outcomes						
	All-cause mortality	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-LC13)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)
ALUR	Y	Y	Y	Y	Y	Y	Y

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus; Y: yes

2.2.2 Risk of bias

Table 9 describes the risk of bias for the relevant outcomes.

Table 9: Risk of bias at study and outcome level – RCT, direct comparison: alectinib vs. chemotherapy (pemetrexed or docetaxel)

Study	Study level	Outcomes						
		All-cause mortality	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-LC13)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)
ALUR	L	H[a]	H[b]	H[b]	H[b]	H[c]	H[d]	H[c]

a: Large proportion of patients who switched from treatment with chemotherapy to treatment with alectinib (68.6%) and large difference in observation periods under the study medication originally allocated.
b: Lack of blinding in subjective recording of outcomes and large difference in observation periods under the study medication originally allocated. This is also associated with a possibly large proportion of potentially informative censorings.
c: Large difference in observation periods under the study medication originally allocated. This is also associated with a possibly large proportion of potentially informative censorings.
d: Lack of blinding in partly subjective recording of outcomes, and large difference in observation periods.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus; Y: yes

The risk of bias for all relevant outcomes was rated as high.

The outcome “overall survival” had a high risk of bias because of the large proportion of patients who switched from treatment with chemotherapy to treatment with alectinib (68.6%) and a large difference in observation periods under the study medication originally allocated. The outcomes on symptoms and health-related quality of life had a high risk of bias because of the lack of blinding in subjective recording of outcomes. In addition, there was the large difference in observation periods under the study medication originally allocated. This is also associated with a possibly large proportion of potentially informative censorings. The outcomes on side effects also had a high risk of bias because of the large difference in observation periods under the study medication originally allocated and the associated possibly large proportion of potentially informative censorings. For the outcome “discontinuation due to AEs”, there was additionally the lack of blinding in partially subjective recording of outcomes.

2.2.3 Results

Due to the large differences in treatment duration between the study arms, only analyses using survival time analysis were used.

Table 10 shows the results of the ALUR study. If available, Kaplan-Meier curves on the outcomes included are presented in Appendix A.

Table 10: Results – RCT, direct comparison: alectinib vs. chemotherapy (pemetrexed or docetaxel)

Study Outcome category Outcome	Alectinib N	Alectinib Median time to event in months [95% CI] Patients with event n (%)	Chemotherapy N	Chemotherapy Median time to event in months [95% CI] Patients with event n (%)	Alectinib vs. chemotherapy HR[a] [95% CI]; p-value[b]
ALUR					
Mortality					
Overall survival	72	12.6 [9.7; NA] 16 (22.2)	35	NA [NA; NA] 7 (20.0)	0.89 [0.35; 2.24]; 0.797
Morbidity (symptoms)					
EORTC QLQ-C30 symptom scales – time to deterioration[c]					
Pain	72	2.8 [1.4; NA] 31 (43.1)	35	3.4 [1.4; NA] 8 (22.9)	1.45 [0.65; 3.27]; 0.364
Dyspnoea	72	NA [2.8; NA] 23 (31.9)	35	NA [1.2; NA] 9 (25.7)	0.81 [0.36; 1.82]; 0.615
Insomnia	72	9.7 [5.8; NA] 20 (27.8)	35	NA [1.9; NA] 6 (17.1)	0.88 [0.33; 2.35]; 0.801
Fatigue	72	2.7 [1.4; 9.7] 32 (44.4)	35	1.4 [0.8; NA] 15 (42.9)	0.65 [0.33; 1.27]; 0.207
Diarrhoea	72	NA [NA; NA] 7 (9.7)	35	NA [NA; NA] 5 (14.3)	0.21 [0.05; 0.89]; 0.021
Nausea and vomiting	72	NA [NA; NA] 14 (19.4)	35	3.3 [1.7; NA] 7 (20.0)	0.57 [0.21; 1.56]; 0.267
Appetite loss	72	9.7 [3.0; NA] 20 (27.8)	35	NA [2.0; NA] 6 (17.1)	1.03 [0.39; 2.70]; 0.956
Constipation	72	4.1 [1.3; NA] 30 (41.7)	35	NA [NA; NA] 4 (11.4)	3.26 [1.12; 9.48]; 0.023

(continued)

Table 10: Results – RCT, direct comparison: alectinib vs. chemotherapy (pemetrexed or docetaxel) (continued)

