Non-small cell lung cancer: horizon scanning for SHARE TO CARE

Kleijnen Systematic Reviews Ltd

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Kleijnen Systematic Reviews Ltd
Unit 6, Escrick Business Park
Riccall Road
Escrick
York
YO19 6FD
United Kingdom
Telephone: +44 (0)1904 727980
Fax: +44 (0)1904 720429
Email: robert@systematic-reviews.com
Website: www.systematic-reviews.com

Pawel Posadzki
Kevin McDermott
Steven Duffy
Jos Kleijnen
Robert Wolff

1. PROJECT OBJECTIVES

A key aim of the research project is to inform patients as part of shared decision making (SDM). Kleijnen Systematic Reviews (KSR) Ltd has prepared a horizon scanning of the treatment options for non-small cell lung cancer (NSCLC).

2. METHODS

2.1 LITERATURE SEARCHES

Literature searches were undertaken to identify ongoing studies investigating anaplastic lymphoma kinase (ALK) inhibitors for NSCLC. The search strategies were developed using the recommendations of the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and the Cochrane Handbook.[1, 2] The search strategies included generic terms for 'ALK inhibitors' and specific named ALK inhibitors, such as alectinib, brigatinib, ceritinib, crizotinib, etc. Searches were conducted in trials registries.

Ongoing and recently completed trials were identified by searching the following resources:

- ClinicalTrials.gov (http://www.clinicaltrials.gov/): up to 23 June 2022
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/): up to 23 June 2022
- EU Clinical Trials Register (https://www.clinicaltrialsregister.eu): up to 23 June 2022

Full details of the search strategies are provided in Appendix 1.

2.1.1 Handling of citations

Identified references from the literature searches were downloaded into EndNote bibliographic management software for further assessment and handling.

2.2 INCLUSION CRITERIA

The relevant characteristics of participants, intervention, comparators, outcomes, and study design (PICOS), see Table 1 were based on the scoping document prepared by the commissioner. Randomised controlled trials evaluated herein aim to inform clinicians, patients, researchers, and health policy makers on relevant evidence pertaining to the current treatment options for 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 2. Disease- and progression-free survival 3. Quality of life	Other than the specified

	Included	Excluded
	4. Development of resistance 5. Remission 6. Risks/side effects	
Study design	Randomised controlled trials	Other than the specified

[*] Crizotinib and certitinib 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.
ALK = anaplastic lymphoma kinase; NSCLC = non-small cell lung cancer

2.3 STUDY SELECTION AND DATA EXTRACTION

One reviewer (PP) screened all trial registries identified by the searches. For each study, one reviewer (PP) extracted the data whereas another (KM) validated the entries. A third reviewer (RW) arbitrated in case of any discrepancies or disagreements.

3. RESULTS

Searches were conducted in June 2022 to identify all relevant ongoing trials. A total of 843 records were retrieved from the electronic literature searches. After removing duplicate records, a total of 564 references were screened. A total of 22 records were shortlisted representing 15 trials.

A summary of the study selection process according to modified PRISMA reporting guidelines is reported in Figure 1.[3] Of those 15, seven randomised controlled trials (RCTs) are ongoing and seven have been completed and one was early terminated.

The following drugs were evaluable:

- ALK inhibitors such as crizotinib, or ceritinib (both included as comparators);
- next-generation ALK inhibitors, i.e. brigatinib, lorlatinib, alectinib

One study evaluated TQ-B3139.[4] One study evaluated ensartinib[5] as a comparator, however the drug is currently not licensed in the EU. The sample sizes ranged from 110 in two studies[6, 7] to 660 in one study.[5] The trial duration ranged from one year in a RCT of brigatinib 180 mg[6] to 12 years in a study of alectinib.[8] Please refer to the Table 2 below for more details including comparators, outcome measures, funding source or principal investigator.

