NHS England Evidence Review:

Crizotinib for individuals with anaplastic lymphoma kinase-positive (ALK-positive) relapsed or refractory anaplastic large cell lymphoma (ALCL)

NHS England URN: 2330a

NHS England Evidence Review

Crizotinib for individuals with anaplastic lymphoma kinase-positive (ALK-positive) relapsed or refractory anaplastic large cell lymphoma (ALCL)

Completed: November 2023

Prepared by Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of crizotinib compared to current standard care in people with anaplastic lymphoma kinase-positive (ALK-positive) relapsed or refractory anaplastic large cell lymphoma (ALCL).

ALCL is a rare type of blood cancer that occurs when white blood cells, known as T-cells, become abnormal. ALCL is a type of non-Hodgkin lymphoma (NHL). ALK-positive ALCL is the most common type of ALCL. In ALK-positive ALCL, the abnormal T cells have a genetic change (mutation) that means they make a protein called ALK on their surface. The ALK mutation drives the abnormal growth of the cancer cells and can be detected using tests.

Crizotinib is an ALK inhibitor (blocker) which targets the ALK mutation found in ALK-positive ALCL. Dosing for this indication is based on body surface area. Crizotinib is taken orally.

Current standard first line treatment for ALCL is with a combination of chemotherapy agents. Some patients with early stage ALK-positive ALCL may also have radiotherapy. Treatment for relapsed or refractory ALCL is usually with an alternative chemotherapy regimen. Following this, some patients may be suitable for an allogenic stem cell transplant to increase their chances of staying in remission.

The evidence review scope included the identification of possible subgroups of patients within the included studies who might benefit from treatment with crizotinib more than others, as well as information on the dosing of crizotinib used by the included studies.

2. Executive summary of the review

This review examines the clinical effectiveness, safety and cost effectiveness of crizotinib compared to current standard care in people with anaplastic lymphoma kinase-positive (ALK-positive) relapsed or refractory anaplastic large cell lymphoma (ALCL). The searches for evidence published since January 2013 were conducted on 15 September 2023 and identified 1467 references pertaining to people with ALK-positive unresectable inflammatory myofibroblastic tumour (IMT) or ALK-positive relapsed or refractory ALCL. These were screened using their titles and abstracts and 19 references potentially relating to the use of crizotinib in people with IMT and/or ALCL were obtained in full text and assessed for relevance. Papers relating to the use of crizotinib in people with unresectable IMT were included in a separate evidence review.

Three studies were identified for inclusion in this review. All three studies are single-arm, phase II trials (Brugières et al 2023; Gambacorti-Passerini et al 2018; Mossé et al 2017). The studies included between 18 and 26 subjects with relapsed or refractory ALK-positive ALCL, aged between one and 60 years. Median follow-up of 45 months was reported in Brugières et al 2023; duration of follow-up was not reported in the other two studies. The studies were conducted in France, Europe, Asia and the USA. No studies comparing crizotinib for ALK-positive relapsed or refractory ALCL with other treatments were identified.

No cost effectiveness evidence was identified.

In terms of clinical effectiveness:

- **Response to treatment (critical outcome)**. One single-arm trial provided very low certainty evidence of a best overall response to treatment with crizotinib at eight weeks after treatment initiation of nine out of 24 subjects with complete response and seven out of 24 with partial response. The same single-arm trial provided very low certainty evidence of a best overall response to treatment with crizotinib after a median duration of treatment of 3.7 months (range 0.37 to 47.2 months) of 12 out of 24 subjects with complete response and four out of 24 with partial response. Two single-arm trials provided very low certainty evidence of a best overall response to treatment with crizotinib of between 47% and 83% complete response, 0% and 10% partial response, 10% and 18% stable disease and 0% and 18% progressive disease, at an unspecified duration of follow-up. Median treatment duration in these studies varied between 0.4 years and 35 months. Three single-arm trials provided very low certainty evidence of an objective response to treatment of 67% (8 weeks after treatment initiation) and between 53% and 90% (at an unspecified duration of follow-up). Two single-arm trials provided very low certainty evidence that the median duration of response was between 136 weeks and 43 months.
- **Progression-free survival (critical outcome).** Two single-arm trials provided very low certainty evidence of 2-year progression-free survival of 63% at unspecified duration of follow-up, and 3-year progression-free survival of 40% at median follow-up of 45 months with a median progression-free survival of 11 months.
- **Overall survival (critical outcome)**. One single-arm trial provided very low certainty evidence of 3-year overall survival of 63% at median follow-up of 45 months.
- **Quality of life (important outcome)**. No evidence was identified for quality of life.
- **Activities of daily living (important outcome)**. No evidence was identified for activities of daily living.

- **Treatment-related hospitalisation (important outcome)**. No evidence was identified for treatment-related hospitalisation.
- **Treatment adherence (important outcome)**. Two single-arm trials provided very low certainty evidence on treatment adherence. At least 18% patients from the two studies stopped treatment due to poor adherence (further treatment refusal, adverse events, non-compliance) with a further 72% who discontinued due to switching treatment or disease progression, and 8% who discontinued for other reasons.

In terms of safety:

- **Adverse events**. All three included single-arm trials provided very low certainty evidence that the majority of patients with relapsed or refractory ALCL reported adverse events (AEs) during crizotinib treatment. One trial provided very low certainty evidence that 83% of those treated with crizotinib 165mg/m^2 twice daily experienced at least one grade 3 or 4 AE, of which 33% were considered to be related to crizotinib therapy. 100% of those treated with crizotinib 280mg/m^2 twice daily experienced at least one grade 3 or 4 AE; 85% were considered likely to be related to crizotinib therapy. A second trial provided very low certainty evidence that around 55% of patients treated with crizotinib 250mg twice daily experienced a grade 3, 4 or 5 AE.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness**.**

In terms of subgroups:

- One single-arm trial reported unplanned subgroup analyses comparing treatment response and survival outcomes in children and adolescents (aged ≤18 years) and adults (aged >18 years). They reported higher response and survival rates in the children and adolescents, but outcomes for the two groups were not statistically significantly different and no p-values were reported.

In terms of crizotinib dose:

- Crizotinib dosing regimens in the three single-arm trials were:
  - 165 mg/m^2 twice daily for patients aged 1 to 17 years and 250 mg twice daily for adults aged 18 to 60 years; median treatment duration was 3.7 months (range 0.37 to 47.2 months);
  - 250mg twice daily in a population aged 15 to 37 years; median treatment duration was 35 months;
  - 165mg/m^2 in a population aged 3.7 to 13.4 years, with a median treatment duration of 2.79 years (95% CI 0.31 years to n/a); and 280mg/m^2 twice daily in a population aged 6.1 to 20.8 years, with a median treatment duration of 0.4 years (95% CI 0.18 to 1.0 years).

Definitions of relapsed or refractory ALK-positive ALCL:

- One single-arm trial defined inadequate response to available therapies in children as '*a relapse after a first well-conducted standard treatment or a situation without any standard treatment and a survival <10%*'. No other definitions of relapsed or refractory were provided.

Please see the results table (section 5) in the review for further details of outcomes and definitions.

Limitations

All three studies were considered to be at high risk of bias and certainty about the evidence for the critical and important outcomes was very low when assessed using modified GRADE. All the studies were small, with between 18 and 26 relevant subjects. Limitations reducing certainty for the outcomes reported include uncertainty about whether the inclusion of participants was complete or consecutive, and in the adverse event data reported by Gambacorti-Passerini et al 2018, the inclusion of patients with conditions other than ALCL who therefore did not meet the PICO definition. Duration of follow-up was only reported in one study. All of the studies only presented statistical analyses or summary statistics for some of the outcomes reported and none of the studies had a comparator group. Limitations due to the lack of blinding of patients and assessors, particularly of more subjective outcome measures (such as adverse events), also reduced certainty for some of the outcomes across all three studies. While standardised criteria were used to evaluate treatment response, in one study there were appeared to have been differences between local investigators and the central study team in how these were applied. It was not clear in any of the studies how standardised and repeatable across the sites the conduct of assessments was.

Conclusions

This evidence review includes three single-arm, phase II clinical trials, each with between 18 and 26 subjects with ALK-positive relapsed or refractory ALCL who were treated with crizotinib. One study included children and adults (age range 1 to 60 years), one included adolescents and adults (age range 15 to 37 years) and one included children, adolescents and young adults aged up to 21 years. All studies included a majority of male subjects.

None of the studies included a comparator group and the evidence for all the outcomes of interest was of very low certainty.

Evidence was available for crizotinib use in patients with relapsed or refractory ALCL for all the critical outcomes of interest. All of the included studies provided very low certainty evidence that the majority of patients (between 53% and 90% across the studies) had a complete or partial response to treatment with crizotinib, with a median duration of response between about 30 and 43 months. Two of the studies also provided evidence of a 2-year progression-free survival rate of 63% and 3-year progression-free survival rate of 40%, and one provided evidence of 3-year overall survival of 63%. No minimal clinically important differences were defined for any outcomes, and limited statistical analyses were reported.

Data were available for the important outcomes of treatment adherence and safety. Two single-arm studies reported information relating to treatment adherence; one out 26 patients in one study stopped treatment due to noncompliance, but a number of patients in both studies also stopped for reasons which were not specified. Three single-arm studies reported data on adverse events (AEs). Most patients reported AEs during crizotinib treatment. In one trial 83% of those treated with crizotinib 165mg/m^2 twice daily and 100% of those treated with crizotinib

280mg/m^2 twice daily experienced at least one grade 3 or 4 AE, with 33% and 85% respectively being considered possibly, probably, or definitely related to the study drug. In a second trial around 55% of patients treated with crizotinib 250mg twice daily experienced a grade 3, 4 or 5 AE (although of the 44 patients for whom this outcome was reported, only 18 had ALCL).

One single-arm trial carried out unplanned subgroup analyses which found that patients aged ≤18 years appeared to have better treatment response and survival outcomes than those aged >18 years, although the differences were not statistically significant and no p-values were reported.

No evidence on cost effectiveness was identified.

None of the studies included patients from the UK and it is not clear how similar the patients in the studies are to patients seen in clinical practice in England.