Study Outcome category Outcome	Alectinib N	Alectinib Median time to event in months [95% CI] Patients with event n (%)	Chemotherapy N	Chemotherapy Median time to event in months [95% CI] Patients with event n (%)	Alectinib vs. chemotherapy HR[a] [95% CI]; p-value[b]
EORTC QLQ-LC13 symptom scales – time to deterioration[c]					
Dyspnoea	72	2.8 [0.9; NA] 33 (45.8)	35	4.2 [1.2; NA] 11 (31.4)	1.05 [0.51; 2.17]; 0.890
Cough	72	NA [6.7; NA] 17 (23.6)	35	NA [NA; NA] 4 (11.4)	1.16 [0.37; 3.67]; 0.797
Haemoptysis	72	NA [NA; NA] 2 (2.8)	35	NA [NA; NA] 1 (2.9)	< 0.01 [0.00; NA]; 0.068
Pain (thorax)	72	NA [8.1; NA] 15 (20.8)	35	NA [2.0; NA] 3 (8.6)	1.74 [0.48; 6.26]; 0.392
Pain in arm or shoulder	72	8.1 [4.1; NA] 23 (31.9)	35	1.9 [1.6; NA] 9 (25.7)	0.56 [0.23; 1.37]; 0.198
Pain (other parts)	72	9.7 [2.8; NA] 25 (34.7)	35	NA [2.0; NA] 3 (8.6)	2.06 [0.60; 7.05]; 0.239
Sore mouth	72	NA [NA; NA] 12 (16.7)	35	NA [1.4; NA] 4 (11.4)	0.93 [0.29; 3.01]; 0.903
Dysphagia	72	NA [6.7; NA] 17 (23.6)	35	NA [1.6; NA] 6 (17.1)	0.59 [0.21; 1.69]; 0.325
Neuropathy peripheral	72	8.5 [4.2; NA] 20 (27.8)	35	2.8 [1.6; NA] 6 (17.1)	0.60 [0.21; 1.71]; 0.334
Alopecia	72	NA [9.7; NA] 11 (15.3)	35	1.4 [0.8; NA] 15 (42.9)	0.13 [0.05; 0.33]; < 0.001
Health-related quality of life					
EORTC QLQ-C30 functional scales – time to deterioration[d]					
Global health status	72	9.7 [7.0; 11.0] 18 (25.0)	35	NA [0.9; NA] 8 (22.9)	0.51 [0.20; 1.29]; 0.148
Physical functioning	72	9.7 [2.8; NA] 24 (33.3)	35	NA [1.4; NA] 8 (22.9)	0.90 [0.39; 2.10]; 0.814
Role functioning	72	9.7 [2.6; NA] 27 (37.5)	35	2.0 [1.4; NA] 11 (31.4)	0.75 [0.35; 1.59]; 0.452
Emotional functioning	72	9.7 [8.5; 11.1] 22 (30.6)	35	NA [1.4; NA] 7 (20.0)	0.71 [0.27; 1.87]; 0.486
Cognitive functioning	72	9.7 [2.8; 11.0] 25 (34.7)	35	2.0 [1.4; NA] 11 (31.4)	0.70 [0.32; 1.55]; 0.374
Social functioning	72	4.4 [2.8; 9.7] 30 (41.7)	35	2.0 [0.9; NA] 9 (25.7)	0.78 [0.34; 1.76]; 0.542

(continued)

Table 10: Results – RCT, direct comparison: alectinib vs. chemotherapy (pemetrexed or docetaxel) (continued)

Study Outcome category Outcome	Alectinib N	Alectinib Median time to event in months [95% CI] Patients with event n (%)	Chemotherapy N	Chemotherapy Median time to event in months [95% CI] Patients with event n (%)	Alectinib vs. chemotherapy HR[a] [95% CI]; p-value[b]
Side effects[e]					
AEs (supplementary information)	70	0.7 [0.4; 1.2] 54 (77.1)	34	0.2 [0.1; 0.3] 29 (85.3)	–
SAEs	70	ND 13 (18.6)	34	ND 5 (14.7)	0.89 [0.31; 2.60]; 0.835
Severe AEs (CTCAE grade ≥ 3)	70	ND [7.2; ND] 19 (27.1)	34	4.9 [0.9; ND] 14 (41.2)	0.36 [0.17; 0.76]; 0.005
Discontinuation due to AEs	70	ND [7.2; ND] 4 (5.7)	34	NA [3.3; ND] 3 (8.8)	RR: 0.65[f] [0.15; 2.73]; 0.618[g]

a: Cox proportional hazards model stratified by ECOG PS, CNS metastases at baseline and prior radiotherapy.
b: Log-rank test stratified by the factors mentioned above.
c: Time to increase in score by at least 10 points versus the baseline value.
d: Time to decrease in score by at least 10 points versus the baseline value.
e: Side effects are presented for the first treatment phase until disease progression.
f: Institute's calculation of effect and CI (asymptotic).
g: Institute's calculation, unconditional exact test (CSZ method according to [12]).
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Due to the high risk of bias, no more than "hints" of an added benefit can be derived for all outcomes.

