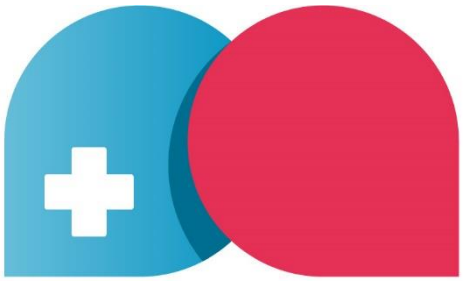
ALK-inhibitors for patients with advanced, i.e. stage III or IV ALK-positive, inoperable NSCLC



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LIST OF ABBREVIATIONS

AE	Adverse events
ALK	Anaplastic lymphoma kinase
CI	Confidence interval
DA	Decision Aid
N/A	Not applicable
NR	Not reported
NSCLC	Non-small cell lung cancer
OR	Odds ratio
PICOS	Participants, intervention, comparators, outcomes, and study design
PRISMA	Preferred Reporting of Systematic Reviews and Meta-Analyses
QOL	Quality of life
RCT	Randomised controlled trial
RR	Risk ratio
SDM	Shared decision making
SD	Standard deviation
SEAE	Serious adverse events
SMD	Standardised mean difference
SR	Systematic review
TKI	Tyrosine kinase inhibitors
UKSH	Universitätsklinikum Schleswig-Holstein

1. PROJECT OBJECTIVES

A key aim of the research project "Making SDM a reality" is to inform patients as part of shared decision making (SDM).

For each of SHARE TO CARE's Decision Aids we prepare and regularly update evidence reports, that cover the relative effects of defined interventions defined in the inclusion criteria (PICOS).

2. BACKGROUND

Current cancer therapy is oriented towards molecularly stratified drug treatment. In patients with anaplastic lymphoma kinase (ALK) translocation, ALK-inhibitors (subgroup of tyrosine kinase inhibitors, TKIs) are usually used in the first-line therapy.

Exceptions can arise if there is acute remission or psychological pressure, and therapy must be started even before the molecular genetic results are available.

In addition to therapy with ALK-inhibitors, further therapies may be necessary depending on the individual indication (e.g. radiation or surgery for metastases). Patients should be prepared for this in the introductory section of the decision aid (DA). However, they are not presented individually with benefits and side effects.

The planned decision support should be used at the point in the diagnosis and treatment pathway where the molecular genetic results are available. The available ALK-inhibitors and best supportive care are to be compared with each other.

3. METHODS

3.1 INCLUSION CRITERIA

The frequently asked questions (FAQs) underpinning the literature searches were developed in collaboration with clinicians of the decision aid working group. These questions pertain to the relevant characteristics of participants, intervention, comparators, outcomes, and study design (PICOS), see Table 1. Randomised controlled trials (RCTs) or Systematic reviews (SRs) of RCTs evaluated herein will aim to inform patients, clinicians, researchers, and health policy makers on relevant evidence relating to the treatment options for advanced ALK-positive NSCLC.

Table 1: Inclusion and exclusion criteria

	Included	Excluded
Population	Patients with advanced, i.e. stage III or IV ALK-positive, inoperable NSCLC	Other than the specified
Intervention	ALK-inhibitors (Alectinib, Brigatinib, and Lorlatinib)*	Other than the specified
Comparator	Best Supportive Care**	Other than the specified
Outcomes	1. Overall survival	Other than the specified

	Included	Excluded
	2. Disease- and progression-free survival / remission 3. Quality of life 4. Development of resistance 5. Risks and side effects	
Study design	Systematic reviews (SRs) of Randomised controlled trials (RCTs), clinical practice guidelines with Systematic searches, RCTs***, RCTs	narrative reviews; expert opinions; letters' overviews of reviews**
* Crizotinib and Ceritinib are no longer used due to their side effects profile. However, these should be mentioned in the background of the decision aid, as they are sometimes still used in smaller hospitals. Ensartinib is currently not approved in Europe. ** Non-molecular stratified drug therapy (chemo- and chemo-immunotherapy) will not be presented as a comparator, as it is not an equivalent alternative in known ALK-positive stage. Nevertheless, it will be described in the background as a possible precursor therapy. *** The dosage form and the treatment-related effort are presented comparatively in the section "How does the treatment work for me".		

3.2 Frequently asked questions

The following FAQs were identified:

1. What does the treatment involve?
2. Will it prolong my life?
3. Will it impact my chance of a remission?
4. Will it impact my quality of life?
5. Will I develop a resistance against the inhibitor?
6. What are the risks or side effects?