Although all the studies provided very low certainty evidence of the outcomes, there was some congruence in the results reported. The studies identified in this review provide evidence, for a range of pre-specified critical and important outcomes, that patients with ALK-positive relapsed or refractory ALCL respond to treatment with crizotinib, and that in some patients the response is maintained for some time. The lack of comparator data means that no conclusions can be drawn about the effectiveness of crizotinib compared with other treatments for this patient group.

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. In people with relapsed or refractory ALK-positive ALCL what is the clinical effectiveness of crizotinib compared with standard care?
2. In people with relapsed or refractory ALK-positive ALCL what is the safety of crizotinib compared with standard care?
3. In people with relapsed or refractory ALK-positive ALCL what is the cost effectiveness of crizotinib compared with standard care?
4. From the evidence selected, are there any subgroups of patients that may benefit from crizotinib more than the wider population of interest?
5. From the evidence selected, what was the treatment dose of crizotinib in the population of interest?
6. From the evidence selected, what were the definitions of relapsed or refractory used in relation to ALK-positive ALCL?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its '*Guidance on conducting evidence reviews for Specialised Services Commissioning Products*' (2020).

The searches for evidence were informed by the PICO document and were conducted on 15th September 2023.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

4. Summary of included studies

Three papers were identified for inclusion (Brugières et al 2023, Gambacorti-Passerini et al 2018, Mossé et al 2017). All three reported single-arm studies. One included adults and children (Brugières et al 2023), one included adolescents and adults (Gambacorti-Passerini et al 2018) and one included children, adolescents and young adults (Mossé et al 2017). No comparative studies were identified and there were no studies reporting cost effectiveness.

Table 1 provides a summary of these included studies and full details are given in Appendix E.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported

Brugières et al 2023
 	
Single-arm study (phase II trial)
 	
France (17 centres)
	25 patients aged 12 months or older with ALK-positive ALCL
	
	Male: 16/25 (64%)
	Median age: 19 years
	Age range: 1 to 60 years
	
	Among those aged ≤18 years:
	Median age: 11 years
	Age range: 1 to 17 years
	
	Among those aged >18 years:
	Median age: 25.5 years
	Age range: 19 to 60 years
	
	Subgroups reported: adults vs children
		Intervention
		
		Crizotinib 165 mg/m2 twice daily (BID) for patients aged 1 to 17 years and 250 mg BID in adults
		
		Comparison
		
		No comparator group
			Median follow-up 45 months (95% CI 28 to 50.9 months)
			
			Critical outcomes
			
			• Response to treatment[a]
			  ○ ORR
			  ○ Median DOR
			• Progression-free survival
			  ○ 3-year PFS
			  ○ Median PFS
			• Overall survival
			  ○ 3-year OS
			
			Important Outcomes
			
			• Treatment adherence
			• Safety
			  ○ Treatment-related adverse events[b]

Gambacorti-Passerini et al 2018
 	
Single-arm study (phase II trial)
 	
Multi-centre (Italy, Russia, China, Japan, South Korea, USA)
	18 patients aged ≥15 years with ALK-positive ALCL
	
	Male: 66.7%
	Median age: 25 years
	Age range: 15 to 37 years
	
	Race:
	White: 66.7%
	Japanese: 11.1%
	Korean: 11.1%
	Chinese: 11.1%
	
	No subgroups reported
		Intervention
		
		Crizotinib 250mg twice daily (starting dose)
		
		Comparison
		
		No comparator group
			Duration of follow-up not reported
			
			Critical outcomes
			
			• Response to treatment[c]
			  ○ BOR
			  ○ ORR
			  ○ Median DOR
			• Progression-free survival
			  ○ 2-year PFS
			
			Important Outcomes
			
			• Safety
			  ○ Treatment-related adverse events[b]

Mossé et al 2017
 	
Single-arm study (phase II trial)
 	
USA (multicentre)
	26 patients aged < 22 with ALK-positive relapsed/ refractory ALCL
	
	Characteristics: treated with crizotinib 165mg/m^2 (n=6); treated with crizotinib 280mg/m^2 (n=20)
	
	Male: 83%; 65%
		Intervention
		
		Crizotinib 165mg/m^2 or 280mg/m^2 twice daily
		
		Comparison
		
		No comparator group
			Duration of follow-up not reported
			
			Critical outcomes
			
			• Response to treatment[d]
			  ○ BOR
			  ○ ORR
			
			Important Outcomes

Study	Population	Intervention and comparison	Outcomes reported
	Median age at enrolment: 5.9 years; 12.2 years Age range: 3.7 to 13.4 years; 6.1 to 20.8 years Race: White: 67%; 50% Black: 0%; 25% Asian: 17%; 5% Unknown: 17%; 20%		• Treatment adherence • Safety ○ Adverse events[b]

Abbreviations
ALCL: anaplastic large cell lymphoma; ALK: anaplastic lymphoma kinase; BOR: best overall response; DOR: duration of response; ORR: objective response rate; OS: overall survival; PFS: progression-free survival

a Response to treatment was based on RECIST v1.1 criteria for conventional imaging or according to the Lugano criteria in patients evaluated by FDG-PET/CT
b Adverse events were classified according to the Common Terminology Criteria for Adverse Events version 4
c Response to treatment was evaluated using RECIST v1.1
d Response to treatment was evaluated centrally using the Lugano classification

5. Results

In people with relapsed or refractory ALK-positive ALCL what is the clinical effectiveness and safety of crizotinib compared with standard care?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Response to Treatment **Certainty of evidence:** Very low	Response rate is important to patients as it represents whether the treatment can improve disease burden. In total, three studies (three single-arm trials) provided evidence relating to response to treatment with crizotinib. *Best overall treatment response* **At 8 weeks post-treatment initiation**: • One single-arm trial (Brugières et al 2023) (n=24) reported best overall response[1] of 9/24 complete response and 7/24 partial response. (**VERY LOW)** **Over duration of treatment (median duration 3.7 months (range 0.37 to 47.2 months))** • One single-arm trial (Brugières et al 2023) (n=24) reported best overall response of 12/24 complete response and 4/24 partial response. (**VERY LOW)** **At unspecified duration of follow-up**: • One single-arm trial (Gambacorti-Passerini et al 2018) (n=17) reported a best overall response[2] of complete response: 47.1%; partial response: 5.9%; stable disease: 17.6%; objective progression: 17.6%; early death: 5.9%; indeterminate: 5.9%, after a median treatment duration of 35 months. **(VERY LOW)** • One single-arm trial (Mossé et al 2017) (n=26) reported a best overall response3 for patients treated with crizotinib 165mg/m2 for a median 2.79 years of complete response: 83%; partial response: 0%; stable disease: 17%; progressive disease: 0%; and for patients treated with crizotinib 280mg/m2 for a median of 0.4 years of complete response: 80%; partial response: 10%; stable disease: 10%; progressive disease: 0%. (VERY LOW) *Objective response rate* **At 8 weeks post-treatment initiation**: • One single-arm trial (Brugières et al 2023) (n=24) reported an objective response rate of 67% (95% CI 47% to 82%). (**VERY LOW)** **At unspecified duration of follow-up**: • One single-arm trial (Gambacorti-Passerini et al 2018) (n=17) reported an objective response rate of 52.9% (95% CI 27.8% to 77%) after a median treatment duration of 35 months (VERY LOW) • One single-arm trial (Mossé et al 2017) (n=26) reported an objective response rate of 83% (95% CI 36% to 99.6%) for patients treated with crizotinib 165mg/m2 for a median 2.79 years, and 90% (95% CI 68% to 99%) for

[1] Response to treatment in Brugières et al 2023 was based on RECIST 1.1 criteria for conventional imaging or according to the Lugano criteria in patients evaluated by FDG-PET/CT. Both use defined criteria to categorise the treatment response. Objective response defined as complete (CR) or partial response (PR).
[2] Response to treatment in Gambacorti-Passerini et al 2018 was evaluated using RECIST v1.1 which uses defined criteria to categorise the treatment response as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). Objective response rate is CR + PR.
[3] Response in Mossé et al 2017 was assessed at treatment sites; response was then evaluated using the Lugano classification applied during central review as a retrospective scoring of response.

Outcome	Evidence statement
	patients treated with crizotinib 280mg/m2 for a median of 0.4 years. (VERY LOW) *Duration of response* • One single-arm trial (Brugières et al 2023) (n=24) reported a median duration of response of 43.4 months (95% CI 8.3 to not reached) after a median treatment duration of 3.7 months. (**VERY LOW)** • One single-arm trial (Gambacorti-Passerini et al 2018) (n=17) reported a median duration of response of 135.8 weeks (range 6 to 205.9 weeks) after a median treatment duration of 35 months. **(VERY LOW)** **One single-arm trial provided very low certainty evidence of a best overall response to treatment with crizotinib at 8 weeks after treatment initiation of 9/24 subjects with complete response and 7/24 with partial response. The same single-arm trial provided very low certainty evidence of a best overall response to treatment with crizotinib after a median duration of treatment of 3.7 months (range 0.37 to 47.2 months) of 12/24 complete response and 4/24 partial response. Two single-arm trials provided very low certainty evidence of a best overall response to treatment with crizotinib of between 47% and 83% complete response, 0% and 10% partial response, 10% and 18% stable disease and 0% and 18% progressive disease, at an unspecified duration of follow-up. Three single-arm trials provided very low certainty evidence of an objective response to treatment of 67 % (8 weeks after treatment initiation) and between 53% and 90% (at unspecified duration of follow-up). Two single-arm trials provided very low certainty evidence that the median duration of response was between 136 weeks and 43.4 months.**
Progression-free Survival **Certainty of evidence:** Very low	This outcome is important to patients because it represents the time for which their disease is not progressing. Stable disease might represent longer survival and disease stability may result in patients experiencing fewer symptoms from the disease itself. It can be determined sooner than overall survival outcome measures. In total, two studies (two single-arm trials) provided evidence relating progression-free survival (PFS). Both estimated survival using the Kaplan-Meier method. **At median follow-up 45 months (95% CI 28 to 50.9 months):** • One single-arm trial (Brugières et al 2023) (n=24) reported 3-year PFS of 40% (95% CI 23% to 59%). **(VERY LOW)** • One single-arm trial (Brugières et al 2023) (n=24) reported median PFS of 11.0 months (95% CI 1.7 to 47.6 months). **(VERY LOW)** **At unspecified duration of follow-up**: • One single-arm trial (Gambacorti-Passerini et al 2018) (n=17) reported 2-year PFS of 63% (95% CI 35.3% to 81.4%). **(VERY LOW)** **Two single-arm trials provided very low certainty evidence of 2-year progression-free survival of 63% at unspecified duration of follow-up, and 3-year progression-free survival of 40% at median follow-up 45 months with a median progression-free survival of 11 months.**
Overall Survival **Certainty of evidence:** Very low	Overall survival is important to patients as individuals with relapsed or refractory ALK-positive ALCL have a high mortality rate due to advanced disease. Improved survival is an important marker of effective treatment. Overall survival does not give any indication of a patient's quality of life during this time. In total, one study (one single-arm trial) provided evidence relating to overall survival (OS), estimated using the Kaplan-Meier method. **At median follow-up 45 months (95% CI 28 to 50.9 months):** • One single-arm trial (Brugières et al 2023) (n=24) reported 3-year OS of 63% (95% CI 43% to 79%). **(VERY LOW)**