Mortality

There was no statistically significant difference between the treatment groups for the outcome "overall survival". Hence there was no hint of an added benefit of alectinib in comparison with docetaxel or pemetrexed; an added benefit is therefore not proven.

Morbidity

Outcomes of symptoms were recorded with the symptom scales of the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-LC13.

Diarrhoea, alopecia

Statistically significant differences in favour of alectinib in comparison with docetaxel or pemetrexed were shown for the outcomes “diarrhoea” and “alopecia”. This led to a hint of an added benefit of alectinib for these outcomes.

Constipation

A statistically significant difference to the disadvantage of alectinib in comparison with docetaxel or pemetrexed was shown for the outcome “constipation”. This led to a hint of lesser benefit of alectinib for this outcome.

Further outcomes on symptoms

No statistically significant differences between the treatment groups were shown for any further outcomes on symptoms. This led to no hint of an added benefit of alectinib in comparison with docetaxel or pemetrexed for the further symptom outcomes; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life was recorded with the functional scales and with the scale for the recording of the global health status of the disease-specific instrument EORTC QLQ-C30.

No statistically significant differences between the treatment groups were shown for the outcomes on health-related quality of life. This led to no hint of an added benefit of alectinib in comparison with docetaxel or pemetrexed for the outcomes on health-related quality of life; an added benefit is therefore not proven.

Side effects

Severe adverse events (CTCAE grade ≥ 3)

There was a statistically significant difference in favour of alectinib in comparison with docetaxel or pemetrexed for the outcome “severe AEs (CTCAE grade ≥ 3)”. This resulted in a hint of lesser harm from alectinib in comparison with docetaxel or pemetrexed for this outcome.

Serious adverse events, discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcomes “SAEs” and “discontinuation due to AEs”. Hence, for these outcomes, there was no hint of greater or lesser harm from alectinib in comparison with docetaxel or pemetrexed; greater or lesser harm from alectinib is therefore not proven.

2.3 Extent and probability of added benefit

The derivation of probability and extent of the added benefit of the added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [13].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.3.1 Assessment of added benefit at outcome level

From the available information, it could not be inferred for all outcomes considered in the present benefit assessment whether they were non-severe/non-serious or severe/serious. The assessment regarding the outcome category of the EORTC QLQ-C30 and EORTC QLQ-LC13 symptom scales, which showed an added benefit, depends on the severity of the respective symptom. The results on common AEs recorded in the ALUR study were used by CTCAE grades to be able to assess the severity of these symptoms. The corresponding AEs were mostly non-severe (CTCAE grade 1 and 2), however. Correspondingly, the results of the symptoms were allocated to the outcome category “non-serious/non-severe symptoms/late complications”.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 11).

Table 11: Extent of added benefit at outcome level: alectinib vs. chemotherapy (pemetrexed or docetaxel)

Outcome category **Outcome**	**Alectinib vs. chemotherapy** **Median of time to event or proportion of events** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
Overall survival	Median: 12.6 vs. NA months HR: 0.89 [0.35; 2.24] p = 0.797	Lesser benefit/added benefit not proven
Morbidity (symptoms)		
EORTC QLQ-C30 symptom scales – time to deterioration[c]		
Pain	Median: 2.8 vs. 3.4 months HR: 1.45 [0.65; 3.27] p = 0.364	Lesser benefit/added benefit not proven
Dyspnoea	Median: NA vs. NA months HR: 0.81 [0.36; 1.82] p = 0.615	Lesser benefit/added benefit not proven
Insomnia	Median: 9.7 vs. NA months HR: 0.88 [0.33; 2.35] p = 0.801	Lesser benefit/added benefit not proven
Fatigue	Median: 2.7 vs. 1.4 months HR: 0.65 [0.33; 1.27] p = 0.207	Lesser benefit/added benefit not proven
Diarrhoea	Median: NA vs. NA months HR: 0.21 [0.05; 0.89] p = 0.021 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 90$ added benefit, extent: "minor"
Nausea and vomiting	Median: NA vs. 3.3 months HR: 0.57 [0.21; 1.56] p = 0.267	Lesser benefit/added benefit not proven
Appetite loss	Median: 9.7 vs. NA months HR: 1.03 [0.39; 2.70] p = 0.956	Lesser benefit/added benefit not proven
Constipation	Median: 4.1 vs. NA months HR: 3.26 [1.12; 9.48] HR: 0.31 [0.11; 0.89][d] p = 0.023 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 90$ lesser benefit, extent: "minor"

(continued)

Table 11: Extent of added benefit at outcome level: alectinib vs. chemotherapy (pemetrexed or docetaxel) (continued)