Figure 1: Study selection process

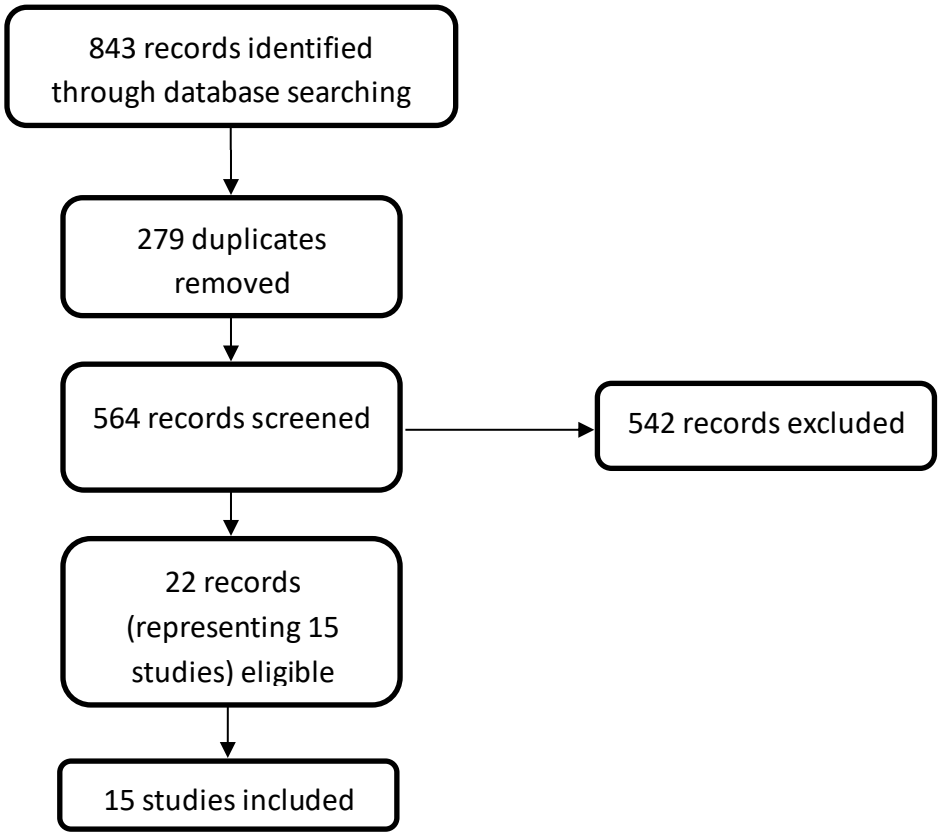

Table 2 Studies of anaplastic lymphoma kinase (ALK) inhibitors for non-small cell lung cancer

Registry number/ study type	N	Intervention/ class of drugs	Comparator(s)	Outcomes	FUP (yrs)	Current status/ comp. date	PI/ funder
NCT02094573[9] **RCT**	222	Brigatinib 90 mg Next-generation ALKI	Brigatinib 90-180 mg	ORR, PR, CR, PFS, TTR, DOR, ToT, DCR, OS, TEAE, QoL	3	Complete (27/02/2020)*	NR Takeda
NCT02737501[10] **cRCT**	275	Brigatinib 90 mg Next-generation ALKI	Crizotinib 250 mg	OS, PFS, ORR, DOR, TTR, DCR, TEAE, QoL	4.5	Complete (29/01/2021)	NR Takeda
Eudract:2018-001957-29/ NCT03596866[11] **RCT**	246	Brigatinib 180 mg** Next-generation ALKI	Alectinib 600 mg	OS, PFS, ORR, DOR, TTR, HRQoL	5	Ongoing (07/05/2024)	NR Takeda
NCT04009317[4] **RCT**	260	TQ-B3139 600 mg Novel ALKI	Crizotinib 250 mg	PFS, ORR, DCR, OS	3	Complete (30/04/2022)	Li Zhang Chia Tai Tianqing Pharma-ceutical Group Co., Ltd
JapicCTI-132316[12] **RCT**	207	Alectinib 300 mg TKI	Crizotinib 250 mg	PFS, ORR, OS, AE	2	Complete (22/04/2021)	NR Chugai Pharmaceutical Co., Ltd.,
Eudract: 2013-004133-33/ NCT02075840[8] **RCT**	303	Alectinib 600 mg TKI	Crizotinib 250 mg	ORR, PR, CR, PFS, TTD, DOR, ToT, OS, AE, QoL, HRQoL, CNS progression, pharmacokinetics	12	Ongoing (29/09/2022)	NR Hoffmann-La Roche
Eudract: 2015-000634-29/ NCT02604342[13]	119	Alectinib 600 mg TKI	Docetaxel+ Pemetrexed	ORR, CR, PFS, TTR, DOR, ToT, DCR, OS, AE, QoL, TTD	3	Complete (13/08/2018)***	NR Hoffmann-La Roche

Registry number/ study type	N	Intervention/ class of drugs	Comparator(s)	Outcomes	FUP (yrs)	Current status/ comp. date	PI/ funder
RCT							
Eudract: 2017-004331-37/ NCT03456076[14] RCT	257	Alectinib 600 mg TKI	Cisplatin, Vinorelbine, Gemcitabine, Pemetrexed, Carboplatin	DFS, OS, pharmacodynamics	8	Ongoing (19/11/2026)	n/m Hoffmann-La Roche
EC INS No: PER-064-14[15] RCT	286	Alectinib 600 mg TKI	Crizotinib 250 mg	PFS, ORR, DOR, OS, time to CNS progression	4	Terminated (31/08/2015)	C/o Roberto Navarro, Carrasco
JPRN-jRCTs041210103[7] RCT	110	Brigatinib 180 mg** Next-generation ALKI	Brigatinib 180 mg+ Carboplatin, pemetrexed, followed by concurrent Brigatinib and pemetrexed	PFS, ORR, OS, TEAE	NR	Ongoing (NR)	Hirotsugu Kenmotsu Takeda
NCT02838420[16] RCT	187	Alectinib 600 mg TKI	Crizotinib 250 mg	PFS, CR, PR, TTP, TTD, DOR, OS, TEAE, pharmacodynamics	3.3	Ongoing (06/12/2019)	n/m Hoffmann-La Roche
Euctr:2021-002567-22/ NCT05200481[6] RCT	110	Brigatinib 180 mg Next-generation ALKI	Brigatinib 180 mg+ Carboplatin, Pemetrexed	PFS, ORR, TEAE, QoL, HRQoL	1	Ongoing (October 2028)	Michael Duruisseaux Intergroupe Francophone de Cancerologie Thoracique
NCT04318938[17] RCT	116	Brigatinib 180 mg*** + TKI Next-generation	2nd-generation TKI	PFS, OS, ORR, DOR, QoL, TEAE, TTP, TNT, phenotyping	6	Ongoing (31/12/2025)	Salah-Eddin Al-Batran Institut für Klinische Krebs-forschung GmbH at Krankenhaus Nordwest