Outcome	Evidence statement
	One single-arm trial provided very low certainty evidence of 3-year overall survival of 63% at median follow-up 45 months.
Important outcomes	
Quality of life **Certainty of evidence:** Not applicable	Quality of life is important to patients as it provides an indication of an individual's general health, their self-perceived well-being and their ability to participate in activities of daily living. Measurement of quality of life can help inform patient-centred decision making and inform health policy. No evidence was identified for quality of life.
Activities of daily living (ADLs) **Certainty of evidence:** Not applicable	ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home, and recreational settings. They encompass patients' individual needs and facilitate inclusion and participation. **No evidence was identified for ADLs.**
Treatment-related hospitalisation **Certainty of evidence:** Not applicable	This is important to patients as it may represent either disease progression or treatment toxicity and it may have a bearing on the patient's quality of life. **No evidence was identified for treatment-related hospitalisation**
Treatment adherence **Certainty of evidence:** Very low	Adherence to treatment is important to patients as it provides an indication of how the treatment is tolerated. If a treatment has adherence challenges, it can increase the risk of treatment failure and add to tumour progression. In total, two single-arm studies provided evidence relating to treatment adherence, reported as narrative text. • One single-arm trial (Mossé et al 2017) (n=26) reported that 24 (92%) patients discontinued crizotinib therapy for a range of reasons including further treatment refusal (n=2), adverse events (n=2) and non-compliance (n=1). Other discontinuation reasons were treatment with SCT (n=12), disease progression (n=3), withdrawal from the study (n=2), lost to follow up (n=1) and protocol criteria (n=1). **(VERY LOW)** • One single-arm trial (Brugières et al 2023; n=24) reported that all patients discontinued treatment due to no further treatment (n=2), switching to other treatment (n=13), disease progression (n=8) and previous toxicity due to allo-SCT (n=2). **(VERY LOW)** **Two single-arm trials provided very low certainty evidence on treatment adherence. At least 18% patients from the two studies stopped treatment due to poor adherence (further treatment refusal, adverse events, non-compliance) with a further 72% who discontinued due to switching treatment or disease progression, and 8% who discontinued for other reasons.**
Safety	
Adverse events (AEs) **Certainty of evidence:** Very low	The safety of crizotinib is important to patients as it informs treatment decisions and allows comparison of interventional approaches. In total, three studies (three single-arm trials) provided evidence relating to adverse events (AEs)[4]. **At unspecified duration of follow-up:** • One single-arm trial (Mossé et al 2017) (n=26) reported that 83% of those treated with crizotinib 165mg/m^2 and 100% of those treated with crizotinib 280mg/m^2 experienced at least one grade 3 or 4 AE. 33% of patients on the lower dose of crizotinib and 85% of patients on the higher dose of crizotinib had at least one grade 3 or 4 AE which was considered *'possibly, probably, or definitely'* related to the study drug. **(VERY LOW)**

[4] Adverse events were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4

Outcome	Evidence statement
	• One single-arm trial (Gambacorti-Passerini et al 2018) (n=44, including n=18 patients with ALCL and n=26 with other malignancies) reported that 88.6% of patients experienced any AE, with 36.4% experiencing a grade 3 AE, 13.6% experiencing a grade 4 AE and 4.5% experiencing a grade 5 AE. **(VERY LOW)** **At median follow-up 45 months (95% CI 28 to 50.9 months):** • One single-arm trial (Brugières et al 2023; n=24) reported that the most common Grade 3 or 4 AEs were neutropaenia (32%), anaemia (20%) and lymphopaenia (12%), while the most common AEs (all grades) were ALAT increase (72%), anaemia (68%), lymphopaenia (64%), neutropaenia (56%) and leucopaenia (56%). **(VERY LOW)** **At unspecified duration of follow-up:** • One single-arm trial (Mossé et al 2017) (n=26) reported that between 33% and 70% patients had at one neutrophil count decrease. (VERY LOW) • One single-arm trial (Gambacorti-Passerini et al 2018) (n=44, including n=18 patients with ALCL and n=26 with other malignancies) reported that the most common AEs (all grades) were diarrhoea (45.5%), vision disorder (45.5%), nausea (38.6%), elevated transaminases (34.1%), vomiting (34.1%) and neutropaenia (31.8%). (VERY LOW) **All three single-arm trials provided very low certainty evidence that the majority of patients with relapsed or refractory ALCL reported adverse events during crizotinib treatment. One trial reported 83% of patients treated with crizotinib 165mg/m^2 twice daily experienced at least one grade 3 or 4 AE, of which 33% were considered to be related to crizotinib therapy. 100% of those treated with higher dose crizotinib 280mg/m^2 twice daily experienced at least one grade 3 or 4 AE; 85% were considered to be related to crizotinib therapy. A second trial provided very low certainty evidence that around 55% of patients treated with crizotinib 250mg twice daily experienced a grade 3, 4 or 5 AE.**
Abbreviations ADL: activities of daily living; AE: adverse event; ALAT: Alanine Transaminase; ALCL: anaplastic large cell lymphoma; ALK: anaplastic lymphoma kinase, BOR: Best Overall Response; CI: confidence interval; DOR: Duration of Response; ECOG: Eastern Cooperative Oncology Group (performance status), ORR: Objective Response Rate; OS: Overall Survival; PFS: Progression-free Survival; RECIST: Response evaluation criteria in solid tumours; WBC: white blood cell	

In people with relapsed or refractory ALK-positive ALCL, what is the cost effectiveness of crizotinib compared with standard care?

Outcome	Evidence statement
Cost effectiveness	No evidence was identified for cost effectiveness

From the evidence selected, are there any subgroups of patients that may benefit from crizotinib more than the wider population of interest?

Outcome	Evidence statement
Response to treatment	**At 8 weeks post-treatment initiation** • One single-arm trial (Brugières et al 2023) (n=24) reported an objective response rate of 80% (95% CI 44% to 97%) in those aged ≤18 years (n=11) and 57% (95% CI 29% to 82%) in those aged >18 years (n=14).
Progression-free survival and overall survival	**At median follow-up 45 months (95% CI 28 to 50.9 months):** • One single-arm trial (Brugières et al 2023) (n=24) reported 3-year progression-free survival of 64% (95% CI 35% to 85%) in those aged ≤18 years (n=11) and 21% (95% CI 8% to 48%) in those aged >18 years (n=14).

Outcome	Evidence statement
	• One single-arm trial (Brugières et al 2023) (n=24) reported 3-year overall survival of 78% (95% CI 45% to 94%) in those aged ≤18 years) (n=11) and 50% (95% CI 27% to 73%) in those aged >18 years (n=14).

From the evidence selected, what was the treatment dose of crizotinib in the population of interest?

Outcome	Evidence statement
Crizotinib dose	Evidence about crizotinib doses came from three single-arm trials. • One single-arm trial (Brugières et al 2023) used treatment doses of crizotinib 165 mg/m^2 twice daily for patients aged 1 to 17 years and 250 mg twice daily for adults aged 18 to 60 years. • One single-arm trial (Gambacorti-Passerini et al 2018) used a starting dose of 250mg twice daily in a population aged 15 to 37 years. • One single-arm trial (Mossé et al 2017) used treatment doses of crizotinib 165mg/m^2 in a population aged 3.7 to 13.4 years or 280mg/m^2 twice daily in a population aged 6.1 to 20.8 years.

From the evidence selected, what were the definitions of relapsed or refractory used in relation to ALK-positive ALCL?

Outcome	Evidence statement
Definitions of relapsed or refractory	• In Brugières et al 2023, patients were stated to have 'confirmed ALK-positive ALCL that had relapsed, progressed, or inadequately responded to the available therapies (meaning for paediatrics a relapse after a first well-conducted standard treatment or a situation without any standard treatment and a survival <10%)', and to have a measurable lesion. • In Gambacorti-Passerini et al 2018, patients were stated to be relapsed, and to have ALCL, IMT, or other advanced malignancy (excluding NSCLC) for which no standard therapy is available. No further definition was provided. • In Mossé et al 2017, patients were stated to have recurrent ALCL. No further definition was provided.

6. Discussion

This evidence review considered the clinical effectiveness, safety and cost effectiveness of crizotinib compared to current standard care in people with ALK-positive relapsed or refractory ALCL. The critical outcomes of interest were response to treatment, progression-free survival and overall survival. Important outcomes were quality of life, activities of daily living (ADLs), treatment-related hospitalisation, treatment adherence and safety. Evidence on cost effectiveness was also sought.

Three studies were identified for inclusion in this review, reported in three papers. All three were single-arm, phase II trials (Brugières et al 2023; Gambacorti-Passerini et al 2018; Mossé et al 2017). No comparator evidence or cost effectiveness evidence was identified.

Brugières et al (2023) reported an open-label, phase II trial of patients with ALK-positive ALCL which had relapsed, progressed or inadequately responded to the available therapies. Twenty-five patients, aged between one and 60 years, were included from centres across France, with a median follow-up of 45 months. Response to treatment, survival, treatment adherence and adverse event outcomes were reported.

Gambacorti-Passerini et al (2018) reported an open label phase II study of 44 patients with ALK-positive ALCL, IMT or other advanced malignancy, of whom eighteen aged 15 to 37 years had advanced, refractory or relapsed ALK-positive ALCL and were analysed separately for disease response and survival outcomes. Adverse event outcomes were also reported for the whole cohort of 44 subjects, the majority of whom did not meet the PICO definition. Patients were from centres across six countries in Europe, Asia and the USA. Duration of follow-up was not reported.