Outcome category **Outcome**	**Alectinib vs. chemotherapy** **Median of time to event or proportion of events** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
EORTC QLQ-LC13 symptom scales – time to deterioration[c]		
Dyspnoea	Median: 2.8 vs. 4.2 months HR: 1.05 [0.51; 2.17] p = 0.890	Lesser benefit/added benefit not proven
Cough	Median: NA vs. NA months HR: 1.16 [0.37; 3.67] p = 0.797	Lesser benefit/added benefit not proven
Haemoptysis	Median: NA vs. NA months HR: < 0.01 [0.00; NA] p = 0.068	Lesser benefit/added benefit not proven
Pain (thorax)	Median: NA vs. NA months HR: 1.74 [0.48; 6.26] p = 0.392	Lesser benefit/added benefit not proven
Pain in arm or shoulder	Median: 8.1 vs. 1.9 months HR: 0.56 [0.23; 1.37] p = 0.198	Lesser benefit/added benefit not proven
Pain (other)	Median: NA vs. NA months HR: 2.06 [0.60; 7.05] p = 0.239	Lesser benefit/added benefit not proven
Sore mouth	Median: NA vs. NA months HR: 0.93 [0.29; 3.01] p = 0.903	Lesser benefit/added benefit not proven
Dysphagia	Median: NA vs. NA months HR: 0.59 [0.21; 1.69] p = 0.325	Lesser benefit/added benefit not proven
Neuropathy peripheral	Median: 8.5 vs. 2.8 months HR: 0.60 [0.21; 1.71] p = 0.334	Lesser benefit/added benefit not proven
Alopecia	Median: NA vs. 1.4 months HR: 0.13 [0.05; 0.33] p = < 0.001 probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 added benefit, extent: “considerable”

(continued)

Table 11: Extent of added benefit at outcome level: alectinib vs. chemotherapy (pemetrexed or docetaxel) (continued)

Outcome category **Outcome**	**Alectinib vs. chemotherapy** **Median of time to event or proportion of events** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Health-related quality of life		
EORTC QLQ-C30 functional scales – time to deterioration[e]		
Global health status	Median: 9.7 vs. NA months HR: 0.51 [0.20; 1.29] p = 0.148	Lesser benefit/added benefit not proven
Physical functioning	Median: 9.7 vs. NA months HR: 0.90 [0.39; 2.10] p = 0.814	Lesser benefit/added benefit not proven
Role functioning	Median: 9.7 vs. 2.0 months HR: 0.75 [0.35; 1.59] p = 0.452	Lesser benefit/added benefit not proven
Emotional functioning	Median: 9.7 vs. NA months HR: 0.71 [0.27; 1.87] p = 0.486	Lesser benefit/added benefit not proven
Cognitive functioning	Median: 9.7 vs. 2.0 months HR: 0.70 [0.32; 1.55] p = 0.374	Lesser benefit/added benefit not proven
Social functioning	Median: 4.4 vs. 2.0 months HR: 0.78 [0.34; 1.76] p = 0.542	Lesser benefit/added benefit not proven
Side effects		
SAEs	Median: NA vs. NA months HR: 0.89 [0.31; 2.60] p = 0.835	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	Median: NA vs. 4.9 months HR: 0.36 [0.17; 0.76] p = 0.005 probability: “hint”	Outcome category: serious/severe side effects $0.75 \leq CI_u < 90$ lesser harm, extent: “considerable”
Discontinuation due to AEs	Proportion: 5.7% vs. 8.8% RR: 0.65 [0.15; 2.73] p = 0.618	Greater/lesser harm not proven

(continued)

Table 11: Extent of added benefit at outcome level: alectinib vs. chemotherapy (pemetrexed or docetaxel) (continued)

a: Probability provided if a statistically significant and relevant effect is present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Time to increase in score by at least 10 points versus the baseline value.
d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e: Time to decrease in score by at least 10 points versus the baseline value.
AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; NC: not calculable; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RR: relative risk; SAE: serious adverse event; vs.: versus

2.3.2 Overall conclusion on added benefit

Table 12 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 12: Positive and negative effects from the assessment of alectinib compared with chemotherapy (pemetrexed or docetaxel)

Positive effects	**Negative effects**
Non-serious/non-severe symptoms/late complications ▪ alopecia: hint of an added benefit – extent "considerable" ▪ diarrhoea: hint of an added benefit – extent "minor"	Non-serious/non-severe symptoms/late complications ▪ constipation: hint of lesser benefit – extent "minor"
Serious/severe side effects ▪ severe AEs (CTCAE grade ≥ 3): hint of lesser harm – extent "considerable"	
AE: adverse event; CTCAE: Common Terminology Criteria of Adverse Events	

Overall, there are positive effects and 1 negative effect.