3.3 Literature searches

Preliminary literature searches were conducted to identify systematic reviews and evidence-based guidelines about ALK-positive NSCLC. We identified a Cochrane review [1] a network metaanalysis [2] and 3 IQWiG-AMNOG reports (plus addenda), and 3 Technology Appraisals of the National Institute for Health and Clinical Excellence for each of the ALK-inhibitors of this topic (Alectinib, Brigatinib, and Lorlatinib). We also identified a section on ALK-positive NSCLC treatment in the German S3-guideline [3].

None of the identified SRs had any comparison of ALK-inhibitors versus best supportive care. Therefore, we used the SRs for identifying primary studies (RCTs) and used the intervention arms to extract absolute numbers. To reassure the size and direction of the relative effects, we compared these data with the comparisons against first generation ALK-inhibitors (Crizotinib), as they are reported in the Cochrane review [1].

We also conducted a systematic search for ongoing studies with these drugs or other ALK-inhibitors (see separate "horizon scanning" document by Kleijnen Systematic Reviews).

4. RESULTS

4.1 OVERVIEW OF INCLUDED STUDIES

In the systematic Reviews we found 4 RCTs with relevant data for 3 comparisons [4-7].

Table 2 summarises the sources of evidence used to answer the six FAQs.

Table 2: Evidence sources

Study/year reference	Evidence source	Intervention(s)	FAQ1: What does the treatment involve?	FAQ2: Will it prolong my life?	FAQ3: Will it impact my chance of a remission (PFS / ORR)	FAQ4: Will it impact my quality of life?	FAQ5: Will I develop a resistance against the inhibitor?	FAQ6: What are the risks or side effects?
ALESIA [4]	RCT	Alectinib vs. Crizotinib*	✓	✓	✓			✓
ALEX [7]	RCT	Alectinib vs. Crizotinib*	✓	✓	✓			✓
ALTA-1L [6]	RCT	Brigatinib vs. Crizotinib*	✓	✓	✓	✓		✓
CROWN [5]	RCT	Lorlatinib vs. Crizotinib*	✓	✓	✓			✓

IV = intravenous; RCT = randomised controlled trial; SC = subcutaneous
*Only the intervention-arm was used for data extraction

4.2 FAQ 1: What does the treatment involve?

This section covers the 3 main treatment options for ALK-positive, non-operable advanced stage NSCLC: the 3 second- and third-generation ALK-inhibitors (Alectinib, Brigatinib, and Lorlatinib) All 3 treatment options alongside the purported mechanisms of action are described in Table 3 (below). This is relatively new and fast developing field of research.

Table 3: Description of treatments

Alectinib
Alectinib is a second-generation, highly selective, CNS-active ALK-inhibitor with activity against several ALK mutations reported to confer resistance to Crizotinib [4,7].
Brigatinib
Brigatinib , a second-generation anaplastic lymphoma kinase (ALK) inhibitor, has originally been approved in patients with ALK-positive non–small-cell lung cancer (NSCLC) that is refractory to Crizotinib. In a second step it has been tested for therapy-naïve patients [6].
Lorlatinib
Lorlatinib is a novel third generation ALK-inhibitor that is more potent than second generation inhibitors in biochemical and cellular assays and claims to have the broadest coverage of ALK resistance mutations that have been identified. Lorlatinib was designed to cross the blood-brain barrier in order to achieve high exposures in the CNS [5].

4.3 FAQ 2: Will it prolong my life?

Table 4: FAQ 2 – Evidence synthesis

Author	Type of study	Follow-up time	Intervention	Comparator (Crizotinib)	Effect estimate with 95% CIs, e.g., mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (Reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate n/N (%)				
Risk of death (Monoclonal antibodies)							
Alectinib							
ALESIA [4]	RCT	20 months	8/125 (6.4)	13/62 (20.9)	HR 0.28 (0.12–0·68)	Low (data immature)*	Difference in favour of Alectinib ⇗
ALEX [7]	RCT	36 months	43/152 (28.3)	48/151 (31.8)	HR 0.76 (0.50-1.15)	High (data immature)*	Difference in favour of Alectinib ⇗
Brigatinib							
ALTA-1L [6]	RCT	36 months 48 months	n.n. (29.0) 41/137 (29.9)	n.n. (32.0) 51/138 (36.9)	HR 0.81 (0.53–1.22)	High*	Difference in favour of Brigatinib ⇗
Lorlatinib							
CROWN [5]	RCT	36 months	23/149 (15.4)	28/147 (19.0)	HR 0.72 (0.41–1.25)	Low (interim analysis)*	Difference in favour of Lorlatinib ⇗
*Quality of evidence is assessed for the single study. For the indirect comparison between the intervention arms (cohort studies) it is generally assessed as high (due to imprecision). **own calculation							

Conclusion for DA: Due to low quality of evidence (indirect comparisons) and no data on natural cause of disease we would not give quantitative numbers on survival benefit. We would state, that for all ALK-inhibitors it is likely, that more than half of the patients survive 36 months.