Mossé et al (2017) reported a phase II study of patients aged between three and 21 years with relapsed or refractory ALK-positive ALCL. Twenty-six patients, from centres in the USA, were treated with two different crizotinib dosing regimens. Treatment response, treatment adherence and safety outcomes were reported. Duration of follow-up was not reported.

Baseline characteristics of all patients are included in Appendix E. All three studies included a majority of male subjects. Patients were variously described as having recurrent ALCL, or having relapsed, progressed, not responded to treatment or having no standard treatment available; one study defined this as '*for paediatrics a relapse after a first well-conducted standard treatment or a situation without any standard treatment and a survival <10%'*, but no more detailed descriptions of relapsed or refractory ALCL were provided. None of the studies reported recruiting patients from the UK and it is not clear if the patients in the studies reflect the range of patients seen in clinical practice in England.

Evidence was identified for all the critical outcomes of interest for this review and for the important outcomes treatment adherence and safety. The studies did not report the important outcomes quality of life, activities of daily living and treatment-related hospitalisation. Brugières et al 2023 reported a median follow-up period of 45 months and reported response to treatment outcomes at eight weeks following treatment initiation. The other two studies did not report duration of follow-up or the time point at which outcomes were reported.

No minimal clinically important thresholds or differences were reported for the outcomes considered.

The treatment response outcomes were evaluated using either RECIST v1.1 criteria or the Lugano classification. Both use defined criteria to categorise the response to treatment as complete or partial response, stable disease or disease progression. The criteria are pre-

defined based on imaging and may also include clinical or other assessments depending on the site and type of the lesion. While these defined criteria increase the likelihood of a uniform approach to evaluation across sites, Mossé et al 2017 reported that in six out of 26 patients there was a difference in the evaluation of treatment response between local investigators and the central study team. It was also not clear how standardised and repeatable the conduct of assessments was across the sites in each study; while two of the studies described the approach to assessment, the third (Mossé et al 2017) did not, but stated that imaging was carried out '*at the treating institution's discretion'*. Survival was calculated using the Kaplan-Meier method. Treatment adherence was not formally reported, but two studies listed reasons for discontinuing treatment in narrative text.

Brugières et al 2023 also reported a subgroup analysis, which did not appear to have been pre-planned, comparing treatment and survival outcomes in those aged ≤18 years and those aged >18 years.

All three studies were considered to be at high risk of bias and certainty about the evidence for the critical and important outcomes was very low when assessed using modified GRADE. All the studies were small, with between 18 and 26 relevant subjects. Limitations reducing certainty for the outcomes reported include uncertainty about whether the inclusion of participants was complete or consecutive, and in the adverse event data reported by Gambacorti-Passerini et al 2018, the inclusion of patients with conditions other than ALCL who therefore did not meet the PICO definition. Duration of follow-up was not reported in two of the studies. All of the studies only presented statistical analyses or summary statistics for some of the outcomes reported; a lack of comparator was also a limitation across all of the studies. Limitations due to the lack of blinding of patients and assessors also reduced certainty for some of the outcomes across all three studies.

7. Conclusion

This evidence review includes three single-arm, phase II clinical trials, each with between 18 and 26 subjects with ALK-positive relapsed or refractory ALCL who were treated with crizotinib. One study included children and adults (age range 1 to 60 years), one included adolescents and adults (age range 15 to 37 years) and one included children, adolescents and young adults aged up to 21 years. All studies included a majority of male subjects.

None of the studies included a comparator group and the evidence for all the outcomes of interest was of very low certainty.

Evidence was available for crizotinib use in patients with relapsed or refractory ALCL for all the critical outcomes of interest. All of the included studies provided very low certainty evidence that the majority of patients (between 53% and 90% across the studies) had a complete or partial response to treatment with crizotinib, with a median duration of response between about 30 and 43 months. Two of the studies also provided evidence of a 2-year progression-free survival rate of 63% and 3-year progression-free survival rate of 40%, and one provided evidence of 3-year overall survival of 63%. No minimal clinically important differences were defined for any outcomes, and limited statistical analyses were reported.

Data were available for the important outcome of treatment adherence. No evidence was available for the other specified important outcomes of quality of life, activities of daily living and hospitalisation. Two single-arm studies reported information relating to treatment adherence; nine (18%) patients discontinued treatment due to adherence-related reasons (further treatment refusal, adverse events, non-compliance) and a further 80% discontinued for other reasons.

Three single-arm studies reported data on safety in the form of adverse events (AEs). Most patients reported AEs during crizotinib treatment. In one trial, 83% of those treated with crizotinib 165mg/m2 twice daily and 100% of those treated with crizotinib 280mg/m2 twice daily experienced at least one grade 3 or 4 AE, with 33% and 85% respectively being considered ‘possibly, probably, or definitely’ related to crizotinib therapy. In a second trial around 55% of patients treated with crizotinib 250mg twice daily experienced a grade 3, 4 or 5 AE (although of the 44 patients for whom this outcome was reported, only 18 had ALCL).

One single-arm trial carried out unplanned subgroup analyses which found that patients aged ≤18 years appeared to have better treatment response and survival outcomes than those aged >18 years, although the differences were not statistically significant and no p-values were reported.

No evidence on cost effectiveness was identified.

Limitations reducing certainty for the outcomes in the studies included uncertainty about selection of the participants, the small size of the studies, limited statistical analyses and a lack of comparator. The lack of blinding of patients and assessors also reduced certainty for some of the outcomes across all three studies. While standardised criteria were used to evaluate treatment response, in one study there were appeared to have been differences between local investigators and central study team in how these were applied. It was not clear in any of the studies how standardised and repeatable across the sites the conduct of assessments was.

None of the studies included patients from the UK and it is not clear how similar the patients in the studies are to patients seen in clinical practice in England.

Although all the studies provided very low certainty evidence of the outcomes, there was some congruence in the results reported. The studies identified in this review provide evidence, for a

range of pre-specified critical and important outcomes, that patients with ALK-positive relapsed or refractory ALCL respond to treatment with crizotinib. The lack of comparator data means that no conclusions can be drawn about the effectiveness of crizotinib compared with other treatments for this patient group.

Appendix A PICO document

The review question(s) for this evidence review are:

1. In people with ALK-positive relapsed or refractory ALCL what is the clinical effectiveness of crizotinib compared with standard care?
2. In people with ALK-positive relapsed or refractory ALCL, what is the safety of crizotinib compared with standard care?
3. In people with ALK-positive relapsed or refractory ALCL what is the cost effectiveness of crizotinib compared with standard care?
4. From the evidence selected, are there any subgroups of patients that may benefit from crizotinib more than the wider population of interest?
5. From the evidence selected, what was the treatment dose of crizotinib in the population of interest?
6. From the evidence selected, what were the definitions of relapsed or refractory used in relation to ALK-positive ALCL?

P –Population and Indication	Patients with relapsed or refractory ALK-positive ALCL Subgroups of interest include: age [One definition of refractory disease is disease that returns within 3 months of treatment, or disease which is non-responsive to treatment; relapsed disease is disease that recurs 3 months or later following treatment. Other definitions of relapsed and refractory are also acceptable.] [Some patients may go on to receive autologous or allogenic haematopoietic stem cell transplantation following treatment with crizotinib]
I – Intervention	Crizotinib + best supportive care [The recommended dosage of crizotinib for paediatric patients with ALCL or IMT is 280mg/m^2 orally twice daily until disease progression or unacceptable toxicity.] [Evidence for the dosing of crizotinib in ALCL and IMT demonstrated that dosing regimes are varied and include 150mg twice daily, 165 mg/m^2 and 280 mg/m^2.] [Patients will receive best supportive care alongside crizotinib. Best supportive care is defined as care aimed at controlling symptoms, including the use of analgesia and antifungals etc.]
C – Comparator(s)	For patients with relapsed or refractory ALK-positive ALCL standard care would be any of the following options alongside best supportive care: • Chemotherapy (including but not limited to: multiagent regimens such as CCNU and Ara-C or vindesine, dexamethasone, Ara-C, platinum agents and etoposide) • Palliative care [Patients will receive best supportive care alongside standard care options.]
O – Outcomes	**<u>Clinical Effectiveness</u>**

Minimally clinically important difference (MCIDs) are not known unless stated.

Critical to decision-making:

- Response to treatment

Response rate is important to patients as it represents whether the treatment can improve disease burden.

[Response to treatment for ALCL is measured used the International Working Group Revised Response Criteria for Malignant Lymphoma which typically employs positron emission topography (PET) scans (including FDG-PET) in addition to CT scans and non-radiographic evaluations, such as of the bone marrow. Classification of response can be measured using the Lugano Classification or the response evaluation criteria in lymphoma (RECIL). Outcomes measured at 3 months are of particular clinical relevance.]

- Progression-free survival

This outcome is important to patients because it represents the time for which their disease is not progressing. Stable disease might represent longer survival and disease stability may result in patients experiencing fewer symptoms from the disease itself. It can be determined sooner than overall survival outcome measures.

- Overall Survival

Overall survival is important to patients as individuals with relapsed or refractory ALK-positive ALCL have a high mortality rate due to advanced disease. Improved survival is an important marker of effective treatment. Overall survival does not give any indication of a patient's quality of life during this time.

Important to decision-making:

- Quality of life

Quality of life is important to patients as it provides an indication of an individual's general health, their self-perceived well-being and their ability to participate in activities of daily living. Measurement of quality of life can help inform patient-centred decision making and inform health policy.

[Examples of generic quality of life tools include: SF-36, QLQ-OV28, QLQ-C30 and the EQ-5D
Examples of specific quality of life tools for patients with cancer, including lymphoma, include but are not limited to:

- Functional assessment of Cancer Therapy Lymphoma (FACT-Lym)
- Functional assessment of Cancer Therapy- General (FACT-General)
- Pediatric Quality of Life Inventory (PedsQL)

Activities of daily living (ADLs)
ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home, and recreational settings. They encompass patients' individual needs and facilitate inclusion and participation.