On the side of positive effects, there are hints of lesser harm in the outcome category "side effects" (the symptoms "alopecia" and "diarrhoea", recorded with the EORTC QLQ-C30 and QLQ-LC13 are typical side effects of chemotherapy and hence also to be allocated to this outcome category) with the extent "considerable" or "minor". This accompanied by a negative effect for the symptom "constipation". There is a hint of lesser benefit with the extent "minor" for this outcome.

In the present assessment, the derivation of the added benefit was solely based on a reduction of side effects. In this situation, it has to be checked whether the results on benefit outcomes exclude a disadvantage on the benefit side with sufficient certainty. The interpretability of the outcome "overall survival" was limited because of the large proportion of patients who

switched from treatment with chemotherapy to treatment with alectinib (68.6%). In the overall consideration of the results, including those on the outcome categories of morbidity and health-related quality of life, the available data produced no indication of lesser benefit of alectinib compared with chemotherapy, however.

In summary, there is a hint of considerable added benefit of alectinib in comparison with the ACT docetaxel or pemetrexed for patients with ALK-positive advanced NSCLC who are eligible for treatment with docetaxel or pemetrexed after pretreatment with platinum-based chemotherapy.

The result of the assessment of the added benefit of alectinib in comparison with the ACT is summarized in Table 13.

Table 13: Alectinib – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT[a]**	**Probability and extent of added benefit**
2	Crizotinib-pretreated adult patients with ALK-positive advanced NSCLC who are eligible for treatment with docetaxel or pemetrexed after pretreatment with platinum-based chemotherapy	**Docetaxel** or **pemetrexed**	Hint of considerable added benefit

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4 List of included studies

Hoffmann-La Roche. Alectinib versus pemetrexed or docetaxel in anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) participants previously treated with platinum-based chemotherapy and crizotinib: full text view [online]. In: ClinicalTrials.gov. 08.05.2017 [Accessed: 23.06.2017]. URL: https://clinicaltrials.gov/ct2/show/NCT02604342.

Hoffmann-La Roche. Randomized, multicenter, phase III, open-label study of alectinib versus pemetrexed or docetaxel in anaplastic lymphoma kinase-positive advanced non-small cell lung cancer patients previously treated with platinum-based chemotherapy and crizotinib: study MO29750 (ALUR); protocol version number 5.0 [unpublished]. 2016.

Hoffmann-La Roche. Randomized, multicenter, phase III, open-label study of alectinib versus pemetrexed or docetaxel in anaplastic lymphoma kinase-positive advanced non-small cell lung cancer patients previously treated with platinum-based chemotherapy and crizotinib: study MO29750 (ALUR); primary clinical study report [unpublished]. 2017.

Hoffmann-La Roche. Randomized, multicenter, phase III, open-label study of alectinib versus pemetrexed or docetaxel in anaplastic lymphoma kinase-positive advanced non-small cell lung cancer patients previously treated with platinum-based chemotherapy and crizotinib: study MO29750 (ALUR); statistical analysis plan version number 2.0 [unpublished]. 2017.

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4. Hoffmann-La Roche. Randomized, multicenter, phase III, open-label study of alectinib versus pemetrexed or docetaxel in anaplastic lymphoma kinase-positive advanced non-small cell lung cancer patients previously treated with platinum-based chemotherapy and crizotinib: study MO29750 (ALUR); protocol version number 5.0 [unpublished]. 2016.

5. Hoffmann-La Roche. Randomized, multicenter, phase III, open-label study of alectinib versus pemetrexed or docetaxel in anaplastic lymphoma kinase-positive advanced non-small cell lung cancer patients previously treated with platinum-based chemotherapy and crizotinib: study MO29750 (ALUR); statistical analysis plan version number 2.0 [unpublished]. 2017.

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Appendix A – Kaplan-Meier curves on results of the ALUR study