4.4 FAQ 3: Will it impact my chance of a remission?

Table 5: FAQ 3 – Evidence synthesis (ORR)

Author	Type of study	Follow-up time	Intervention	Comparator (Crizotinib)	Effect estimate (95% CI), e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (Reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate n/N (%)				
Objective response rate (ORR)*							
Alectinib							
ALEX [7]	RCT	36 months	126/152 (82.9)	114/151 (75.5)	dORR 7.40 (–1.71-16.50)	high**	Difference in favour of Alectinib: not significant
Brigatinib							
ALTA-1L [6]	RCT	48 months	102/137 (74.0)	86/138 (62.0)	OR 1.74 (1.04–2.91)	High**	Difference in favour of Brigatinib ⇗

*ORR = Complete response + Partial response

** Quality of evidence is assessed for the single study. For the indirect comparison between the intervention arms (cohort studies) it is generally assessed as high (due to imprecision).

ORR: Objective response rate; dORR: Difference in ORR; CI: confidence interval;

Conclusion for DA: Due to low quality of evidence (indirect comparisons) and no data on natural cause of disease and due to missing Data on ORR for Lorlatinib we would not give quantitative numbers on ORR. We would state, that for Alectinib and Brigatinib it is likely, that more than half of the patients survive 36 months. For Lorlatinib we do not have published data, jet. However, it seems likely, that this time span is even longer with Lorlatinib.

Table 6: FAQ 3 – Evidence synthesis (PFS)

Author	Type of study	Follow-up time	Intervention	Comparator (Crizotinib)	Effect estimate with 95% CIs, e.g., mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (Reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate n/N (%)				
Risk of disease progression or death (investigator-assessed systemic progression free survival)							
Alectinib							
ALESIA [4]	RCT	20 months	20/125 (16.0)	30/62 (48.0)	HR 0·22 (0.13–0.38)	low (data immature)*	Difference in favour of Alectinib ⇗
median progression free months			n.r.	11.1 mo			
ALEX [7]	RCT	36 months	72/152 (47.4)	116/151 (76.8)	HR 0.43 (0.32-0.58)	high*	Difference in favour of Alectinib ⇗
median progression free months			34.8 mo	10.9 mo			
Brigatinib							
ALTA-1L [6]	RCT	36 months 48 months	n.n. (55.0) 73/137 (64.0)	n.n. (82.0) 51/138 (84.0)	HR 0.43 (0.31–0.58) HR 0.48 (0.35–0.66)	High*	Difference in favour of Brigatinib ⇗
median progression free months			30.8 mo	9.2 mo			
Lorlatinib							
CROWN [5]	RCT	12 months	n.r. (20.0)	n.r. (65.0)	HR 0.21 (0.14 - 0.31)	low (data immature)*	Difference in favour of Lorlatinib ⇗
median progression free months			n.r.	9.3			
*Quality of evidence is assessed for the single study. For the indirect comparison between the intervention arms (cohort studies) it is generally assessed as high (due to imprecision). **own calculation							

Conclusion for DA: Risk of disease progression or death is reported for different follow up periods in the 3 AKL-TKIs. Time to Progression was not reached in CROWN. It is more than 30 months for Alectinib and Brigatinib. For Lorlatinib we do not have published data, jet. However, it seems likely, that this time span is even longer, here.

4.5 FAQ 4: Will it impact my quality of life?

Table 7: FAQ 4 – Evidence synthesis

Author	Type of study	Follow-up time	Intervention	Comparator (Crizotinib)	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate n/N (%)				
Health related quality of life (HRQoL)							
Brigatinib							
ALTA-1L [6]	RCT	Median time to worsening GHS/QoL	26.7 mo	8.3 mo	HR 0.69 (0.49-0.98)	High*	Difference in favour of Brigatinib ⇗
*Quality of evidence is assessed for the single study. For the indirect comparison between the intervention arms (cohort studies) it is generally assessed as high (due to imprecision).							

Conclusion for DA: Data from PROMs is only available for ALTA-1L. We believe that it will be similar for other ALK-TKIs. If the patients' symptoms improve and they can be more active in everyday life again, their quality of life should also increase. Whether one of the ALK inhibitors improves the quality of life more than the other two has not yet been sufficiently investigated.

4.6 FAQ 5: Will I develop a resistance against the inhibitor?

This FAQ will be answered in the introductory section ("Allgemeine Hinweise für Patientinnen und Patienten") in a qualitative way.

4.7 FAQ 6: What are the risks or side effects

Table 8: FAQ 6 – Evidence synthesis

study	Alesia		Alex		Alta-1L		CROWN	
	Alectinib	Crizotinib	Alectinib	Crizotinib	Brigatinib	Crizotinib	Lorlatinib	Crizotinib
n	125	62	152	151	136	137	149	142
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any adverse event (AE)	124 (99)	62 (100)	147 (96,7)	147 (97.4)	136 (100)	137 (100)	149 (100)	140 (99)
Serious AE	19 (15)	16 (26)	46 (30.3)	46 (30.5)	n.r.	n.r.	n.r. (34)	n.r. (27)
Grade 3-5 AE	36 (29)	30 (48)	68 (44.7)	77 (51.0)	95 (70)	77 (56)	108 (72)	79 (55)
AE leading to treatment discontinuation	9 (7)	6 (10)	20 (13.2)	20 (13.2)	18 (13)	12 (9)	10 (7)	13 (9)
AE leading to dose reduction	30 (24)	14 (23)	25 (16.4)	31 (20.5)	60 (44)	34 (25)	31 (21)	22 (15)

Conclusion for DA: We report on individual side effects in a qualitative way from the expert information (“Fachinformationen”). To give comparative estimates we report quantitative data on grade ≥ 3 AEs and on AEs leading to treatment discontinuation.

5. DISCUSSION

5.1 SUMMARY OF MAIN FINDINGS

To be able to interpret these findings it is important to understand the history of ALK-inhibitors from their discovery in the early 2000ers to the third-generation inhibitors that are widely used in up-to-date oncologic health care. Fukui et al. illustrate it in figure 1 of their narrative review [8]

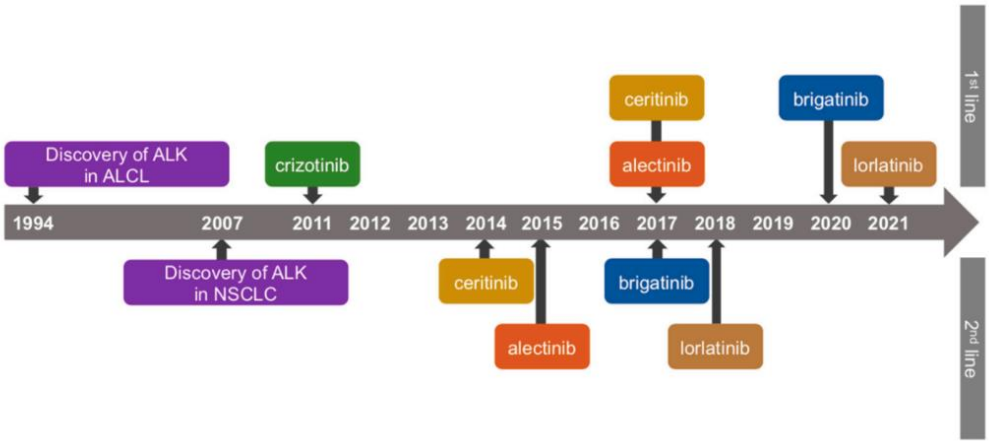

Figure 1: Timeline of discovery of ALK and US FDA approval of ALK-TKIs

Currently fife ALK-TKIs are approved by FDA and EMA. Crizotinib and Certitinib are no longer used due to their side effects profiles. However, they are sometimes still used in smaller hospitals in Germany. Ensartinib is currently not approved in Europe. Therefore Alectinib, Brigatinib and Lorlatinib are the 3 ALK-TKIs most relevant in current service.

Since the advent of ALK-Inhibitors Non-molecular stratified drug therapy (chemo- and chemo-immunotherapy) are not regarded as an equivalent alternative in known ALK-positive stage. Therefore, there will be no studies comparing these non-molecular therapies with modern ALK-TKIs. Also, first line therapy will always be ALK-TKIs once an ALK-mutation is diagnosed. A randomised comparison to best supportive care (BSC) or no (additional) therapy in the first-line therapy will therefore be unethical.

In this report we could only use the intervention arms of RCTs comparing second- and third generation ALK-TKIs to Crizotinib. We therefore used the intervention Arms as indirect comparisons of separate cohort studies. To our best knowledge there is no data available on the natural course of ALK-positive NSCLC. We can only compare absolute numbers between the ALK-TKIs, not against best supportive care. Because of the indirect comparisons, the evidence has overall low certainty (imprecise). That's why we didn't report the individual rates of the TKIs, but only the range of rates. However, at least for the adverse events and side effects the evidence seems sufficient to inform patients and their relatives in a balanced and comprehensible way.

5.2 STRENGTH, LIMITATIONS AND UNCERTAINTIES

This report has several limitations that ought to be noted. First, as mentioned above, it is based only on indirect comparisons that might be biased i.e., by confounding (selection bias etc.). Also, we did not identify data on the natural course of ALK-positive NSCLC. In general, the number of primary studies is scarce (only for Alectinib we could identify 2 independent RCTs) and most of them are not too big (about 300 patients each). Some replications might be desirable in the future.

The strength of this report is, that we have compared our results with assessments and recommendations by NICE and IQWiG. Our results are largely concordant with these guidances.

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