[ADLs can be measured using assessments such as:

	• Timed task completion (e.g., timed repeatable test such as dressing, meal preparation or patient specific ADL goal) • ADLs assessment using a tool (e.g., Barthel Index (BI) or Independence in Activities of Daily Living (ADL) • Subjective/self-reported assessment (e.g., by the individual, carer, or MDT. This could include self-reported questionnaires such as participation in work and other activities).] **Treatment-related Hospitalisation** This is important to patients as it may represent either disease progression or treatment toxicity and it may have a bearing on the patient's quality of life. **Treatment adherence** Adherence to treatment is important to patients as it provides an indication of how the treatment is tolerated. If a treatment has adherence challenges, it can increase the risk of treatment failure and add to tumour progression. [Examples include, but not limited to: • Missed doses (observed by research staff review of medication/returned medication) • Self-reported adherence measures (e.g., questionnaire methods) • Interview methods] **<u>Safety</u>** The safety of crizotinib is important to patients as it informs treatment decisions and allows comparison of interventional approaches. [Examples of measures include, but are not limited to: • Frequency of adverse events • Frequency of grade 3 or 4 adverse events • Adverse events leading to discontinuation • Treatment related adverse events – e.g., diarrhoea, neutropenia, elevated transaminases, visual disturbance, intracranial haemorrhage, oedema.] **<u>Cost effectiveness</u>**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages

Date limits	2013-2023
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, the Cochrane Library and TRIP were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, commentaries, letters, editorials, non-systematic reviews, trial registrations and case reports were excluded.

Search dates: 1 January 2013 to 14 September 2023

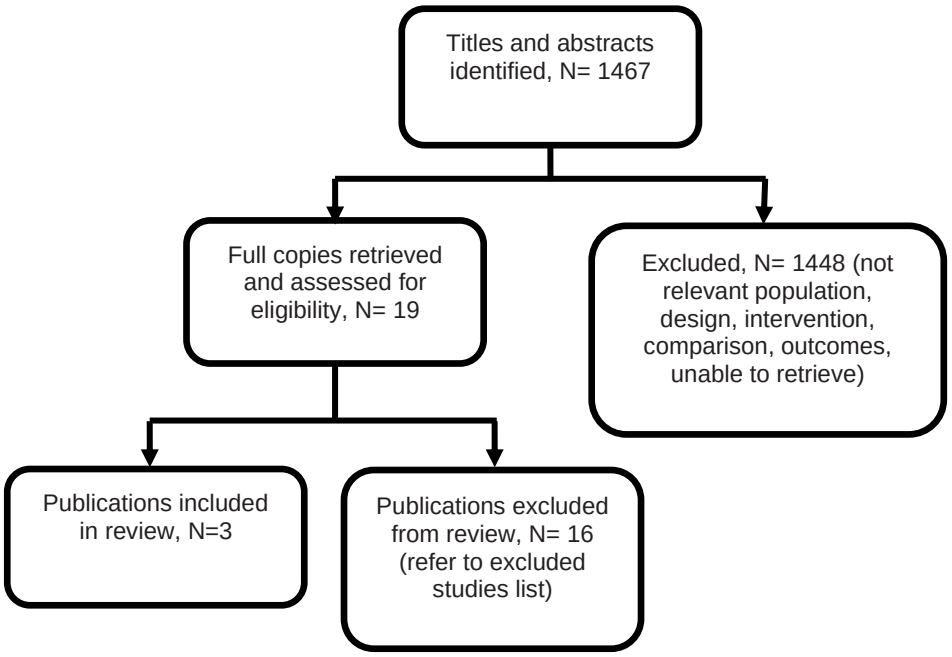
Medline search strategy:

1	Crizotinib/
2	(crizotinib or xalkori).ti,ab,kf.
3	1 or 2
4	*Anaplastic Lymphoma Kinase/ and exp *Neoplasms/
5	(((alk or anaplastic lymphoma kinase) adj positive) and (cancer? or neoplas* or tum?r? or oncolog*)).ti,kf.
6	(((alk or anaplastic lymphoma kinase) adj (positive or mutation*)) and (lymphoma? or alcl)).ti,ab,kf.
7	(((alk or anaplastic lymphoma kinase) adj (positive or mutation?)) and (myofibroblastic tumo?r? or myo-fibroblastic tumo?r? or imt)).ti,ab,kf.
8	Lymphoma, Large-Cell, Anaplastic/
9	(anaplastic large cell lymphoma? or alcl).ti,kf.
10	(inflammatory myofibroblastic tumo?r? or inflammatory myofibroblastic tumo?r? or imt).ti,kf.
11	4 or 5 or 6 or 7 or 8 or 9 or 10
12	3 and 11
13	limit 12 to (english language and yr="2013 -Current")
14	exp animals/ not humans/
15	13 not 14
16	limit 15 to (meta analysis or "systematic review" or "reviews (maximizes specificity)")
17	(comment or editorial or letter or review).pt. or case report.ti.
18	15 not 17
19	16 or 18

Appendix C Evidence selection

The literature searches identified 1467 references pertaining to people with ALK-positive unresectable inflammatory myofibroblastic tumour (IMT) or ALK-positive relapsed / refractory ALCL. These were screened using their titles and abstracts and those potentially relating to the use of crizotinib in people with IMT and/or ALCL were obtained in full text and assessed for relevance. Of these, three references are included in this evidence summary. The remaining 16 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection - decision and rationale if excluded
Mossé, Y.P. et al. (2013) 'Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: A children's oncology group phase 1 consortium study', The Lancet Oncology, 14(6), pp. 472–480. doi:10.1016/s1470-2045(13)70095-0	Excluded n<10, larger case series and cohort studies included, no additional outcomes presented.
Mossé, Y.P. et al. (2017) 'Targeting ALK with crizotinib in pediatric anaplastic large cell lymphoma and inflammatory myofibroblastic tumor: A children's oncology group study', Journal of Clinical Oncology, 35(28), pp. 3215–3221. doi:10.1200/jco.2017.73.4830.	Included
Gambacorti-Passerini, C. et al. (2018) 'Long-term effects of crizotinib in Alk-positive tumors (excluding NSCLC): A phase 1B open-label study', American Journal of Hematology, 93(5), pp. 607–614. doi:10.1002/ajh.25043.	Included

Appendix D Excluded studies table

Study reference	Reason for exclusion
Batra U, Sharma M, Nathany S, Jain P, Soni S, Mehta A. Are all ALK variants created equal? Clinicopathologic features and outcomes: a propensity-matched study. International Journal of Clinical Oncology. 2021;26(7):1221-8.	Incorrect population: not IMT or ALCL.
Gambacorti Passerini C, Farina F, Stasia A, Redaelli S, Ceccon M, Mologni L, et al. Crizotinib in advanced, chemoresistant anaplastic lymphoma kinase-positive lymphoma patients. Journal of the National Cancer Institute. 2014;106(2):djt378.	n<10, larger case series and cohort studies included, no additional outcomes presented.
He Y, Pei K, Zhang H, Wang J, Su X, Gan W, et al. Observation of Alectinib- and Crizotinib- included chemotherapy in children with ALK-positive anaplastic large cell lymphoma: A single institutional experience. Cancer Medicine. 2023;12(6):7182-8.	Incorrect population: newly diagnosed ALCL rather than relapsed/refractory ALCL.
Huang L, Zhang F, Zeng J, Guo H, Liu S, Wei X, et al. ALK expression plays different roles in anaplastic large-cell lymphomas and outcome of crizotinib use in relapsed/refractory ALK+ patients in a Chinese population. Annals of Hematology. 2018;97(1):149-59.	n<10, larger case series and cohort studies included, no additional outcomes presented.
Indhuja MV, Kesana S, Mehra N, Karunakaran P, Rajan AK, Radhakrishnan V, et al. Role of ALK Inhibitors in Anaplastic Large Cell Lymphoma-Experience from an Indian Center. South Asian Journal of Cancer. 2023.	n<10, larger case series and cohort studies included, no additional outcomes presented.
Liu X, Gong C, Zhang J, Feng W, Guo Y, Sang Y, et al. Clinicopathological Analysis and Treatment of Adult Patients with Inflammatory Myofibroblastic Tumor: A 15-Year Single-Center Study. Cancer Research & Treatment. 2023;55(3):1001-10.	Incorrect population: no ALCL patients included, only IMT.
Lopez-Nunez O, John I, Panasiti RN, Ranganathan S, Santoro L, Grelaud D, et al. Infantile inflammatory myofibroblastic tumors: clinicopathological and molecular characterization of 12 cases. Modern Pathology. 2020;33(4):576-90.	No PICO outcomes reported.
Mansfield AS, Wei Z, Mehra R, Shaw AT, Lieu CH, Forde PM, et al. Crizotinib in patients with tumors harboring ALK or ROS1 rearrangements in the NCI-MATCH trial. npj Precision Oncology. 2022;6(1):13.	Incorrect population: not IMT or ALCL.
Mosse YP, Lim MS, Voss SD, Wilner K, Ruffner K, Laliberte J, et al. Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study. Lancet Oncology. 2013;14(6):472-80.	n<10, larger case series and cohort studies included, no additional outcomes presented.
Ruf S, Hebart H, Hjalgrim LL, Kabickova E, Lang P, Steinbach D, et al. CNS progression during vinblastine or targeted therapies for high-risk relapsed ALK-positive anaplastic large cell lymphoma: A case series. Pediatric Blood & Cancer. 2018;65(6):e27003.	n<10, larger case series and cohort studies included, no additional outcomes presented.
Schoffski P, Kubickova M, Wozniak A, Blay JY, Strauss SJ, Stacchiotti S, et al. Long-term efficacy update of crizotinib in patients with advanced, inoperable inflammatory myofibroblastic tumour from EORTC trial 90101 CREATE. European Journal of Cancer. 2021;156:12-23.	Incorrect population: no ALCL patients included, only IMT.