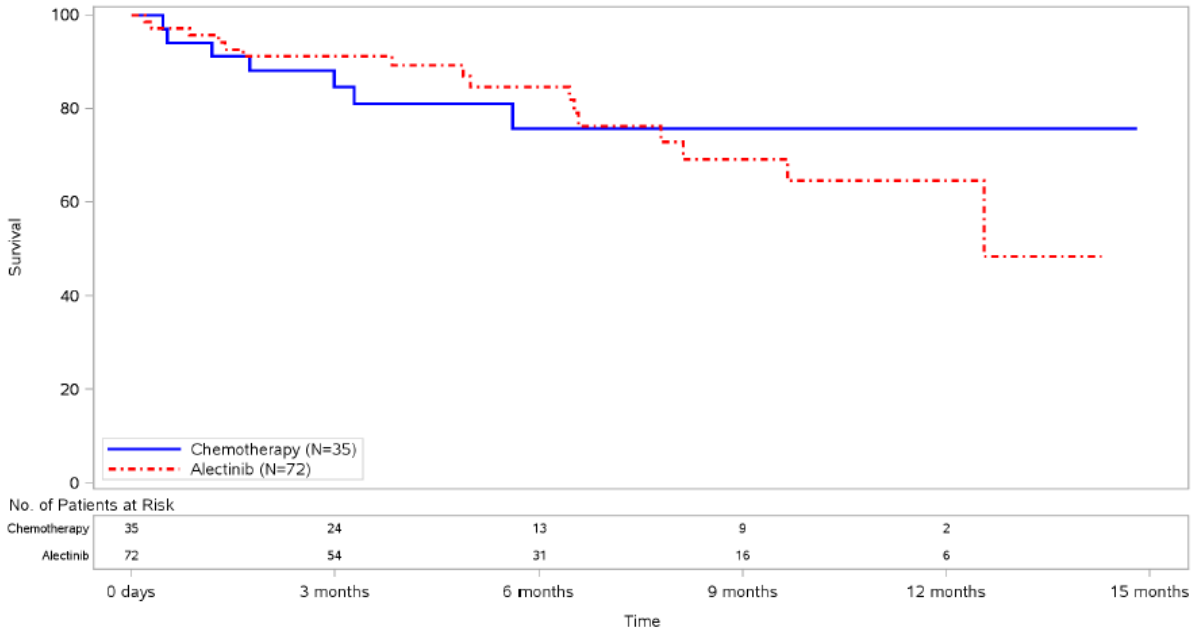

Figure 1: Kaplan-Meier curve for overall survival – RCT, direct comparison: alectinib vs. chemotherapy (pemetrexed or docetaxel)

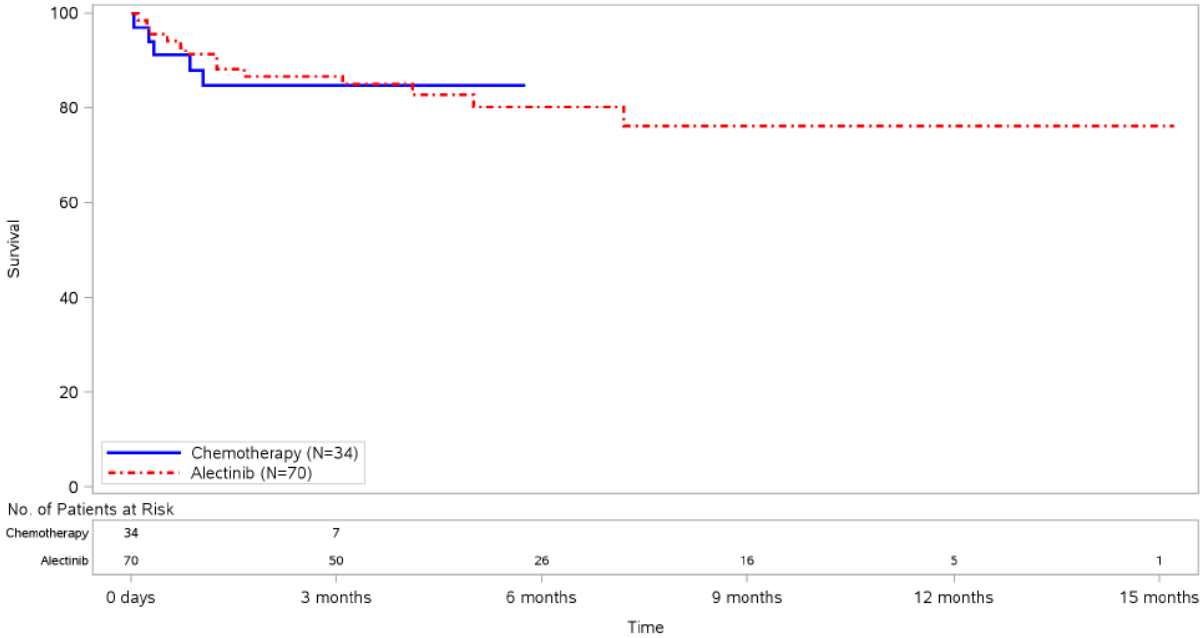

Figure 2: Kaplan-Meier curve for SAEs – RCT, direct comparison: alectinib vs. chemotherapy (pemetrexed or docetaxel)