Registry number/ study type	N	Intervention/ class of drugs	Comparator(s)	Outcomes	FUP (yrs)	Current status/ comp. date	PI/ funder
		ALKI					
NCT03737994[5] **RCT**	660	Alectinib, Brigatinib, Lorlatinib** Next-generation ALKI	Ceritinib, Crizotinib, Ensartinib, Crizotinib, Carboplatin, Cisplatin, Pemetrexed**	ORR, PFS, DOR, OS, AE, cfDNA mutation	7	Ongoing (13/12/2025)	Jessica J Lin National Cancer Institute
NCT04632758[18] **RCT**	330	WX-0593 (Iruplinalkib) Next-generation ALKI	Crizotinib	PFS, OS, ORR, TTR, DOR, CNS RR, TTD, TEAE, HRQoL, pharmaco-kinetics	2.5	Complete (01/12/2021)	Shunjiang Yu Qilu Pharmaceutical Co

* There might be further publications from this trial; **preceded by Brigatinib 90 mg, orally, once daily for 7 days; ***in different combinations/configurations

AE = Adverse event; ALKI = anaplastic lymphoma kinase inhibitor; cfDNA = circulating free deoxyribonucleic acid; CNS = central nervous system; CR = complete response; cRCT = crossover-randomised controlled trial; DCR = disease control rate; DFS = disease-free survival; DOR = duration of response; FUP = follow-up; HRQoL = health - related quality of life; NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression free survival; PI = principal investigator; PR = partial response; QoL = quality of life; RCT = randomised controlled trial; TEAE = Treatment-Emergent Adverse Event; TKI = tyrosine kinase inhibitor; TNT = time-to-next treatment; ToT = time on treatment; TTD = time to deterioration; TTP = time to progression; TTR = time to response.

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APPENDIX 1: SEARCH STRATEGIES

Shared Decision Making: horizon scanning for non-small cell lung cancer:

Table 3: Trials registry and conference proceedings search results

Database	Dates	Results
ClinicalTrials.gov	up to 23 June 2022	402
WHO ICTRP	up to 23 June 2022	371
EUCTR	up to 23 June 2022	70
Total		**1839**
Total after de-duplication		**1244**

Search strategies: Trials Registries

ClinicalTrials.gov (Internet): up to 23 June 2022
https://clinicaltrials.gov/ct2/home
Searched: 23.6.22
(anaplastic lymphoma kinase inhibitor OR anaplastic lymphoma kinase inhibitors OR ALK inhibitor OR ALK inhibitors OR ALKI inhibitor OR ALKI inhibitors OR ALKIS inhibitor OR ALKIS inhibitors OR alectinib OR alecensa OR brigatinib OR alunbrig OR ceritinib OR zykadia OR spexib OR crizotinib OR xalkori OR ensartinib OR entrectinib OR rozlytrek OR lorlatinib OR loratinib OR lorbrena OR lorviqua OR repotrectinib OR ropotrectinib)
402 records

WHO International Clinical Trials Register Platform (ICTRP) (Internet): up to 23 June 2022
https://www.who.int/clinical-trials-registry-platform/the-ictrp-search-portal
Searched: 23.6.22
Advanced search option

	Results
Intervention: anaplastic lymphoma kinase inhibitor OR anaplastic lymphoma kinase inhibitors OR ALK inhibitor OR ALK inhibitors OR ALKI inhibitor OR ALKI inhibitors OR ALKIS inhibitor OR ALKIS inhibitors OR alectinib OR alecensa OR brigatinib OR alunbrig OR ceritinib OR zykadia OR spexib OR crizotinib OR xalkori OR ensartinib OR entrectinib OR rozlytrek OR lorlatinib OR loratinib OR lorbrena OR lorviqua OR repotrectinib OR ropotrectinib	628 records for **371** trials found

EU Clinical Trials Register (EUCTR) (Internet): up to 23 June 2022
https://www.clinicaltrialsregister.eu/ctr-search/search
Searched: 23.6.22
(anaplastic lymphoma kinase inhibitor OR anaplastic lymphoma kinase inhibitors OR ALK inhibitor OR ALK inhibitors OR ALKI inhibitor OR ALKI inhibitors OR ALKIS inhibitor OR ALKIS inhibitors OR alectinib OR alecensa OR brigatinib OR alunbrig OR ceritinib OR zykadia OR spexib OR crizotinib OR xalkori OR ensartinib OR entrectinib OR rozlytrek OR lorlatinib OR loratinib OR lorbrena OR lorviqua OR repotrectinib OR ropotrectinib)
70 records