Study reference	Reason for exclusion
Schoffski P, Sufliarsky J, Gelderblom H, Blay JY, Strauss SJ, Stacchiotti S, et al. Crizotinib in patients with advanced, inoperable inflammatory myofibroblastic tumours with and without anaplastic lymphoma kinase gene alterations (European Organisation for Research and Treatment of Cancer 90101 CREATE): a multicentre, single-drug, prospective, non-randomised phase 2 trial. The Lancet Respiratory Medicine. 2018;6(6):431-41.	Incorrect population: no ALCL patients included, only IMT.
Shen D, Song H, Zhang J, Liao C, Wang Y, Fang M, et al. Treatment of Relapsed and Refractory ALK-Positive Anaplastic Large Cell Lymphoma With ALK-Specific Tyrosine Kinase Inhibitor in Children: A Case Series. Journal of Pediatric Hematology/Oncology. 2022;44(1):e1-e4.	n<10, larger case series and cohort studies included, no additional outcomes presented.
Takeyasu Y, Okuma HS, Kojima Y, Nishikawa T, Tanioka M, Sudo K, et al. Impact of ALK Inhibitors in Patients With ALK-Rearranged Nonlung Solid Tumors. JCO Precision Oncology. 2021;5.	Incorrect population: no ALCL patients included, only IMT.
Trahair T, Gifford AJ, Fordham A, Mayoh C, Fadia M, Lukeis R, et al. Crizotinib and Surgery for Long-Term Disease Control in Children and Adolescents With ALK-Positive Inflammatory Myofibroblastic Tumors. JCO Precision Oncology. 2019;3.	Incorrect population: no ALCL patients included, only IMT.
Zhang YT, Wang LZ, Chang J. Characteristics and Outcomes of Chinese Children With Advanced Stage Anaplastic Large Cell Lymphoma: A Single-Center Experience. Frontiers in Oncology. 2022;12:832752.	n<10, larger case series and cohort studies included, no additional outcomes presented.

Appendix E Evidence table

For abbreviations see list after table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Brugières L, Cozic N, Houot R, Rigaud C, Sibon D, Arfi-Rouche J, Bories P, Cottereau AS, Delmer A, Ducassou S, Garnier N, Lamant L, Leruste A, Millot F, Moalla S, Morschhauser F, Nolla M, Pagnier A, Reguerre Y, Renaud L, Schmitt A, Simonin M, Verschuur A, Hoog Labouret N, Mahier Ait Oukhatar C, Vassal G. Efficacy and safety of crizotinib in ALK-positive systemic anaplastic large-cell lymphoma in children, adolescents, and adult patients: results of the French AcSé-crizotinib trial. Eur J Cancer. 2023 Sep;191:112984. doi: 10.1016/j.ejca.2023.112984. Epub 2023 Jul 17. PMID: 37549532. **Study location** France (17 centres)	Patients aged 12 months or older with ALK-positive ALCL. **Inclusion criteria** • Age 12 months or older • Confirmed ALK-positive ALCL that had relapsed, progressed, or inadequately responded to the available therapies • Presence of a measurable lesion • ECOG[5] performance status <2, or a Lansky[6] score >50 in patients under 12 years of age **Exclusion Criteria** Included: • NSCLC • Previous treatment with crizotinib • Major surgery or tumour embolisation	**Intervention** Crizotinib 165 mg/m^2 twice daily (BID) for patients aged 1 to 17 years and 250 mg BID in adults Median treatment duration, months: 3.7 (range 0.37 to 47.2) **Comparator** No comparator group	Median follow-up (months): 45 (95% CI 28 to 50.9 months) **Critical outcomes** **Response to treatment[7]** *Best Overall Response (BOR) (n=24)[8]* BOR at 8 weeks post treatment initiation: Complete response: 9/24 Partial response: 7/24 BOR over duration of treatment: Complete response: 12/24 Partial response: 4/24 *Objective Response Rate (ORR) (n=24)* ORR at 8 weeks posttreatment initiation**:** 67% (95% CI 47% to 82%) ORR over duration of treatment: 67% (95% CI 47% to 82%) *Duration of Response (n=16)*	This study was appraised using the JBI checklist for Case Series. 1. Yes 2. Yes 3. Yes 4. Unclear 5. Unclear 6. Yes 7. Yes 8. Yes 9. No 10. Yes **Other comments:** This was a phase II clinical trial carried out across 17 centres in France. 28 patients were recruited but three not treated with crizotinib were excluded from the analysis. Inclusion and exclusion criteria were clearly defined but it was not clear if patient recruitment had been consecutive and complete. The study population included both children and adults (age range 1 to 60 years) and almost two-thirds were male. Two patients in the cohort had major deviations from

[5] Performance status scale used in cancer patients which measures level of functioning in terms of their ability to care for themself, daily activity, and physical ability.
[6] A play-performance scale for paediatric patients which uses parent description of their child's activity to assess ability and response to treatment.
[7] Response to treatment based on RECIST 1.1 criteria for conventional imaging or according to the Lugano criteria in patients evaluated by FDG-PET/CT. Both use defined criteria to categorise the treatment response. Objective response defined as complete (CR) or partial response (PR).
[8] One patient was not evaluable because they discontinued crizotinib after 11 days due to significant clinical improvement.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Study type Non-controlled, open-label, phase II trial (single-arm trial) **Study aim** To evaluate the safety and efficacy of Crizotinib in patients with ALK, ROS1, and MET-driven malignancies, including ALK-positive anaplastic large -cell lymphoma (ALK+ ALCL) **Study dates** February 2014 to March 2018	within 4 weeks or minor surgery within 2 weeks • Other concurrent severe and/or uncontrolled medical disease • Taking one or more of a number of specified drugs **Total sample size** n = 25 **Baseline characteristics** *Age* • Median age: 19 years • Age range: 1 to 60 years Among those aged ≤18 years: • Median age: 11 years Age range: 1 to 17 years Among those aged >18 years: • Median age: 25.5 years • Age range: 19 to 60 years *Male*: 16/25 (64%) *Number of prior therapies, n (%):*		Median duration of response (among responders): 43.4 months (95% CI 8.3 months to not reached) **Progression-free Survival (PFS)[9]** (n=25) Median PFS (months): 11.0 (95% CI 1.7 to 47.6 months) 3-year PFS: 40% (95% CI 23% to 59%) **Overall Survival (OS)** (n=25) 3-year OS: 63% (95% CI 43% to 79%) Median OS (months): not reached **Important Outcomes** **Treatment adherence** Treatment adherence was not formally reported. The authors commented that all patients had discontinued treatment, for the following reasons: Disease progression: n=8 Toxicity related to former allo-SCT: n=2 Switched to another treatment: n=13 Stopped without any further treatment: n=2 **Safety** *Treatment-related adverse events (AEs) (n=25)[10]*	the inclusion criteria: one was not fit enough for chemotherapy and the other had an evaluable but not measurable disease. Both were included in the analysis. One patient was excluded from the treatment outcomes analysis because they discontinued crizotinib after 11 days due to significant clinical improvement. Patients had clinical assessments every 4 weeks until disease progression and were assessed using CT and/or MRI scans at baseline then every 8 weeks. Patients were to receive crizotinib until disease progression, unacceptable toxicity, or decision made by the investigator, the sponsor, or the patient/parents. AEs were assessed by clinical and paraclinical examinations at every scheduled visit during the treatment period. It was not stated that assessors were blinded, leading to potential bias in the assessment of more subjective outcomes. Treatment response was evaluated using either RECIST or Lugano criteria depending on type of imaging used. Survival was calculated using the Kaplan-Meier method. The analyses comparing outcomes in those aged ≤18 years and >18 years did not appear to have been pre-planned.

[9] Progression was assessed using radiological or FDG-PET/CT evaluation, or by clinical evaluation if these were not available. Survival was calculated using the Kaplan-Meier method.
[10] Classified according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	0: 1 (4%) 1: 8 (33%) 2: 10 (41%) 3: 5 (20%) 4: 1 (4%) *Prior therapies, n* • Front-line chemotherapy: 24 • Autologous SCT: 4 • Allogeneic HSCT: 1 • Brentuximab Vedotin: 13		At least one grade 3 or 4 AE: 8 (32%) The commonest grade 3 or 4 AEs were: Neutropaenia: 8 (32%) Anaemia: 5 (20%) Lymphopenia: 3 (12%) a The commonest grade 1 to 4 AEs were: ALAT increase: 18 (72%) Anaemia: 17 (68%) Lymphopaenia: 16 (64%) Neutropaenia: 14 (56%) Leucopaenia: 14 (56%) Nausea: 12 (48%) ASAT increase: 12 (48%) Fatigue: 11 (44%) Diarrhoea: 11 (44%) Alkaline phosphatases increase: 10 (40%) **Subgroup analyses** Outcomes for children and adolescents (aged ≤18 years) (n=11) vs adults (aged >18 years) (n=14) *ORR* at 8 weeks posttreatment initiation: 80% (95% CI 44% to 97%) vs 57% (95% CI 29% to 82%) *Progression-free survival at 3 years*: 64% (95% CI 35% to 85%) vs 21% (95% CI 8% to 48%] *Overall survival at 3 years*: 78% (95% CI 45% to 94%) vs 50% (95% CI 27% to 73%)	**Source of funding:** The authors stated: 'This programme was founded by the Institut Nationale du Cancer, the ARC Foundation for Cancer Research, and Unicancer's personalised medicine research partners. This work was institutionally supported by Pfizer.'

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			AEs: frequency of AEs in the two groups was reported but no statistical tests were reported.	
Gambacorti-Passerini C, Orlov S, Zhang L, Braiteh F, Huang H, Esaki T, et al. Long-term effects of crizotinib in ALK-positive tumors (excluding NSCLC): A phase 1b open-label study. American Journal of Hematology. 2018;93(5):607-14. **Study location** Multi-centre (Italy, Russia, China, Japan, South Korea, USA) **Study type** Single-arm open label phase II Study **Study aim** To evaluate the safety and antitumour activity of single-agent oral crizotinib among patients with advanced ALCL, IMT, or other advanced ALK-positive malignancies different from NSCLC **Study dates**	Patients aged ≥15 years with ALK-positive ALCL, IMT, or other advanced malignancy (excluding NSCLC) **Inclusion criteria** • Age ≥15 years • ALK-positive • ECOG performance status 0–3 • Histologically or cytologically proven diagnosis of ALCL, IMT, or other advanced malignancy (excluding NSCLC) for which no standard therapy is available **Exclusion Criteria** Patients with: • mutations or amplifications involving c-MET • receiving concurrent treatment on another clinical trial • receiving prior therapy specifically directed against ALK	**Intervention** Crizotinib 250mg twice daily (starting dose) Median treatment duration 35 months **Comparator** No comparator group	Duration of follow-up not reported **Critical Outcomes** **Response to treatment**[11] **(**n=17)[12] *Best Overall Response* Complete response: 47.1% Partial response: 5.9% Stable Disease: 17.6% Objective Progression: 17.6% Early Death: 5.9% Indeterminate: 5.9% *Objective Response Rate* ORR: 52.9% (95% CI 27.8 to 77%) *Duration of Response (weeks)* Median: 135.9; Range 6 to 205.9 weeks **Progression-free survival** (n=17) 2-year progression-free survival: 63.0% (95% CI 35.3% to 81.4%) **Important Outcomes** **Safety** *Treatment-related adverse events*[13] *(n=44)*	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. Unclear 5. Unclear 6. Yes 7. Yes 8. Yes 9. No 10. Yes **Other comments:** The patients included in this analysis were part of a larger cohort with a range of ALK-positive malignancies who were treated with crizotinib. Eighteen had ALCL of whom 17 were included in the analysis (one was excluded as found not to have measurable disease). Subjects were aged between 15 and 37 years and two-thirds were male. Inclusion and exclusion criteria were clearly defined but it was not clear if recruitment of study subjects was consecutive and complete.

[11] Response to treatment was evaluated using RECIST v1.1 which uses defined criteria to categorise the treatment response as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). ORR is CR + PR.
[12] One patient was excluded from analysis as found not to have measurable disease
[13] Classified according to CTCAE

Study details	Population	Interventions	Study outcomes	Appraisal and funding
March 2011 to March 2016	**Total sample size** Total: n=44 ALCL: n = 18 **Baseline characteristics** ALCL group (n=18) *Male:* 66.7% *Age*: • Median: 25 years • Range: 15 to 37 years *ECOG performance*: • 0: 22.2% • 1: 38.9% • 2: 27.8% • 3: 11.1% *Race*: • White: 66.7% • Japanese: 11.1% • Korean: 11.1% • Chinese: 11.1% *Number of prior therapies, n (%):* • 1: 2 (11.1%) • 2: 6 (33.3%) • 3: 5 (27.8%) • 4: 3 (16.7%) • 5: 1 (5.6%) • 6: 1 (5.6%)		Adverse events (AEs) were reported for all study patients combined (n, (%)) Any AE: 39 (88.6%) Grade 3: 16 (36.4%) Grade 4: 6 (13.6%) Grade 5: 2 (4.5%) The commonest AEs (all grades) were (n (%)): Diarrhoea: 20 (45.5%) Vision disorder: 20 (45.5%) Nausea: 17 (38.6%) Elevated transaminases: 15 (34.1%) Vomiting: 15 (34.1%) Neutropenia: 14 (31.8%)	A standard approach to patient assessment was described and tumour assessments were carried out by local investigators. It was not stated that assessors were blinded, leading to potential bias in the assessment of more subjective outcomes. Duration of follow-up was not reported. Patients were permitted to continue treatment with crizotinib if there was evidence of clinical benefit in the opinion of the investigators. Outcomes were evaluated using RECIST. Survival was calculated using the Kaplan-Meier method. All study patients were included in the reported AE outcomes therefore some of the population included in these outcomes does not meet the PICO criteria for this review. **Source of funding:** The authors stated that the study was designed and sponsored by Pfizer Inc. Medical writing support was funded by Pfizer Inc.
Mossé YP, Voss SD, Lim MS, Rolland D, Minard CG, Fox E, et al. Targeting ALK	Patients with ALK-positive relapsed /refractory ALCL	**Interventions**	Duration of follow-up not reported **Critical Outcomes**	This study was appraised using the JBI checklist for case series.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
With Crizotinib in Pediatric Anaplastic Large Cell Lymphoma and Inflammatory Myofibroblastic Tumor: A Children's Oncology Group Study. Journal of Clinical Oncology. 2017;35(28):3215-21. **Study location** USA (multi-centre: exact locations of patient recruitment not stated) **Study type** Phase II study (single-arm trial) **Study aim** To assess activity of the ALK inhibitor crizotinib in patients with ALCL or IMT who had no known curative treatment options at diagnosis or with relapsed/recurrent disease **Study dates** Enrolment September 2009 to October 2015	or unresectable IMT for >12 months **Inclusion Criteria** • aged <22 years • recurrent ALCL or unresectable IMT for >12 months • diagnosis confirmation from pathology • underlying ALK-fusion, detected by immunohistochemistry or by fluorescence in situ hybridization assays **Exclusion Criteria** None stated **Total Sample Size** Total: n= 40 ALCL: n = 26 **No. of participants in each treatment group** ALCL treated with crizotinib 165mg/m^2: 6 ALCL treated with crizotinib 280mg/m^2: 20 **Baseline Characteristics (n=20)** Characteristic: crizotinib 165mg/m^2; crizotinib 280mg/m^2	Crizotinib 165mg/m^2 or 280mg/ m^2 twice daily [14] Median therapy duration, years: Crizotinib 165mg/m^2: 2.79 years (95% CI 0.31 to n/a); Crizotinib 280mg/m^2: 0.4 years (95% CI 0.18 to 1.0) **Comparator** No comparator group	Outcome: treated with crizotinib 165mg/m^2 (n=6); treated with crizotinib 280mg/m^2 (n=20) **Response to treatment[15]** *Best Overall Response* (n (%)) • Complete Response: 5 (83%); 16 (80%) • Partial Response: 0; 2 (10%) • Stable Disease: 1 (17%); 2 (10%) • Progressive Disease: 0; 0 *Objective response rate[16]* 83% (95% CI 36% to 99.6%); 90% (95% CI 68% to 99%). **Important Outcomes** **Treatment adherence** Treatment adherence was not formally reported. Reasons stated for discontinuing therapy were: AEs: n = 2 Progressive disease: n = 3 Proceeded to SCT: n=12 Refused further treatment: n=2 Refused treatment in study but continued commercial crizotinib: n=2 Failure to meet protocol criteria to continue: n=1 Noncompliance: n=1 Lost to follow-up: n = 1 **Safety**	1. Yes 2. Yes 3. Unclear 4. Unclear 5. Unclear 6. Yes 7. Yes 8. Yes 9. No 10. Yes **Other comments:** Sixteen of the 26 ALCL patients in this study had initially been recruited to a phase I dose escalation study in which they had received crizotinib treatment at either 165mg/m^2 or 280mg/m^2 twice daily. The 10 additional patients recruited for the phase II study were all treated at 280mg/m^2 twice daily. Inclusion criteria were clearly defined but no exclusion criteria were described; it was not clear if recruitment of patients to this study was consecutive and complete. All subjects were aged less than 21 years; the median age of the 165mg/m^2 group was 5.9 years, and of the 280mg/m^2 group was 12.2 years; both groups had a majority of male subjects. Duration of follow-up was not reported. Treatment response was assessed at treatment sites but no

[14] 16 (62%) of the ALCL patients had been recruited through a phase I dose escalation trial
[15] Response was assessed at treatment sites; response was then evaluated using the Lugano Classification applied during central review as a retrospective scoring of response
[16] Objective response was calculated from complete response + partial response

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Age at enrolment (years) • Median: 5.9; 12.2 • Range: 3.7 to 13.4; 6.1 to 20.8 *Male*: 83%; 65% *Race* • White: 67%, 50% • Black: 0%, 25% • Asian: 17%, 5% • Unknown: 17%, 20% *Number of prior therapies (% of subjects)*: • 0: 0%; 0% • 1-2: 83%; 80% • 3-4: 0%; 10% • 5-6: 17%; 10% *Previous therapies, n (%)* Chemotherapy; 6 (100%); 20 (100%) Radiotherapy: 0 (0%); 1 (5%) Stem-cell transplant: 1 (17%); 1 (5%) Surgery: 1 (17%); 1 (5%) Brentuximab: 0 (0%); 1 (5%) MoAb NOS: 1 (17%); 2 (10%)		*Adverse Events (AEs)*[17] AE: treated with crizotinib 165mg/m^2 (n=6); treated with crizotinib 280mg/m^2 (n=20) At least one grade 3 or 4 AE: 83%; 100% Grade 3 or 4 AEs that were possibly, probably, or definitely related to the study drug: 33%; 85%, At least one neutrophil count decrease: 33%; 70%	further details were provided. It was not stated that assessors were blinded, leading to potential bias in the assessment of more subjective outcomes. The authors stated that F-FDG PET/CT imaging was performed at the treating institutions' discretion. Response was retrospectively evaluated centrally using the Lugano classification which has criteria based on the findings from various imaging modalities to evaluate response. The authors reported that there was concordance between central review and site evaluation of response in 20 patients; the remaining six differed by one category (ie. between CR and PR or between PR and SD) and the central assessment was used in the analysis. **Source of funding:** The authors stated that the study was supported by a Children's Oncology Group phase I Consortium Grant from the National Cancer Institute (CA097452), Pfizer Inc and Cookies for Kids Cancer Foundation. Two authors reported research funding from pharmaceutical companies, two reported stock ownership and employment from pharmaceutical companies, and three reported reimbursement from pharmaceutical companies for speaking, travel, accommodations and expenses.

[17] Classified according to CTCAE version 4.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Abbreviations ALAT: Alanine Transaminase; ALCL: anaplastic large cell lymphoma; ALK : anaplastic lymphoma kinase; allo-SCT: allogeneic hematopoietic stem-cell transplantation; ASAT: Aspartate Aminotransferase; CI: confidence interval, c-MET: Mesenchymal-Epithelial Transition factor; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group (performance status); HSCT: haematopoetic stem cell transplant; IMT: inflammatory myofibroblastic tumour; MoAb NOS: monoclonal antibody not otherwise specified; NSCLC: Non-small cell lung cancer; RECIST: Response evaluation criteria in solid tumors; SCT: stem cell transplant; WBC: white blood cell				

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series?
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

Appendix G GRADE profiles

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Crizotinib**	**Comparator**	**Result**		
Response to treatment (3 single-arm studies)									
Best overall response (BOR)[A], 8 weeks after treatment initiation; n									
1 single-arm study Brugières et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	24	0	• Complete response: 9/24 • Partial response: 7/24	Critical	Very Low
Best overall response (BOR)[A], over duration of treatment (median treatment duration 3.7 months (range 0.37 to 47.2 months)); n									
1 single-arm study Brugières et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	24	0	• Complete response: 12/24 • Partial response: 4/24	Critical	Very Low
Best overall response (BOR)[B], duration of follow-up not stated; %									
1 single-arm study Gambacorti-Passerini et al 2018	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	17	0	BOR: • Complete: 47.1% • Partial: 5.9% • Stable Disease: 17.6% • Objective Progression: 17.6% • Early Death: 5.9% • Indeterminate: 5.9%	Critical	Very Low
Best overall response (BOR)[C], duration of follow-up not stated; n (%)									
1 single-arm study Mossé et al 2017	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	26	0	BOR: crizotinib 165mg/m^2 (n=6): • Complete: 5 (83%) • Partial: 0 (0%) • Stable Disease: 1 (17%) • Progressive Disease: 0 (0%) crizotinib 280mg/m^2 (n=20): • Complete: 16 (80%) • Partial: 2 (10%) • Stable Disease: 2 (10%) • Progressive Disease: 0 (0%)	Critical	Very Low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Crizotinib**	**Comparator**	**Result**		
Objective response rate (ORR), 8 weeks after treatment initiation; n (%)									
1 single-arm study Brugières et al 2023	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	24	0	ORR: 67% (95% CI 47% to 82%)	Critical	Very Low
Objective response rate (ORR), duration of follow-up not stated; n (%)									
1 single-arm study Gambacorti-Passerini et al 2018	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	17	0	ORR: 52.9% (95% CI 27.8% to 77%)	Critical	Very Low
1 single-arm study Mossé et al 2017	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	26	0	ORR: • crizotinib 165mg/m^2 (n=6): 83% (95% CI 36% to 99.6%); • crizotinib 280mg/m^2 (n=20): 90% (95% CI 68% to 99%).	Critical	Very Low
Duration of response (DOR), median follow-up 45 months (95% CI 28 to 50.9 months); months									
1 single-arm study Brugières et al 2023	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	16	0	Median DOR: 43.4 months (95% CI 8.3 months to not reached)	Critical	Very Low
Duration of response (DOR), duration of follow-up not stated; weeks									
1 single-arm study Gambacorti-Passerini et al 2018	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	9	0	Median DOR: 135.9 weeks (range: 6 to 205.9 weeks)	Critical	Very Low
Progression-free survival (2 single-arm studies)[D]									
3-year progression-free survival, median follow-up 45 months (95% CI 28 to 50.9 months); %									
1 single-arm study	Very serious limitations[5]	Serious indirectness[2]	Not applicable	Not calculable	25	0	40% (95% CI 23% to 59%)	Critical	Very Low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Crizotinib	Comparator	Result		
Brugières et al 2023									
Median progression-free survival, median follow-up 45 months (95% CI 28 to 50.9 months); months									
1 single-arm study Brugières et al 2023	Very serious limitations[5]	Serious indirectness[2]	Not applicable	Not calculable	25	0	Median PFS: 11.0 months (95% CI 1.7 to 47.6 months)	Critical	Very Low
2-year progression-free survival, duration of follow-up not reported; %									
1 single-arm study Gambacorti-Passerini et al 2018	Very serious limitations[5]	Serious indirectness[2]	Not applicable	Not calculable	17	0	63% (95% CI 35.3% to 81.4%)	Critical	Very Low
Overall survival (1 single-arm study)									
3-year overall survival, median follow-up 45 months (95% CI 28 to 50.9 months); %									
1 single-arm study Brugières et al 2023	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	24	0	63% (95% CI 43% to 79%)	Critical	Very Low
Treatment adherence (2 single-arm studies)									
Reasons for stopping treatment, median follow-up 45 months (95% CI 28 to 50.9 months); n									
1 single-arm study Brugières et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	24	0	Disease progression: n=8 Toxicity related to former allo-SCT: n=2 Switched to another treatment: n=13 Stopped without any further treatment: n=2	Critical	Very Low
Reasons for stopping treatment, duration of follow-up not stated; n									
1 single-arm study Mossé et al 2017	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	26	0	AEs: n = 2 Progressive disease: n = 3 Proceeded to SCT: n=12 Refused further treatment: n=2	Critical	Very Low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Crizotinib	Comparator	Result		
							Refused treatment in study but continued commercial crizotinib: n=2 Failure to meet protocol criteria to continue: n=1 Noncompliance: n=1 Lost to follow-up: n = 1		
Safety (3 single-arm studies)									
Treatment-related adverse events (AEs) (3 single-arm studies)[E]									
Treatment-related adverse events (AEs), median follow-up 45 months (95% CI 28 to 50.9 months); n (%)									
1 single-arm study Brugières et al 2023	Very serious limitations[6]	Serious indirectness[2]	Not applicable	Not calculable	24	0	Most common grade 3 or 4 AEs: Neutropaenia: 8 (32%) Anaemia: 5 (20%) Lymphopaenia: 3 (12%) Most common grade 1 to 4 AEs: ALAT increase: 18 (72%) Anaemia: 17 (68%) Lymphopaenia: 16 (64%) Neutropaenia: 14 (56%) Leucopaenia: 14 (56%) Nausea: 12 (48%) ASAT increase: 12 (48%) Fatigue: 11 (44%) Diarrhoea: 11 (44%) Alkaline phosphatases increase: 10 (40%)	Important	Very Low
Treatment-related adverse events (AEs), duration of follow-up not stated; n (%)									
1 single-arm study Gambacorti-Passerini et al 2018	Very serious limitations[6]	Very serious indirectness[4]	Not applicable	Not calculable	44[F]	0	AEs were reported for all study patients combined • Any AE: 39 (88.6%) • Grade 3: 16 (36.4%) • Grade 4: 6 (13.6%) • Grade 5: 2 (4.5%) The commonest AEs (all grades) were: • Diarrhoea: 20 (45.5%)	Important	Very Low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Crizotinib	Comparator	Result		
							• Vision disorder: 20 (45.5%) • Nausea: 17 (38.6%) • Elevated transaminases: 15 (34.1%) • Vomiting: 15 (34.1%) • Neutropaenia: 14 (31.8%)		
1 single-arm study Mossé et al 2017	Very serious limitations[6]	Serious indirectness[2]	Not applicable	Not calculable	26	0	crizotinib 165mg/m^2 (n=6); • At least one grade 3 or 4 AE: 83% • Grade 3 or 4 AEs that were possibly, probably, or definitely related to the study drug: 33% • At least one neutrophil count decrease: 33% crizotinib 280mg/m^2 (n=20) • At least one grade 3 or 4 AE: 100% • Grade 3 or 4 AEs that were possibly, probably, or definitely related to the study drug: 85% • At least one neutrophil count decrease: 70%	Important	Very Low

Abbreviations
AE: Adverse Event; ALAT: Alanine Transaminase; ALCL: anaplastic large cell lymphoma; ALK: anaplastic lymphoma kinase; allo-SCT: allogeneic hematopoietic stem-cell transplantation; ASAT: Aspartate aminotransferase; BOR: Best Overall Response; CI: confidence interval, c-MET: Mesenchymal-Epithelial Transition factor, CTCAE: Common Terminology Criteria for Adverse Events; DOR: Duration of Response; n: number; ORR: Objective Response Rate; OS: Overall Survival; PFS: Progression-free Survival; RECIST: Response evaluation criteria in solid tumours

1 Risk of bias: very serious limitations due to unclear reporting of study participants (in relation to non-consecutive and incomplete inclusion) and lack of statistical analysis or summary statistic
2 Indirectness: serious indirectness due to lack of comparator group
3 Risk of bas: serious limitations due to unclear reporting of study participants (in relation to non-consecutive and incomplete inclusion)
4 Indirectness: very serious indirectness due to lack of comparator group and inclusion of patients in this outcome who did not meet the PICO definition because they did not have ALCL
5 Risk of bias: very serious limitations due to unclear reporting of study participants (in relation to non-consecutive and incomplete inclusion) and lack of blinding of patients and assessors
6 Risk of bias: very serious limitations due to unclear reporting of study participants (in relation to non-consecutive and incomplete inclusion), lack of statistical analysis or summary statistic and lack of blinding of patients and assessors

A Response to treatment in Brugières et al 2023 based on RECIST 1.1 criteria for conventional imaging or according to the Lugano criteria in patients evaluated by FDG-PET/CT
B Response to treatment in Gambacorti-Passerini et al 2018 based on RECIST 1.1 criteria
C Response to treatment in Mossé et al 2017 based on the Lugano criteria

D Survival calculated using the Kaplan-Meier method
E Adverse events classified according to CTCAE version 4
F This group included n=18 patients with ALCL and n=26 with other malignancies

Glossary

Term	Definition
Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether or not the event is suspected to be related to or caused by the drug, treatment or intervention.
Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias.
Case series	Reports of several patients with a given condition, usually covering the course of the condition and the response to treatment. There is no comparison (control) group of patients.
Clinical importance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals.
Confidence interval (CI)	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
Minimal clinically important difference	The smallest change in a treatment outcome that people with the condition would identify as important (either beneficial or harmful), and that would lead a person or their clinician to consider a change in treatment.
Objective measure	A measurement that follows a standardised procedure which is less open to subjective interpretation by potentially biased observers and people in the study.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results

Term	Definition
	occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.

References

Included studies

- Brugières L, Cozic N, Houot R, Rigaud C, Sibon D, Arfi-Rouche J, Bories P, Cottereau AS, Delmer A, Ducassou S, Garnier N, Lamant L, Leruste A, Millot F, Moalla S, Morschhauser F, Nolla M, Pagnier A, Reguerre Y, Renaud L, Schmitt A, Simonin M, Verschuur A, Hoog Labouret N, Mahier Ait Oukhatar C, Vassal G. Efficacy and safety of crizotinib in ALK-positive systemic anaplastic large-cell lymphoma in children, adolescents, and adult patients: results of the French AcSé-crizotinib trial. Eur J Cancer. 2023 Sep;191:112984. doi: 10.1016/j.ejca.2023.112984. Epub 2023 Jul 17. PMID: 37549532.
- Gambacorti-Passerini C, Orlov S, Zhang L, Braiteh F, Huang H, Esaki T, et al. Long-term effects of crizotinib in ALK-positive tumors (excluding NSCLC): A phase 1b open-label study. American Journal of Hematology. 2018;93(5):607-14.
- Mossé YP, Voss SD, Lim MS, Rolland D, Minard CG, Fox E, et al. Targeting ALK With Crizotinib in Pediatric Anaplastic Large Cell Lymphoma and Inflammatory Myofibroblastic Tumor: A Children's Oncology Group Study. Journal of Clinical Oncology. 2017;35(28):3215-21.

NHS England
Wellington House
133-155 Waterloo Road
London
SE1 8UG