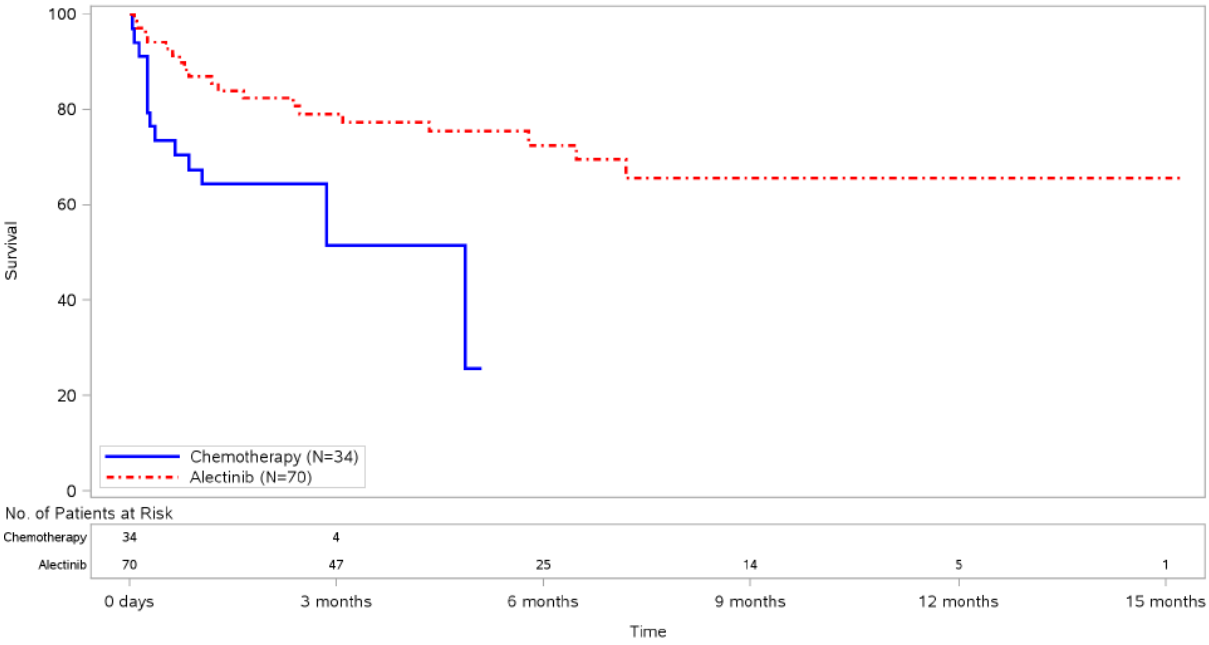

Figure 3: Kaplan-Meier curve for severe AEs (CTCAE grade ≥ 3) – RCT, direct comparison: alectinib vs. chemotherapy (pemetrexed or docetaxel)

Appendix B – Results on side effects

Table 14: Common AEs (in the SOC and in the PT ≥ 3% in at least 1 study arm) – RCT, direct comparison: alectinib vs. chemotherapy (pemetrexed or docetaxel)

Study	Patients with event n (%)	
SOC[a] **PT[a]**	**Alectinib** **N = 70**	**Chemotherapy** **N = 34**
ALUR		
Overall rate of AEs		
Gastrointestinal disorders	19 (27.1)	13 (38.2)
Constipation	13 (18.6)	4 (11.8)
Nausea	1 (1.4)	6 (17.6)
Diarrhoea	2 (2.9)	3 (8.8)
Stomatitis	0 (0)	2 (5.9)
Vomiting	2 (2.9)	2 (5.9)
General disorders and administration site conditions	19 (27.1)	17 (50.0)
Asthenia	7 (10.0)	5 (14.7)
Oedema peripheral	6 (8.6)	2 (5.9)
Fatigue	4 (5.7)	9 (26.5)
Pyrexia	2 (2.9)	3 (8.8)
Infections and infestations	19 (27.1)	7 (20.6)
Bronchitis	4 (5.7)	1 (2.9)
Pneumonia	3 (4.3)	0 (0)
Pneumonia bacterial	0 (0)	2 (5.9)
Musculoskeletal and connective tissue disorders	18 (25.7)	9 (26.5)
Myalgia	6 (8.6)	3 (8.8)
Back pain	4 (5.7)	2 (5.9)
Arthralgia	3 (4.3)	1 (2.9)
Muscle spasms	3 (4.3)	0 (0)
Pain in extremity	0 (0)	2 (5.9)
Nervous system disorders	16 (22.9)	8 (23.5)
Headache	3 (4.3)	2 (5.9)
Dizziness	2 (2.9)	2 (5.9)
Neuropathy peripheral	1 (1.4)	2 (5.9)
Blood and lymphatic system disorders	12 (17.1)	11 (32.4)
Anaemia	10 (14.3)	4 (11.8)
Neutropenia	2 (2.9)	5 (14.7)
Febrile neutropenia	0 (0)	2 (5.9)

(continued)

Table 14: Common AEs (in the SOC and in the PT ≥ 3% in at least 1 study arm) – RCT, direct comparison: alectinib vs. chemotherapy (pemetrexed or docetaxel) (continued)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Alectinib** **N = 70**	**Chemotherapy** **N = 34**
ALUR		
Overall rate of AEs		
Investigations	12 (17.1)	2 (5.9)
Blood bilirubin increased	4 (5.7)	0 (0)
Blood creatinine increased	3 (4.3)	0 (0)
Respiratory, thoracic and mediastinal disorders	12 (17.1)	3 (8.8)
Dyspnoea	6 (8.6)	0 (0)
Cough	3 (4.3)	3 (8.8)
Metabolism and nutrition disorders	7 (10.0)	4 (11.8)
Decreased appetite	5 (7.1)	3 (8.8)
Skin and subcutaneous tissue disorders	7 (10.0)	9 (26.5)
Alopecia	0 (0)	6 (17.6)
Pruritus	0 (0)	3 (8.8)
Psychiatric disorders	6 (8.6)	1 (2.9)
Renal and urinary disorders	6 (8.6)	1 (2.9)
Cardiac disorders	5 (7.1)	0 (0)
Injury, poisoning and procedural complications	5 (7.1)	0 (0)
Vascular disorders	4 (5.7)	1 (2.9)
Eye disorders	2 (2.9)	2 (5.9)

a: MedDRA version 19.1.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 15: Common SAEs (in the SOC and in the PT ≥ 2% in at least 1 study arm) – RCT, direct comparison: alectinib vs. chemotherapy (pemetrexed or docetaxel)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Alectinib** **N = 70**	**Chemotherapy** **N = 34**
ALUR		
Overall rate of SAEs		
Infections and infestations	3 (4.3)	2 (5.9)
Pneumonia	2 (2.9)	0 (0)
Lung infection	0 (0)	1 (2.9)
Pneumonia bacterial	0 (0)	1 (2.9)
Nervous system disorders	4 (5.7)	0 (0)
Injury, poisoning and procedural complications	3 (4.3)	0 (0)
Renal and urinary disorders	3 (4.3)	0 (0)
Acute kidney injury	2 (2.9)	0 (0)
Blood and lymphatic system disorders	0 (0)	3 (8.8)
Anaemia	0 (0)	1 (2.9)
Febrile neutropenia	0 (0)	1 (2.9)
Neutropenia	0 (0)	1 (2.9)
Gastrointestinal disorders	0 (0)	1 (2.9)
Abdominal pain	0 (0)	1 (2.9)
Diarrhoea	0 (0)	1 (2.9)
Nausea	0 (0)	1 (2.9)
Stomatitis	0 (0)	1 (2.9)

a: MedDRA version 19.1.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 16: Common severe AEs (CTCAE grade ≥ 3) (in the SOC and in the PT ≥ 3% in at least 1 study arm) – RCT, direct comparison: alectinib vs. chemotherapy (pemetrexed or docetaxel)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Alectinib** **N = 70**	**Chemotherapy** **N = 34**
ALUR		
Overall rate of severe AEs (CTCAE grade ≥ 3)		
Blood and lymphatic system disorders	1 (1.4)	9 (26.5)
Neutropenia	0 (0)	4 (11.8)
Anaemia	1 (1.4)	2 (5.9)
Febrile neutropenia	0 (0)	2 (5.9)
Infections and infestations	4 (5.7)	3 (8.8)
General disorders and administration site conditions	2 (2.9)	5 (14.7)
Fatigue	0 (0)	3 (8.8)
Nervous system disorders	5 (7.1)	1 (2.9)
Gastrointestinal disorders	0 (0)	4 (11.8)
Stomatitis	0 (0)	2 (5.9)
Injury, poisoning and procedural complications	3 (4.3)	0 (0)

a: MedDRA version 19.1.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 17: Common discontinuations due to AEs – RCT, direct comparison: alectinib vs. chemotherapy (pemetrexed or docetaxel)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Alectinib** **N = 70**	**Chemotherapy** **N = 34**
ALUR		
Discontinuation due to AEs		
Blood and lymphatic system disorders	1 (1.4)	0 (0)
Anaemia	1 (1.4)	0 (0)
Infections and infestations	0 (0)	1 (2.9)
Pneumonia bacterial	0 (0)	1 (2.9)
General disorders and administration site conditions	1 (1.4)	1 (2.9)
General physical health deterioration	1 (1.4)	0 (0)
Generalised oedema	0 (0)	1 (2.9)
Metabolism and nutrition disorders	1 (1.4)	0 (0)
Decreased appetite	1 (1.4)	0 (0)
Renal and urinary disorders	1 (1.4)	0 (0)
Acute kidney injury	1 (1.4)	0 (0)
Gastrointestinal disorders	0 (0)	1 (2.9)
Constipation	0 (0)	1 (2.9)

a: MedDRA version 19.1.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus