NHS England Evidence Review:

Crizotinib for individuals with anaplastic lymphoma kinase-positive (ALK-positive) unresectable inflammatory myofibroblastic tumour (IMT)

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Crizotinib for individuals with anaplastic lymphoma kinase-positive (ALK-positive) unresectable inflammatory myofibroblastic tumour (IMT)

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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) unresectable inflammatory myofibroblastic tumours (IMTs).

IMT is a very rare type of tumour that can form on mucosal surfaces (such as in the eyes, mouth and lungs) and mesentery (which connects the organs in the abdomen). In ALK-positive IMT, the cancerous cells have a mutation in which they produce a protein called ALK on their surface. The ALK mutation drives the abnormal growth of cancer cells and can be detected using tests.

Crizotinib is an ALK inhibitor (blocker) which targets the ALK mutation found in ALK-positive IMT. Crizotinib is taken orally.

IMTs are considered resistant to conventional chemotherapy and radiation; therefore, surgical resection is the main treatment. For some patients, surgical resection is not possible due to tumour proximity to vital organs or in people with advanced disease at diagnosis (unresectable IMT). Patients with unresectable IMT are currently offered chemotherapy, systemic corticosteroid therapy or treatment with non-steroidal anti-inflammatory drugs to relieve symptoms.

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) unresectable inflammatory myofibroblastic tumours (IMTs). 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 IMT or ALK-positive relapsed or refractory anaplastic large cell lymphoma (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 recurrent or refractory ALCL were included in a separate evidence review.

Three studies, reported in four papers, were identified for inclusion in this review. One paper describes a retrospective case series (Liu et al 2023), one a single-arm trial (Mossé et al 2017) and two papers report on the same phase II clinical trial (CREATE; Schöffski et al 2018 and Schöffski et al 2021). No comparator evidence was identified.

The studies included between 14 and 18 patients with ALK-positive IMT; two (Liu et al 2023 and Schoffski et al 2018 and 2021) included adults only and one (Mossé et al 2017) included children only. Schoffski et al (2018 and 2021) reported outcomes at a median follow-up of 50 months; duration of follow-up was not reported for most outcomes in the other two studies. Liu et al (20230 was conducted in Shanghai, China, Mossé et al (2017) across multiple sites in the United States, and Schoffski et al (2018 and 2021) was part of a multi-site phase II clinical trial across eight European countries including the UK.

No cost effectiveness evidence was identified.

In terms of clinical effectiveness:

- **Response to treatment (critical outcome).** A single-arm trial provided very low certainty evidence of an objective response rate of 67% and a disease control rate of 100% at a median 50 months follow-up. Two studies (a single-arm trial and a retrospective case series) provided very low certainty evidence of an objective response rate to crizotinib of at least 80% at unspecified duration of follow-up. Two single arm trials reported a best treatment response of no patients with progressive disease following treatment with crizotinib, at median 50 months follow-up and an unspecified duration of follow-up, whilst 12.5% of patients in a retrospective case series had progressive disease at an unspecified duration of follow-up; all three studies provided very low certainty evidence. A single-arm trial reported very low certainty evidence that all patients with a response to crizotinib responded within the first 12 weeks of treatment (median time to first response: 28.5 days). No results were compared statistically to baseline.
- **Progression free survival (critical outcome).**One retrospective case series provided very low certainty evidence of a 12-month progression-free survival rate of 78% after a median of 23 months follow-up (p-values were not reported for any of the progression-free survival rates). One single-arm trial provided very low certainty evidence of a progression-free survival rate of 58% at 12 months and 42% at 24 and 36 months following a median of 19 months of crizotinib treatment at a median of 50 months follow-up. The included studies provided very low certainty evidence of a median progression-free survival in the range of 18-21 months following crizotinib treatment for adults with unresectable IMT; these estimates were not statistically significant. One study reported

that after a median 50 months of follow-up 42% of study participants were alive with no disease progression.

- **Overall survival (critical outcome).** One single-arm trial provided very low certainty evidence of an overall survival rate of 83% at 12, 24 and 36 months at a median 50 months follow-up. The same single-arm trial reported that after a median 50 months follow-up, three study participants died. Two of the deaths were directly linked to IMT. One retrospective case series provided very low certainty evidence of a 24-month overall survival rate of 71% (p-values were not reported for any of the overall survival rates).
- **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.
- **Hospitalisation (important outcome).** No evidence was identified for hospitalisation.
- **Treatment adherence (importance outcome).** One single-arm trial provided very low certainty evidence that the majority of children with unresectable IMT treated with crizotinib adhered to treatment**.**

In terms of safety:

- **Adverse events.** All three included studies provide very low certainty evidence that many patients with unresectable IMT reported adverse events during crizotinib treatment. A single-arm trial in a paediatric population reported that 57% of participants reported serious adverse events. Two studies (one single-arm trial and one retrospective case series) reported few serious adverse events (Grade 3-4 AEs) in their adult populations; all outcomes were of very low certainty.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- No evidence was identified regarding any subgroups of patients that would benefit more from treatment with crizotinib.

In terms of crizotinib dose:

- Evidence about crizotinib doses came from two single-arm trials and one retrospective case series.
- One single-arm trial and one prospective case series treated adult patients with 250 mg of crizotinib, twice daily. One single-arm, dose-escalation trial treated children with unresectable IMT using three dosing regimens: 100 mg/m^2, 165 mg/m^2 or 280 mg/m^2. Each dose was given twice daily.

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 14 and 20 relevant subjects, and had an increased risk of selection bias and Type I errors due to the study design. Selection bias can impact the generalisability of the results to the wider population. Limitations reducing certainty for the outcomes in the single-arm trials (Mossé et al 2017 and Schöffski et al 2018 and 2021) included uncertainty about whether the inclusion of participants was complete or consecutive and in the retrospective case series (Liu et al 2023) there was uncertainty about the direct relevance of the population selected, particularly about whether the included participants all had unresectable IMT. One single-arm trial (Schöffski et al 2018 and 2021) included both ALK-positive and ALK-negative patients when reporting adverse events, leading to uncertainty about the direct relevance of the population. 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 more subjective outcomes across all three studies.

Conclusion

This evidence review includes two single-arm trials and one retrospective case series, each with between 12 and 16 subjects with unresectable IMT who were treated with crizotinib. Two studies included only adults (one single-arm trial, one retrospective case series) and one study focused on children (one single-arm trial).

All of the studies provided non-comparator data and the evidence for all the outcomes of interest was of very low certainty.

Evidence was available for crizotinib use in patients with unresectable IMT for all the critical outcomes of interest. Between 67% and 86% of patients across the three studies had a complete or partial response to treatment with crizotinib. In the two single-arm trials no patients reported progressive disease following crizotinib treatment while in the retrospective case series two out of 16 patients had progressive disease. The 12-month progression-free survival (PFS) rate was greater than 50% across two studies and the 24- and 36-month PFS was 42% in one study. The median PFS was 18-21 months. The overall survival rate was estimated to be 83% at 36 months in one single arm study, and 71% at 24 months in the retrospective case series. All progression-free and overall survival data were only available for adult populations; no p-values or minimal clinically important differences were reported.

Data were available for the important outcome of treatment adherence.. One single-arm trial reported that two patients ceased crizotinib therapy due to non-compliance during treatment; no further details were reported. No evidence was available for the other specified important outcomes of quality of life, activities of daily living and hospitalisation.

Safety outcomes, in the form of adverse events (AEs), were reported for those receiving crizotinib therapy; most patients reported adverse events during crizotinib treatment. Two studies (one single-arm trial and one retrospective case series) reported few serious adverse events (Grade 3-4 AEs) in their adult populations but a single-arm trial in a paediatric population reported that 57% of participants reported serious adverse events.

No evidence was identified regarding any subgroups of patients that would benefit more from treatment with crizotinib.

No evidence on cost effectiveness was identified.

Although all the studies provided very low certainty evidence on the outcomes, there was 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 unresectable IMT respond to treatment with crizotinib, and that for 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.

3. Methodology

Review questions

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

1. In people with ALK-positive unresectable IMT what is the clinical effectiveness of crizotinib compared with standard care?
2. In people with ALK-positive unresectable IMT, what is the safety of crizotinib compared with standard care?
3. In people with ALK-positive unresectable IMT 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?

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 15 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 studies, reported in four papers, were identified for inclusion (Liu et al 2023, Mossé et al 2017, Schöffski et al 2018 and Schöffski et al 2021). One paper describes a retrospective case series (Liu et al 2023), one a single-arm trial (Mossé et al 2017) and two papers report on the same phase II clinical trial (CREATE; Schöffski et al 2018 and Schöffski et al 2021). Two of the studies focussed on adult patients and one study focussed on paediatric patients. No comparator evidence was 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

Liu et al 2023
 	
Retrospective case series
 	
Shanghai, China
	16 adults with advanced, ALK-positive IMT
	
	• Median age: 28 years (range 21 to 74 years)
	• Male: 4 (25.0%)
	
	No subgroups reported
		Intervention
		
		Oral crizotinib, 250mg, twice daily
		
		Comparison
		
		• No comparator
			Duration of follow-up not reported unless otherwise stated
			
			Critical outcomes
			• Response to treatment
			  ○ Treatment response evaluated by RECIST[a]
			  ○ Objective Response Rate (ORR) and Disease Control Rate (DCR)[b]
			• Progression-free survival at median follow-up of 23 months (95% CI 16.5 to 29.5 months), (PFS)
			  ○ 12-month PFS
			  ○ Median PFS, months
			• Overall survival (OS)
			  ○ 24-month OS
			  ○ Median OS, months
			
			Important Outcomes
			
			• Safety
			  ○ Adverse events (AEs)[c]

Mossé et al 2017
 	
Single-arm trial
 	
Multi-centre, US
	14 children with unresectable, ALK-positive IMT
	
	• Median age: 7.0 years (range 2.0 to 13.5 years)
	• Male: 5 (36%)
	
	• Race, n (%)
	  ○ White: 10 (71%)
	  ○ Black: 1 (7%)
	  ○ Asian: 0 (0%)
	  ○ unknown: 3 (21%)
	
	No subgroups reported
		Intervention
		
		Oral crizotinib
		
		Three dosing levels, twice daily:
		• 100mg/m2
		• 165mg/m2
		• 280mg/m2
		
		Comparison
		
		No comparator
			Duration of follow-up not reported
			
			Critical outcomes
			• Response to treatment
			  ○ Best treatment response evaluated by RECIST
			  ○ Objective Response Rate (ORR)
			  ○ Time to first PR/CR, days and weeks
			
			Important Outcomes
			
			• Treatment adherence
			• Safety
			  ○ Adverse events (AEs)[c]
			  ○ Specific AEs

Schöffski et al 2021 Single-arm trial	12 adults with advanced or metastatic, ALK-positive, IMT deemed incurable by surgery,	**Intervention** Oral crizotinib, 250mg, twice daily	Schöffski et al 2021: Outcomes reported at median follow-up of 50 months; median treatment

Study	Population	Intervention and comparison	Outcomes reported

Schöffski et al 2018 reports additional AE data
 	
Multi-centre (13 sites) in eight European countries
	radiotherapy or systemic therapy
	
	• Median age: 35.5 years (IQR 27.0 to 55.5 years)
	• Male: 6 (50%)
	
	No subgroups reported
		Comparison
		
		No comparator
			duration 18.8 months (range 3.4 to 77.5 months)
			
			Schöffski et al 2018: AEs reported at median follow-up of 863 days (IQR 358 to 1304 days)
			
			Critical outcomes
			• Response to treatment
			  ○ Best treatment response evaluated by RECIST
			  ○ Objective Response Rate (ORR) and Disease Control Rate (DCR)
			• Progression-free survival (PFS)
			  ○ PFS at 12, 24 and 36 months
			  ○ No. of patients alive, with no progression
			  ○ Median PFS, months
			• Overall survival (OS)
			• OS at 12, 24 and 36 months
			  ○ No. of patients that died
			  ○ No. of patients that died due to IMT
			  ○ Median OS, months
			
			Important Outcomes
			
			• Safety
			  ○ Adverse events (AEs)[d]
			  ○ Specific AEs
			  ○ Specific AEs by Grade

Abbreviations

AE: adverse events; ALK: anaplastic lymphoma kinase; CI: confidence interval; CR: complete response; CTCAE: Common Terminology Criteria for Adverse Events; DCR: disease control rate; IMT: inflammatory myofibroblastic tumour; IQR: interquartile range; m: metre; mg: milligram; No.: number; ORR: objective response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumours; SD: stable disease; v: version; US: United States

[a] RECIST: Response Evaluation Criteria in Solid Tumours (ver 1.1). This uses defined criteria to categorise the treatment response as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD)

[b] Objective response rate (ORR). This composite measure was calculated as CR + PR. Disease control rate (DCR). This composite measure was calculated as CR + PR + SD

[c] Adverse events were assessed according to the National Cancer Institute-Common Terminology Criteria for Adverse Events v4.0

[d] Adverse events were assessed according to the International Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

5. Results

In people with ALK-positive unresectable IMT, 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 (two single-arm trials and one retrospective case series) provided evidence relating to response to treatment with crizotinib. All results were compared to baseline. *Best treatment response* **At a median 50 months follow-up**: • One single-arm trial (Schöffski et al 2021) (n=12) reported that two participants demonstrated a complete response, six demonstrated a partial response, four demonstrated stable disease and no participants had progressive disease when evaluated using the RECIST v1.1 criteria[1] following treatment with crizotinib (CR: 16.7%, PR: 50.0%, SD: 33.3%, PD: 0.0%). The results were not compared statistically. **(VERY LOW)** **At unspecified duration of follow-up**: • One single-arm trial (Mossé et al 2017) (n=14) reported that best treatment response was complete response for five patients, partial response for seven patients and stable disease for two patients when evaluated using the RECIST criteria (CR: 36%, PR: 50%, SD: 14%, PD: 0%) following a median of 19.57 months of crizotinib therapy. The results were not statistically compared. **(VERY LOW)** • One retrospective case series (Liu et al 2023) (n=16) reported that three participants demonstrated a complete response, ten demonstrated a partial response, one demonstrated stable disease and two participants had progressive disease evaluated using the RECIST criteria following treatment with crizotinib (CR: 18.8%, PR: 62.5%, SD: 6.3%, PD: 12.5%). The results were not compared statistically **(VERY LOW)** *Objective response rate/ disease control rate* **At a median 50 months follow-up**: • One single-arm trial (Schöffski et al 2021) (n=12) reported that all patients had a response to crizotinib treatment (DCR[2]: 100% (95% CI 73.5% to 100%)) and 67% had an objective response to treatment (ORR[3]: 66.7% (95% CI 21.1% to 78.9%)); p-values were not reported. **(VERY LOW)** **At unspecified duration of follow-up**: • One single-arm trial (Mossé et al 2017) (n=14) reported an ORR to crizotinib of 86% (95% CI 57% to 98%, p-value not reported) following a median of 19.57 months of oral therapy. Statistical significance was not reported. **(VERY LOW)** • One retrospective case series (Liu et al 2023) (n=16) reported an ORR of 81.3% and a DCR of 87.5%. The results were not compared statistically **(VERY LOW)**

[1] RECIST: Response Evaluation Criteria in Solid Tumours (v1.1). This uses defined criteria to categorise the treatment response as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD).
[2] Disease control rate (DCR): this composite measure was calculated as CR + PR + SD.
[3] Objective response rate (ORR): this composite measure was calculated as CR + PR.

Outcome	Evidence statement
	Time to first response **At unspecified duration of follow-up**: • One single-arm trial (Mossé et al 2017) (n=14) reported that the median time to first response to crizotinib was 28.5 days (95% CI 27 to 134 days). The majority of participants had a response within the first four weeks (n=7, 58%), 75% within the first eight weeks (response at eight weeks, n=2, 17%) and 100% within 12 weeks (response at 12 weeks, n=3, 25%). **(VERY LOW)** **A single-arm trial provided very low certainty evidence of an objective response rate of 67% and a disease control rate of 100% at a median of 50 months follow-up. Two studies (a single-arm trial and a retrospective case series) provided very low certainty evidence of an objective response rate to crizotinib of at least 80% at unspecified duration of follow-up. Two single-arm trials reported a best treatment response of no patients with progressive disease following treatment with crizotinib, at median 50 months follow-up and an unspecified duration of follow-up, whilst 12.5% of patients in a retrospective case series had progressive disease at an unspecified duration of follow-up; all three studies provided very low certainty evidence. A single-arm trial reported very low certainty evidence that all patients with a response to crizotinib responded within the first 12 weeks of treatment (median time to first response: 28.5 days). No results were compared statistically to baseline.**
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 (one single-arm trial and one retrospective case series) provided evidence relating progression-free survival (PFS). Both estimated survival using the Kaplan-Meier method. **At a median 23 months follow-up:** • One retrospective case series (Liu et al 2023) (n=16) reported a 12-month PFS of 78.1% (95% CI 63.0% to 93.2%). **(VERY LOW)** • One retrospective case series (Liu et al 2023) (n=16) reported a median PFS of 20.8 months (95% CI unreached); this result was *not statistically significant*. **(VERY LOW)** **At a median 50 months follow-up**: • One single-arm trial (Schöffski et al 2021) (n=12) reported a 12-month PFS of 58.3% (95% CI 27.0% to 80.1%), a 24-month PFS of 41.7% (95% CI 15.2% to 66.5%) and a 36-month PFS of 41.7% (95% CI 15.2% to 66.5%) following a median of 18.8 months of crizotinib treatment (range 3.4 to 77.5 months). **(VERY LOW)** • One single-arm trial (Schöffski et al 2021) (n=12) reported a median PFS of 18.0 months (95% CI 4.0 months to not evaluable) following a median of 18.8 months of crizotinib treatment (range 3.4 to 77.5 months); this result was *not statistically significant*. **(VERY LOW)** • One single-arm trial (Schöffski et al 2021) (n=12) reported that following a median of 18.8 months of crizotinib treatment (range 3.4 to 77.5 months), 41.7% of patients in the study were alive with no disease progression. These results were not statistically compared with baseline. **(VERY LOW)** **One retrospective case series provided very low certainty evidence of a 12-month progression-free survival rate of 78% after a median of 23 months follow-up (p-values were not reported for any of the progression-free survival rates). One single-arm trial provided very low certainty evidence of a progression-free survival rate of 58% at 12 months and 42% at 24 and 36 months following a median of 19 months of crizotinib treatment at a median**

Outcome	Evidence statement
	of 50 months follow-up. The included studies provided very low certainty evidence of a median progression-free survival in the range of 18-21 months following crizotinib treatment for adults with unresectable IMT; these estimates were not statistically significant. One study reported that after a median 50 months of follow-up 42% of study participants were alive with no disease progression.
Overall survival **Certainty of evidence:** Very low	Overall survival is important to patients as individuals with ALK-positive unresectable IMT 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, two studies (one single-arm trial and one retrospective case series) provided evidence relating to overall survival (OS). Both estimated survival using the Kaplan-Meier method. **At a median 50 months follow-up**: • One single-arm trial (Schöffski et al 2021) (n=12) reported a 12-month, 24-month and 36-month OS of 83.3% (95% CI 48.2% to 95.6%) following a median of 18.8 months of crizotinib treatment (range 3.4 to 77.5 months). **(VERY LOW)** • One single-arm trial (Schöffski et al 2021) (n=12) reported that three patients died, two of whom died due to IMT. These results were not compared statistically. **(VERY LOW)** **At unspecified duration of follow-up**: • One retrospective case series (Liu et al 2023) (n=16) reported a 24-month OS of 70.7% (95% CI 58.1% to 83.3%). **(VERY LOW)** **One single-arm trial provided very low certainty evidence of an overall survival rate of 83% at 12, 24 and 36 months at a median 50 months follow-up. The same single-arm trial reported that after a median 50 months follow-up, three study participants died. Two of the deaths were directly linked to IMT. One retrospective case series provided very low certainty evidence of a 24-month overall survival rate of 71% (p-values were not reported for any of the overall survival rates).**
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.**
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 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, one single-arm trial provided evidence relating to treatment adherence. Narrative data was provided from this study.

Outcome	Evidence statement
	• One single-arm trial (Mossé et al 2017; n=14) reported that two patients ceased crizotinib therapy during the study period (median treatment duration 19.57 months) due to non-compliance (15%). **(VERY LOW)** **One single-arm trial provided very low certainty evidence that the majority of children with unresectable IMT treated with crizotinib adhered to treatment.**
Safety	
Adverse events **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 (two single-arm trials and one retrospective case series) provided evidence relating to adverse events (AEs). All results were compared to baseline. **At a median 863 days follow-up**: • One single-arm trial (Schöffski et al 2018) (n=20)[4] reported that the majority of the AEs[5] reported by the adults in their study were Grade 1 or 2 (Grade 1: n=9, 45%; Grade 2: n=6, 30%; Grade 3: n=2, 10%; Grade 4: n=1, 5%). **(VERY LOW)** **At a median 50 months follow-up**: • One single-arm trial (Schöffski et al 2021) (n=20)[6] reported that the most common AEs were increased SGPT (13 events), hypocalcaemia (14 events), increased SGOT (13 events), and nausea (11 events). **(VERY LOW)** **At unspecified duration of follow-up**: • One single-arm trial (Mossé et al 2017) (n=14) provided details on Grade 3-4 adverse events[7] experienced by patients who received crizotinib. A total of 71% of children in their study reported at least one Grade 3-4 AE; 57% of patients experienced Grade 3-4 AEs which were considered possibly, probably or definitely related to crizotinib. Four patients discontinued crizotinib therapy due to AEs. **(VERY LOW)** • One retrospective case series (Liu et al 2023) (n=16) reported that no patients at their hospital experienced Grade 3-4 AEs.[8] One patient had a crizotinib dose reduction due to AEs (6.3%). The most common Grade 1-2 AEs were fatigue, nausea, diarrhoea and rash. **(VERY LOW)** • One single-arm trial (Mossé et al 2017) (n=14) reported that the most common AEs were a decreased neutrophil count (6 patients, 28 events), diarrhoea (1 patient, 1 event), lower limb oedema (1 patient, 1 event), and sinus bradycardia (1 patient, 1 event). **(VERY LOW)** **All three included studies provide very low certainty evidence that many patients with unresectable IMT reported adverse events during crizotinib treatment. A single-arm trial in a paediatric population reported that 57% of participants reported serious adverse events. Two studies (one single-arm trial and one retrospective case series) reported few serious adverse events (Grade 3-4 AEs) in their adult populations; all outcomes were of very low certainty.**
Abbreviations ADL: activities of daily living; AE: adverse events; ALK: anaplastic lymphoma kinase; CI: confidence interval; CR: complete response; CTCAE: Common Terminology Criteria for Adverse Events; DCR: disease control rate; IMT: inflammatory myofibroblastic tumour; n: number; ORR: objective response rate; OS: overall survival; PD: progressive disease; PFS:	

[4] This outcome included both ALK+ and ALK- patients
[5] Adverse events were assessed according to the International Common Terminology Criteria for Adverse Events, version 4.0.
[6] This outcome included both ALK+ and ALK- patients
[7] Adverse events were assessed according to the National Cancer Institute-Common Terminology Criteria for Adverse Events v4.0
[8] Adverse events were assessed according to the National Cancer Institute-Common Terminology Criteria for Adverse Events v4.0

Outcome	Evidence statement
progression-free survival; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumours; SD: stable disease; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase; v: version	

In people with ALK-positive unresectable IMT, 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
Subgroups	**No evidence was identified regarding any subgroups of patients that would benefit more from treatment with crizotinib.**

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 two single-arm trials and one retrospective case series. • One single-arm trial (Schöffski et al 2021) (n=12) and one retrospective case series (Liu et al 2023) (n=16) treated their adult patients with oral crizotinib at a dose of 250 mg twice daily. • Mossé et al 2017 (n=14) reported on a dose-escalation trial in paediatric patients with unresectable IMT. Participants were treated with three different dosing regimens: 100 mg/m^2, 165 mg/m^2 or 280 mg/m^2 twice daily.
Abbreviations IMT: inflammatory myofibroblastic tumour; m: metre; mg: milligram; n: number	

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 unresectable IMT. 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), hospitalisation, treatment adherence and safety. Evidence on cost effectiveness was also sought.

Three studies published in four papers were identified for inclusion in this review. One paper describes a retrospective case series (Liu et al 2023), one a single-arm trial (Mossé et al 2017) and two papers report on the same phase II clinical trial (CREATE; Schöffski et al 2018 and Schöffski et al 2021). No comparator evidence or cost effectiveness evidence was identified.

Liu et al (2023) reported a retrospective case series of ALK-positive, advanced IMT patients treated with crizotinib nested within a larger cohort study of all patients with a diagnosis of IMT from a single hospital in Shanghai, China. Sixteen adults aged 21 years of age and over were analysed as part of the nested case series. Six patients were identified as having had radical surgery prior to receiving crizotinib; it is unclear if their IMT was considered unresectable at the time of enrolment in the study, therefore up to six out of the 16 included subjects may not have met the PICO definition for this review. The patients were followed for a median of 23 months for the progression-free survival outcome; duration of follow-up for other outcomes was not reported.

One single-arm trial (Mossé et al 2017) included children aged under 14 years across multiple sites in the United States. The study formed part of a dose escalation phase II clinical trial and the 14 paediatric patients were treated with three different crizotinib dosing regimens for a median duration of 1.63 years. Duration of follow-up was not reported.

The second single-arm trial was reported across two papers (Schöffski et al 2018 and Schöffski et al 2021). Schöffski et al (2018 and 2021) reported on the advanced or metastatic IMT cohort (n=12 ALK+ out of a total cohort of 20 with IMT) which is part of the larger European Organisation for Research and Treatment of Cancer (EORTC) CREATE trial; the trial is a multi-site phase II clinical trial across eight European countries: Belgium, France, Germany, Italy, the Netherlands, Poland, Slovakia and the UK. Patients, all aged over 25 years, were treated with crizotinib for a median of 18.8 months and followed for a median of 50 months.

Baseline characteristics of all patients are included in Appendix E. One single-arm trial (Schöffski et al 2021) recruited patients for all their cohorts from across eight European countries, including the UK; it is not clear from the data presented if any of the patients in the IMT cohort were from the UK. The other included studies did not include patients from the UK or Europe. It is not clear from the published data if the patients in the studies reflect the range of patients seen in clinical practice in England.

Schöffski et al (2021) reported outcomes at median 50 months follow-up and Liu et al (2023) reported survival at 23.5 months follow-up, but length of follow-up was not reported for other outcomes or for any of the findings in Mossé et al (2017). Median duration of crizotinib treatment was broadly similar in the two studies which reported it (19.57 months in Mossé et al (2017) and 18.8 months in Schöffski et al (2021)); it was not reported in Liu et al 2023.

Evidence was identified for all the critical outcomes of interest for this review, but evidence was not identified for three of the four of the important outcomes of interest: quality of life, activities of daily living (ADLs) and hospitalisation.

All three included studies used the RECIST 1.1 guidelines to evaluate the treatment response. This standardised measure uses defined criteria to categorise the response to treatment as complete response, partial response, stable disease or disease progression. Each of these terms have objective measurements that are pre-defined based primarily on imaging (CT scan, MRI or X-ray) but clinical measures or other assessments, depending on the site of the lesion, may also be used. There was limited information about how assessments were carried out and by whom, for example if they were done in a standardised and repeatable way across sites in the multicentre single arm studies.

Progression-free survival and overall survival were evaluated using Kaplan-Meier methodology, with the RECIST 1.1 guidelines being used to measure progression of disease. Narrative text was the only available evidence for the outcome 'treatment adherence,' providing limited details for this review. Additionally, some detail in the safety outcomes was reported as narrative description. The use of standardised outcome measures allows some interpretation of the level of function associated with specific scores, but it was not clear how clinically significant the changes observed were. No specific detail about what the minimal clinically important thresholds or differences might be was reported for the outcomes considered.

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 14 and 20 relevant subjects, and had an increased risk of selection bias and Type I errors due to the study design. Selection bias can impact the generalisability of the results to the wider population. Limitations reducing certainty for the outcomes in the single-arm trials (Mossé et al 2017 and Schöffski et al 2018 and 2021) included uncertainty about whether the inclusion of participants was complete or consecutive and in the retrospective case series (Liu et al 2023) there was uncertainty about the direct relevance of the population selected, particularly about whether the included participants all had unresectable IMT. One single-arm trial (Schöffski et al 2018 and 2021) included both ALK-positive and ALK-negative patients when reporting adverse events, leading to uncertainty about the direct relevance of the population. 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 more subjective outcomes across all three studies.

No evidence was identified regarding any subgroups of patients that would benefit more from treatment with crizotinib.

7. Conclusion

This evidence review includes two single-arm trials and one retrospective case series, each with between 12 and 16 subjects with unresectable IMT who were treated with crizotinib. Two studies included only adults (one single-arm trial, one retrospective case series) and one study focused on children (one single-arm trial).

All of the studies provided non-comparator data and the evidence for all the outcomes of interest was of very low certainty.

Evidence was available for crizotinib use in patients with unresectable IMT for all the critical outcomes of interest. Between 67% and 86% of patients across the three studies had a complete or partial response to treatment with crizotinib. In the two single-arm trials no patients reported progressive disease following crizotinib treatment while in the retrospective case series two out of 16 patients had progressive disease. The 12-month progression-free survival (PFS) rate was greater than 50% across two studies and the 24- and 36-month PFS was 42% in one study. The median PFS was 18-21 months. The overall survival rate was estimated to be 83% at 36 months in one single arm study, and 71% at 24 months in the retrospective case series. All progression-free and overall survival data were only available for adult populations; no p-values or minimal clinically important differences were reported.

Data were available for the important outcome of treatment adherence. One single-arm trial reported that two patients ceased crizotinib therapy due to non-compliance during treatment; no further details were reported. No evidence was available for the other specified important outcomes of quality of life, activities of daily living and hospitalisation.

Safety outcomes, in the form of adverse events (AEs), were reported for those receiving crizotinib therapy; most patients reported adverse events during crizotinib treatment. Two studies (one single-arm trial and one retrospective case series) reported few serious adverse events (Grade 3-4 AEs) in their adult populations but a single-arm trial in a paediatric population reported that 57% of participants reported serious adverse events.

No evidence was identified regarding any subgroups of patients that would benefit more from treatment with crizotinib.

No evidence on cost effectiveness was identified.

The certainty of the evidence for all of the outcomes reported was considered very low. All of the included studies presented only observed results, due to the study design, which increases the risk of selection bias and Type I errors. Limitations reducing certainty for the outcomes in the single-arm trials (Mossé et al 2017 and Schöffski et al 2021) included uncertainty about whether the inclusion of participants was complete or consecutive. In the retrospective case series (Liu et al 2023) there was uncertainty about the direct relevance of the population selected as it was unclear if the included participants all had unresectable IMT, and both Schöffski et al (2018 and 2021) papers included ALK-negative patients when reporting adverse events. All the studies were small and only one study reported longer-term follow-up data. Limited statistical analyses were reported and none of the studies included a comparator. Limitations due to the lack of blinding also reduced certainty for some of the outcomes across all three studies.

Although all the studies provided very low certainty evidence on the outcomes, there was 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 unresectable IMT respond to treatment with crizotinib, and that for 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.

Appendix A PICO document

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

1. In people with ALK-positive unresectable IMT what is the clinical effectiveness of crizotinib compared with standard care?
2. In people with ALK-positive unresectable IMT, what is the safety of crizotinib compared with standard care?
3. In people with ALK-positive unresectable IMT 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?

P –Population and Indication	Patients with ALK-positive unresectable IMT Subgroups of interest include: age
I – Intervention	Crizotinib + best supportive care [The licensed dosage of crizotinib for paediatric patients with ALCL or IMT is 280mg/m^2 orally twice daily until disease progression or unacceptable toxicity. Unlicensed dosing regimes are varied and include 150mg twice daily, 165 mg/m^2 and 280 mg/m^2. All doses are acceptable for inclusion.] [Patients will receive best supportive care alongside crizotinib. Best supportive care is defined as care aimed at controlling symptoms, including the use of analgesia, antifungals and antibiotics etc.]
C – Comparator(s)	For patients with ALK-positive unresectable IMT standard care would be any of the following options alongside best supportive care: • Chemotherapy (including but not limited to: vinblastine and low-dose methotrexate, anthracycline-based regimens, ifosfamide-based regimen, vinorelbine/vinblastine-regimen) • Systemic corticosteroid therapy • Non-steroidal anti-inflammatory drugs • Palliative care [Patients will receive best supportive care alongside comparator options.]
O – Outcomes	**Clinical Effectiveness** 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 IMT is measured using the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Other outcome measures are also acceptable. Outcomes reported 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 ALK-positive unresectable IMT 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.

<u>Important to decision-making:</u>

- **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- 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).] • **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

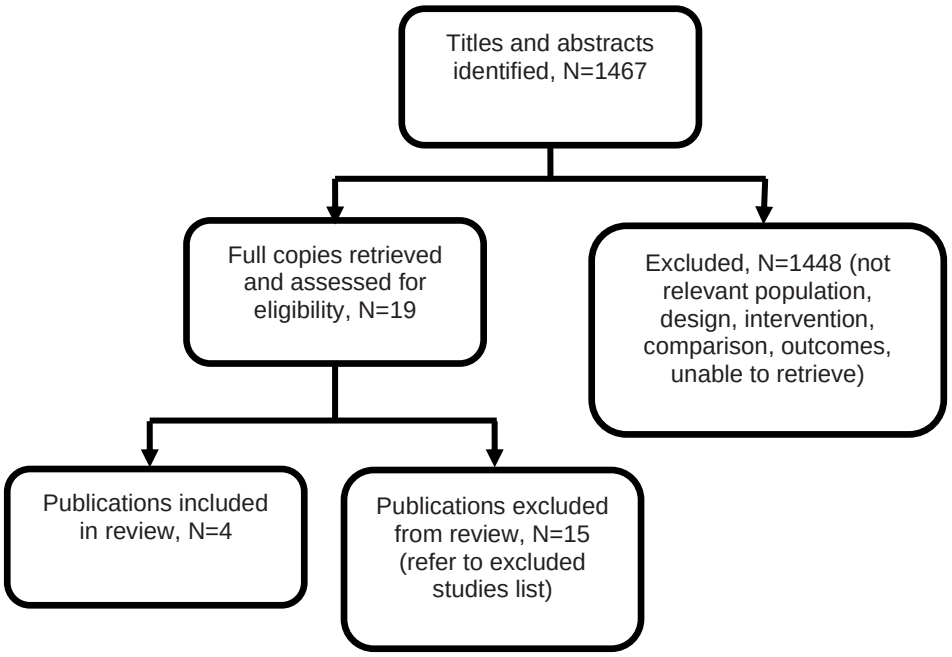
Medline search strategy:

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 IMT or ALK-positive relapsed / refractory anaplastic large cell lymphoma (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. Four references are included in this evidence summary. The remaining 15 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection
Mossé 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.	Excluded n<10, larger case series and cohort studies included. No additional outcomes were 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.	Excluded n<10, larger case series and cohort studies included. No additional outcomes were presented.

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
Brugieres L, Cozic N, Houot R, Rigaud C, Sibon D, Arfi-Rouche J, et al. Efficacy and safety of crizotinib in ALK-positive systemic anaplastic large-cell lymphoma in children, adolescents, and adult patients: results of the French AcSe-crizotinib trial. European Journal of Cancer. 2023;191:112984.	Incorrect population: no IMT patients included, only 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.	Incorrect population: no IMT patients included, only ALCL
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.	n<10, larger case series and cohort studies included. No additional outcomes were 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.	Incorrect population: no IMT patients included, only ALCL
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.	Incorrect population: no IMT patients included, only ALCL
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
Mossé 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	n<10, larger case series and cohort studies included. No additional outcomes were presented.

Study reference	Reason for exclusion
Group phase 1 consortium study. Lancet Oncology. 2013;14(6):472-80.	
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.	Incorrect population: no IMT patients included, only ALCL
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.	Incorrect population: no IMT patients included, only ALCL
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.	n=1 IMT patient treated with crizotinib. Case study design excluded by PICO
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.	n<10, larger case series and cohort studies included. No additional outcomes were presented.
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.	Incorrect population: no IMT patients included, only ALCL

Appendix E Evidence table

For abbreviations see list after table

Study details	Population	Interventions	Study outcomes	Appraisal and funding

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.
 	
Study location
Shanghai, China
 	
Study type
Nested case series in a retrospective cohort study (retrospective case series)
 	
Study aim
Explore the clinicopathological characteristics and treatment of adult IMT patients
 	
Study dates
January 2006 to December 2021
	Adults with a histologically confirmed diagnosis of IMT
	
	Inclusion criteria
	• aged ≥18 years
	• histologically confirmed diagnosis of IMT by the Department of Pathology, Fudan University Shanghai Cancer Center (FUSCC)
	• Received treatment at FUSCC between 2006 and 2021
	
	Exclusion Criteria
	• insufficient follow-up data, including:
	  ○ unknown clinicopathological characteristics
	  ○ no treatment record
	  ○ no follow-up information
	
	Total sample size
	total n=30
	advanced, ALK-positive IMT, treated with crizotinib, n=16
		Interventions
		crizotinib
		250mg, twice daily
		
		Comparators
		No comparator
			Duration of follow-up not reported unless otherwise stated
			
			Critical outcomes (n=16)
			Response to treatment *response evaluated by* RECIST[9]
			n (%);
			• Complete response: 3 (18.8%)
			• Partial response: 10 (62.5%)
			• Stable disease: 1 (6.3%)
			• Progressive disease: 2 (12.5%)
			
			• Objective response rate (ORR) and Disease control rate (DCR)[10]
			n (%);
			• ORR: 13 (81.3%)
			• DCR: 14 (87.5%)
			
			Progression-free survival (PFS)
			• 12-month PFS: 78.1% (95% CI 63.0% to 93.2%)
			• Median PFS: 20.8 months (95% CI unreached)
			
			Overall Survival (OS)
				This study was appraised using the JBI checklist for case series.
				1. Yes
				2. Yes
				3. Unclear
				4. Yes
				5. Yes
				6. Yes
				7. Yes
				8. Yes
				9. No
				10. No
				
				Other comments:
				This was a nested case series within a retrospective cohort study of IMT patients at a single hospital site in China. The overall cohort study included 30 patients, of whom 16 adults were identified as having advanced, ALK-positive IMT and were treated with crizotinib in the nested case series.
				
				Though the patients in the nested case series were identified as having advanced IMT, six (37.5%) had radical surgery prior to receiving crizotinib. Further details were not given; it is not possible to

[9] Response to treatment outcomes were evaluated using RECIST: Response Evaluation Criteria in Solid Tumours (v1.1). This uses defined criteria to categorise the treatment response as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD).
[10] Objective response rate (ORR). This composite measure was calculated as CR + PR. Disease control rate (DCR). This composite measure was calculated as CR + PR + SD.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Baseline characteristics (n=16 treated with crizotinib) • *Age years*, median (range): 28 (21 to 74) • *Male*, n (%): 4 (25.0%) • Primary tumour site, n (%) ○ abdominopelvic region: 12 (75.0%) ○ lung: 2 (12.5%) ○ uterus: 1 (6.3%) ○ rectum: 1 (6.3%) • Previous Therapies, n (%) ○ No previous therapy: 10 (62.5%) ○ Radical Surgery: 6 (37.5%) •		• 24-month OS: 70.7% (95% CI 58.1% to 83.3%) • Median OS: not determined **Important outcomes (n=16)** **Safety** *Adverse Events (AEs)*[11]; n (%) • Most common Grade 1-2 AEs: fatigue, nausea, diarrhoea, rash • Grade 3-4 AEs: 0 (0%) • Reduction in crizotinib dose due to AEs: 1 (6.3%)	ascertain if these patients were unresectable at the time of crizotinib administration, so it is possible that these patients did not fully align with the PICO population of interest (ALK-positive unresectable IMT). The study had a majority of female patients and patients with tumours in the abdominopelvic region. This may not be representative of adult IMT patients in the UK. Response to treatment was evaluated using the RECIST v1.1 criteria but no details of the approach to patient assessment were provided. As this was a retrospective case review, all patients in the nested case series received the drug of interest, crizotinib, so it was not possible to blind participants or assessors. **Source of funding:** Funding and conflicts of interest relevant to this study were not reported.
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	Patients with ALK positive relapsed/ refractory ALCL or unresectable IMT for >12 months **Inclusion criteria** • aged <22 years	**Interventions** crizotinib Dosing levels: 100mg/m^2, n=1 165mg/m^2, n=1 280mg/m^2, n=12	Duration of follow-up not reported **Critical outcomes** **Response to treatment**	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Unclear 4. Unclear 5. Unclear

[11] Adverse events were assessed according to the National Cancer Institute-Common Terminology Criteria for Adverse Events v4.0

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Inflammatory Myofibroblastic Tumor: A Children's Oncology Group Study. Journal of Clinical Oncology. 2017;35(28):3215-21. **Study location** United States **Study type** Phase I / Phase II expansion clinical trial (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** September 2009 to October 2015	• recurrent ALCL or unresectable IMT for >12 months • no prior exposure to therapeutic agents (IMT only) • 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 IMT n=14 **Baseline characteristics (n=14)** • *Age years*, median (range): 7.0 (2.0 to 13.5) • *Male*, n (%): 5 (36%) • *Race*, n (%) ○ White: 10 (71%) ○ Black: 1 (7%) ○ Asian: 0 (0%) ○ unknown: 3 (21%) • Previous Therapies, n (%)	Median therapy duration, years; 1.63 (95% CI 0.55 to 2.30) **Comparators** No comparator	*Best treatment response evaluated by RECIST*[12] n (%); n=14 • Complete response: 5 (36%) • Partial Response: 7 (50%) • Stable disease: 2 (14%) • Progressive disease: 0 (0%) • Objective response rate (ORR)[13] • ORR: 86% (95% CI 57% to 98%) • Time to first PR/CR, n=12 • days, median • 28.5 (95% CI 27 to 134) • weeks, n (%) • 4 weeks: 7 (58%) • 8 weeks: 2 (17%) • 12 weeks: 3 (25%) **Important outcomes** **Treatment adherence** • Two patients reported ceasing crizotinib therapy due to non-compliance **Safety (n=14)** *Adverse Events (AEs)*[14] • Grade 3-4 AEs: 71%	6. Yes 7. Yes 8. Yes 9. No 10. Yes **Other comments:** This was an expanded Phase I / Phase II clinical trial across multiple oncology centres in the United States. It is not clear from the documentation how many recruiting sites were included. It was not clear if all potentially eligible patients were included in the study. As this was a phase II clinical trial, all patients received the study drug, crizotinib, so it was not possible to blind participants or assessors. The primary aim of the Phase I trial was to determine maximum dose tolerance amongst paediatric (<22 years) ALK-positive ALCL[15] patients; Phase II opened the trial to other ALK-driven malignancies, including unresectable IMT. The study was designed to include patients up to the age of 22 years, but all IMT patients were under the age of 14 years.

[12] RECIST: Response Evaluation Criteria in Solid Tumours (v1.1). This uses defined criteria to categorise the treatment response as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD).
[13] Objective response rate (ORR). This composite measure was calculated as CR + PR.
[14] Adverse events were assessed according to the National Cancer Institute-Common Terminology Criteria for Adverse Events v4.0
[15] ALCL: anaplastic large cell non-Hodgkin's lymphoma. Crizotinib is used in a subset of these patients with recurrent or refractory ALK-positive ALCL.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	○ no previous therapy: 2 (14%) ○ chemotherapy: 4 (29%) ○ surgery: 8 (57%) ○ anti-inflammatory: 4 (29%) ○ Radical Surgery: 6 (37.5%)		• Grade 3-4 AEs possibly, probably or definitely related to crizotinib: 57% • Most common Grade 3-4 AE: decrease in neutrophil count • Percent of patients that experienced at least one neutrophil count decrease: 43% • Cessation of crizotinib due to AEs: n=4 (Grade 4 neutrophil count and Grade 4 lower extremity oedema) *Specific* AEs Grade 3-4 AEs possibly, probably or definitely related to crizotinib • Neutrophil count decreased ○ No. of patients: n=6 ○ No. of events: n=28 • Diarrhoea ○ No. of patients: n=1 ○ No. of events: n=1 • Lower limb oedema ○ No. of patients: n=1 ○ No. of events: n=1 • Sinus bradycardia ○ No. of patients: n=1 ○ No. of events: n=1	Response to treatment was evaluated using a validated instrument for solid tumours, RECIST v1.1. No details were provided of patient assessment, who it was done by, and whether it was consistent across centres. Imaging was reported to be performed at the treating institutes' discretion. No patients reported progressive disease during the follow-up period. It was noted by the authors that two patients discontinued crizotinib due to non-compliance. No further details were given as to how this was measured or if these patients had reached PR/CR. **Source of funding:** Funding was provided by a Children's Oncology Group Phase I Consortium Grant from the National Cancer Institute, Pfizer Inc and Cookies for Cancer Foundation. Two authors report research funding from pharmaceutical companies (Novartis, Bristol-Myers Squibb, Celgene, Pfizer and Roche). Two authors report stock ownership and employment from pharmaceutical companies (Johnson & Johnson, Merck and Pfizer). Three authors report reimbursement from pharmaceutical companies for speaking, travel,

Study details	Population	Interventions	Study outcomes	Appraisal and funding
				accommodations and expenses (Seattle Genetics, Roche, Celgene, Nektar, Bayer, Eisai, AstraZeneca and Takada).
Schöffski 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. **Study location** Europe: Belgium, France, Germany, Italy, Netherlands, Poland, Slovakia and the UK **Study type**	Patients with advanced or metastatic IMT deemed incurable by surgery, radiotherapy or systemic therapy Full information on inclusion and exclusion criteria can be found in Schöffski et al 2021 below **Total sample size** n=20 (ALK+ and ALK-) ALK+, n=12 **Baseline characteristics (n=12)** • *Age years*, median (IQR): 35.5 (27.0 to 55.5) • *Male*, n (%): 6 (50%) • ECOG performance status[17], n (%) ○ 0: 7 (58%) ○ 1: 5 (42%) ○ 2: 0 (0%)	**Interventions** crizotinib 250mg, twice daily Treatment continued until documented disease progression, unacceptable toxicity or patient refusal **Comparators** No comparator	Median follow-up, days; median (IQR): 863 (358 to 1304) **Important Outcomes** **Safety (n=20)** *Adverse Events (AEs)*[19] Total AEs by Grade, n (%) • Grade 1: 9 (45%) • Grade 2: 6 (30%) • Grade 3: 2 (10%) • Grade 4: 1 (5%)	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Unclear 4. Unclear 5. Unclear 6. No 7. Yes 8. Yes 9. Yes 10. Yes **Other comments:** This was a Phase II clinical trial across 13 specialty hospitals (five university hospitals and eight specialty clinics) in eight European countries. Schöffski et al 2021, presented below, followed the same cohort of patients for a median of 50 months. The patients did not receive any additional crizotinib treatment. Results for response to treatment, PFS and OS at median 50 months follow-up are presented in the Schöffski et al 2021 paper. The results for the same outcomes in the same

[17] The ECOG performance status is a measure of a patient's level of functioning, sometimes referred to as activities of daily living (ADLs). The ECOG performance status uses a Likert scale of 0-5. 0=Fully active, able to carry on all pre-disease performance without restriction; 1=Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2=Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours; 3=Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours; 4=Completely disabled; cannot carry on any selfcare; totally confined to bed or chair; 5=dead.
[19] Adverse events were assessed according to the International Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
CREATE[16] Phase II clinical trial (single-arm trial) **Study aim** Assess the activity and safety of crizotinib in patients with advanced or metastatic IMT **Study dates** 3 October 2012 to 12 April 2017	• Previous Therapies, n (%)[18] ○ any previous major surgery: 7 (58%) ○ any systemic anticancer treatment: 6 (50%) ○ chemotherapy: 5 (42%) ○ other anticancer therapy: 2 (17%)			patients at shorter duration of follow-up reported in this paper have, therefore, not been presented here. This paper provided additional adverse event data so was included in the review. Full comments on the trial methodology and biases can be found in Schöffski et al 2021 below. **Source of funding:** The trial was legally sponsored by the EORTC and financially supported by Pfizer (manufacturer of crizotinib). The report was supported by the EORTC Cancer Research Fund and the National Institute of Health Research (UK).
Schöffski 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.	Patients with advanced or metastatic IMT deemed incurable by surgery, radiotherapy or systemic therapy **Inclusion criteria** • aged ≥15 years • local diagnosis of advanced or metastatic IMT deemed incurable	**Interventions** crizotinib 250mg, twice daily Duration of treatment, months; median: 18.8 (range 3.4 to 77.5) Treatment continued until documented disease progression,	Median follow-up: 50 months **Critical outcomes** (n=12) **Response to treatment** Best treatment response evaluated by RECIST[23] n (%); • Complete response: 2 (16.7%) • Partial response: 6 (50.0%) • Stable disease: 4 (33.3%)	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Unclear 4. Unclear 5. Unclear 6. No 7. Yes 8. Yes 9. Yes 10. Yes

[16] The European Organisation for Research and Treatment of Cancer (EORTC) initiated a multinational, multi-tumour, prospective phase II clinical trial (EORTC 90101 CREATE) to assess the activity and safety of crizotinib in patients with advanced tumours characterised by changes in *ALK* or *MET*. CREATE included six types of tumour. The results of the IMT cohort are presented here.
[18] Patients may have had more than one previous therapy; percentages may not equal 100%.
[23] RECIST: Response Evaluation Criteria in Solid Tumours (v1.1). This uses defined criteria to categorise the treatment response as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD).

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Study location Europe: Belgium, France, Germany, Italy, Netherlands, Poland, Slovakia and the UK **Study type** CREATE Phase II clinical trial (single arm trial) **Study aim** Assess the activity and safety of crizotinib in patients with ALK+, advanced or metastatic IMT; updated results **Study dates** 3 October 2012 to 28 January 2021	by surgery, radiotherapy or systemic therapy • available formalin-fixed, paraffin-embedded tumour-containing tissue block from primary tumour or metastatic site • confirmation of diagnosis from central biorepository • Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 • adequate haematological, renal and liver function • measurable disease according to RECIST v1.1 with a target lesion of at least 20mm • adequate birth control methods must be used by all patients of childbearing age (male and female) **Exclusion Criteria** • previous exposure to crizotinib or other specific ALK-inhibiting drugs • acute or chronic severe gastrointestinal conditions • current congestive heart failure	unacceptable toxicity or patient refusal **Comparators** No comparator	• Progressive disease: 0 (0.0%) • Objective response rate (ORR) and Disease control rate (DCR)[24] % • ORR: 66.7% (95% CI 21.1% to 78.9%) • DCR: 100% (95% CI 73.5% to 100%) **Progression-free survival (PFS)** PFS rate, % • 12-months: 58.3% (95% CI 27.0% to 80.1%) • 24-months: 41.7% (95% CI 15.2% to 66.5%) • 36-months: 41.7% (95% CI 15.2% to 66.5%) • No. of patients alive, with no progression at end of follow-up: 5 (41.7%) • Median PFS, months: 18.0 (95% CI 4.0 to not evaluable) **Overall Survival (OS)** OS rate, % • 12-months: 83.3% (95% CI 48.2% to 95.6%) • 24-months: 83.3% (95% CI 48.2% to 95.6%) • 36-months: 83.3% (95% CI 48.2% to 95.6%)	**Other comments:** This was a Phase II clinical trial across 13 specialty hospitals (five university hospitals and eight specialty clinics) in eight European countries. Eligible patients were at least 15 years of age and had incurable advanced or metastatic IMT; all patients included in the study were over 25 years of age. It was not clear if all potentially eligible patients were included in the study. As this was a phase II clinical trial, all patients received the study drug, crizotinib, so it was not possible to blind participants or assessors. Patients continued to receive the study drug until documented disease progression, unacceptable toxicity or patient refusal. Tumour assessments were performed by local investigators or radiologists. Response to treatment was reported using a validated instrument for solid tumours, RECIST v1.1. No details were provided of patient assessment, who it was done by, and whether it was consistent across centres. No patients reported progressive disease during the follow-up period.

[24] Objective response rate (ORR). This composite measure was calculated as CR + PR. Disease control rate (DCR). This composite measure was calculated as CR + PR + SD.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	• cardiac dysrhythmias of grade 2 or more,[20] including uncontrolled atrial fibrillation • previous systemic anticancer therapy must have been completed at least 4 weeks prior to crizotinib administration • surgery must have been completed at least 4 weeks prior to crizotinib administration **Total sample size** n=20 (ALK+ and ALK-) ALK+, n=12 **Baseline characteristics (n=12)** • *Age years*, median (IQR): 35.5 (27.0 to 55.5) • *Male*, n (%): 6 (50%) • ECOG performance status[21], n (%) ○ 0: 7 (58%) ○ 1: 5 (42%) ○ 2: 0 (0%)		• No. of deaths during follow-up: 3 (25.0%) • No. of deaths due to IMT: 2 (16.7%) • Median OS, months: not evaluable **Important Outcomes** **Safety (n=20)** *Specific AEs*[25] • Most common, non-haematological AEs: nausea, fatigue, blurred vision, vomiting and diarrhoea • Most common haematological AEs: increased SGPT, increased SGOT, hypalbuminaemia, hypocalcaemia, serum creatinine, hyperkalaemia, hyponatremia *Specific AEs, by Grade*[26] n (%) • increased SGPT ○ Grade 1: 9 (45%) ○ Grade 2: 1 (5%) ○ Grade 3: 2 (10%) ○ Grade 4: 1 (5%) • hypocalcaemia ○ Grade 1: 8 (40%)	Adverse event data was not stratified by ALK+ / ALK- patients. Inclusion of the data leads to increased indirectness of the outcome data as the population does not match that of the PICO (ALK-positive unresectable IMT; Appendix A). **Source of funding:** The trial was legally sponsored by the EORTC and financially supported by Pfizer (manufacturer of crizotinib). The funder provided the drug but had no role in study design, data collection, data analysis, data interpretation or writing of the report. Three authors report research support and three authors report honoraria from pharmaceutical companies (Pfizer and Lilly). Two authors report advisory roles outside the scope of this study.

[20] according to the National Cancer Institute Common Toxicity Criteria
[21] The ECOG performance status is a measure of a patient's level of functioning, sometimes referred to as activities of daily living (ADLs). The ECOG performance status uses a Likert scale of 0-5. 0=Fully active, able to carry on all pre-disease performance without restriction; 1=Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2=Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours; 3=Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours; 4=Completely disabled; cannot carry on any selfcare; totally confined to bed or chair; 5=dead.
[25] Adverse events were assessed according to the International Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.
[26] Five most common AEs. Additional AEs can be found in the full paper.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	• Previous Therapies, n (%)[22] ○ any previous major surgery: 7 (58%) ○ any systemic anticancer treatment: 6 (50%) ○ chemotherapy: 5 (42%) ○ other anticancer therapy: 2 (17%)		○ Grade 2: 6 (30%) • increased SGOT ○ Grade 1: 8 (40%) ○ Grade 2: 1 (5%) ○ Grade 3: 3 (15%) ○ Grade 4: 1 (5%) • nausea ○ Grade 1: 6 (30%) ○ Grade 2: 5 (25%)	

Abbreviations
ADL: activities of daily living; AE: adverse events; ALCL: anaplastic large cell non-Hodgkin's lymphoma; ALK: anaplastic lymphoma kinase; CI: confidence interval; CR: complete response; CTCAE: Common Terminology Criteria for Adverse Events; DCR: disease control rate; ECOG: Eastern Cooperative Oncology Group; EORTC: European Organisation for Research and Treatment of Cancer; FUSCC: Fudan University Shanghai Cancer Center; IMT: inflammatory myofibroblastic tumour; IQR: interquartile range; m: metre; MET: mesenchymal epithelial transition; mg: milligram; mm: millimetre; n: number; No.: number; ORR: objective response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PICO: population, intervention, comparison, outcomes; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumours; SD: stable disease; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase; v: version; UK: United Kingdom

[22] Patients may have had more than one previous therapy; percentages may not equal 100%.

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 (2 single-arm trials, 1 retrospective case series)									
Best treatment response evaluated by RECIST[A], median follow-up 50 months; n (%)									
1 single-arm trial Schöffski et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	12	0	• CR: 2 (16.7%) • PR: 6 (50.0%) • SD: 4 (33.3%) • PD: 0 (0.0%)	Critical	Very low
Best treatment response evaluated by RECIST[A], duration of follow-up not stated; n (%)									
1 single-arm trial Mossé et al 2017	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	14	0	• CR: 5 (36%) • PR: 7 (50%) • SD: 2 (14%) • PD: 0 (0%)	Critical	Very low
1 retrospective case series Liu et al 2023	Serious limitations[3]	Very serious indirectness[4]	Not applicable	Not calculable	16	0	• CR: 3 (18.8%) • PR: 10 (62.5%) • SD: 1 (6.3%) • PD: 2 (12.5%)	Critical	Very low
ORR / DCR[B], median follow-up 50 months ; %									
1 single-arm trial Schöffski et al 2021	Serious limitations[5]	Serious indirectness[2]	Not applicable	Not calculable	12	0	• ORR: 66.7% (95% CI 21.1% to 78.9%) • DCR: 100% (95% CI 73.5% to 100%)	Critical	Very low
ORR[C], duration of follow-up not stated ; %									
1 single-arm trial Mossé et al 2017	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	14	0	86% (95% CI 57% to 98%)	Critical	Very low
ORR / DCR[B], duration of follow-up not stated; n (%)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Crizotinib**	**Comparator**	**Result**		
1 retrospective case series Liu et al 2023	Serious limitations[3]	Very serious indirectness[4]	Not applicable	Not calculable	16	0	• ORR: 13 (81.3%) • DCR: 14 (87.5%)	Critical	Very low
Time to first PR/CR, duration of follow-up not stated (benefit is indicated by higher number); median (95% CI)									
1 single-arm trial Mossé et al 2017	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	12	0	days, median • 28.5 (95% CI 27 to 134) • weeks, n (%) • 4 weeks: 7 (58%) • 8 weeks: 2 (17%) • 12 weeks: 3 (25%)	Critical	Very low
Progression-Free Survival (PFS) (1 single-arm trial, 1 retrospective case series)									
12-month PFS, median follow-up 23 months; K-M%[D]									
1 retrospective case series Liu et al 2023	Serious limitations[6]	Very serious indirectness[4]	Not applicable	Not calculable	16	0	78.1% (95% CI 63.0% to 93.2%)	Critical	Very low
Median PFS, median follow-up 23 months (benefit is indicated by higher result); months									
1 retrospective case series Liu et al 2023	Serious limitations[6]	Very serious indirectness[4]	Not applicable	Not calculable	16	0	20.8 months (95% CI unreached)	Critical	Very low
12-month PFS, median follow-up 50 months; K-M%[D]									
1 single-arm trial Schöffski et al 2021	Very serious limitations[7]	Serious indirectness[2]	Not applicable	Not calculable	12	0	58.3% (95% CI 27.0% to 80.1%)	Critical	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Crizotinib	Comparator	Result		
24-month PFS, median follow-up 50 months; K-M%[D]									
1 single-arm trial Schöffski et al 2021	Very serious limitations[7]	Serious indirectness[2]	Not applicable	Not calculable	12	0	41.7% (95% CI 15.2% to 66.5%)	Critical	Very low
36-month PFS, median follow up 50 months; K-M%[D]									
1 single-arm trial Schöffski et al 2021	Very serious limitations[7]	Serious indirectness[2]	Not applicable	Not calculable	12	0	41.7% (95% CI 15.2% to 66.5%)	Critical	Very low
Median PFS, median follow-up 50 months (benefit is indicated by higher result); months									
1 single-arm trial Schöffski et al 2021	Very serious limitations[7]	Serious indirectness[2]	Not applicable	Not calculable	12	0	18.0 months (95% CI 4.0 to not evaluable)	Critical	Very low
No. of patients alive, with no progression at the end of follow-up, median follow-up 50 months; n (%)									
1 single-arm trial Schöffski et al 2021	Very serious limitations[7]	Serious indirectness[2]	Not applicable	Not calculable	12	0	No. of patients alive, with no progression at end of follow-up: 5 (41.7%)	Critical	Very low
Overall Survival (OS) (1 single-arm trial, 1 retrospective case series)									
12-month OS, median follow-up 50 months; K-M%[D]									
1 single-arm trial Schöffski et al 2021	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	12	0	83.3% (95% CI 48.2% to 95.6%)	Critical	Very low
24-month OS, median follow-up 50 months; K-M%[D]									
1 single-arm trial Schöffski et al 2021	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	12	0	83.3% (95% CI 48.2% to 95.6%)	Critical	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Crizotinib	Comparator	Result		
36-month OS, median follow-up 50 months; K-M%[D]									
1 single-arm trial Schöffski et al 2021	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	12	0	83.3% (95% CI 48.2% to 95.6%)	Critical	Very low
No. of patients that died during follow-up, median follow-up 50 months; n (%)									
1 single-arm trial Schöffski et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	12	0	• No. of patients that died during follow-up: 3 (25.0%) • No. of deaths due to IMT: 2 (16.7%)	Critical	Very low
24-month OS, duration of follow-up not stated; K-M%[D]									
1 retrospective case series Liu et al 2023	No serious limitations	Very serious indirectness[4]	Not applicable	Not calculable	16	0	70.7% (95% CI 58.1% to 83.3%)	Critical	Very low
Treatment adherence (1 single-arm trial)									
Treatment adherence, duration of follow-up not reported; n									
1 single-arm trial Mossé et al 2017	Very serious limitations[8]	Serious indirectness[2]	Not applicable	Not calculable	14	0	Two patients reported ceasing crizotinib therapy due to non-compliance	Important	Very low
Safety (2 single-arm trials, 1 retrospective case series)									
Adverse Events (AEs) by Grade[E], median follow-up 863 days; n (%)									
1 single-arm trial Schöffski et al 2018	Very serious limitations[8]	Very serious indirectness[9]	Not applicable	Not calculable	20[a]	0	• Grade 1: 9 (45%) • Grade 2: 6 (30%) • Grade 3: 2 (10%) • Grade 4: 1 (5%)	Important	Very low
Specific AEs[E], median follow-up 50 months									
1 single-arm trial	Very serious limitations[8]	Very serious indirectness[9]	Not applicable	Not calculable	20[a]	0	• Most common, non-haematological AEs: nausea, fatigue, blurred vision, vomiting and diarrhoea	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Crizotinib**	**Comparator**	**Result**		
Schöffski et al 2021							• Most common haematological AEs: increased SGPT, increased SGOT, hypalbuminaemia, hypocalcaemia, serum creatinine, hyperkalaemia, hyponatremia		
Specific AEs[E] by Grade, median follow-up 50 months; n (%)									
1 single-arm trial Schöffski et al 2021	Very serious limitations[8]	Very serious indirectness[9]	Not applicable	Not calculable	20[a]	0	• increased SGPT ○ Grade 1: 9 (45%) ○ Grade 2: 1 (5%) ○ Grade 3: 2 (10%) ○ Grade 4: 1 (5%) • hypocalcaemia ○ Grade 1: 8 (40%) ○ Grade 2: 6 (30%) • increased SGOT ○ Grade 1: 8 (40%) ○ Grade 2: 1 (5%) ○ Grade 3: 3 (15%) ○ Grade 4: 1 (5%) • nausea ○ Grade 1: 6 (30%) ○ Grade 2: 5 (25%) ○	Important	Very low
Adverse Events (AEs)[F], duration of follow-up not reported; n or %									
1 single-arm trial Mossé et al 2017	Very serious limitations[8]	Serious indirectness[2]	Not applicable	Not calculable	14	0	• Grade 3-4 AEs: 71% • Grade 3-4 AEs possibly, probably or definitely related to crizotinib: 57% • Most common Grade 3-4 AE: decrease in neutrophil count • Percent of patients that experienced at least one neutrophil count decrease: 43% • Cessation of crizotinib due to AEs: n=4 (Grade 4 neutrophil count and Grade 4 lower extremity oedema) •	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Crizotinib	Comparator	Result		
Specific AEs[F] – Grade 3-4 AEs possibly, probably or definitely related to crizotinib; duration of follow-up not reported; n									
1 single-arm trial Mossé et al 2017	Very serious limitations[8]	Serious indirectness[2]	Not applicable	Not calculable	14	0	• Neutrophil count decreased o No. of patients: n=6 o No. of events: n=28 • Diarrhoea o No. of patients: n=1 o No. of events: n=1 • Lower limb oedema o No. of patients: n=1 o No. of events: n=1 • Sinus bradycardia o No. of patients: n=1 o No. of events: n=1	Important	Very low
Adverse Events (AEs)[F], duration of follow-up not reported; n (%)									
1 retrospective case series Liu et al 2023	Very serious limitations[10]	Very serious indirectness[4]	Not applicable	Not calculable	16	0	• Most common Grade 1-2 AEs: fatigue, nausea, diarrhoea, rash • Grade 3-4 AEs: 0 (0%) • Reduction in crizotinib dose due to AEs: 1 (6.3%)	Important	Very low

Abbreviations
AE: adverse events; ALK: anaplastic lymphoma kinase; CI: confidence interval; CR: complete response; CTCAE: Common Terminology Criteria for Adverse Events; DCR: disease control rate; IMT: inflammatory myofibroblastic tumour; K-M: Kaplan-Meier; n: number; No.: number; ORR: objective response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PICO: population, intervention, comparison, outcomes; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumours; SD: stable disease; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase

1 Risk of bias: very serious limitations due to both unclear reporting of study participants (in relation to non-consecutive and/or incomplete inclusion) and lack of any statistical analysis or summary statistic.
2 Indirectness: serious indirectness due to lack of comparator group.
3 Risk of bias: serious limitations due to the lack of any statistical analysis or summary statistic.
4 Indirectness: very serious indirectness due to lack of comparator group and the study population as it was unclear if all the participants had unresectable IMT at the time of enrolment (the PICO population is patients with ALK-positive unresectable IMT).
5 Risk of bias: serious limitations due to unclear reporting of study participants (in relation to non-consecutive and/or incomplete inclusion).
6 Risk of bias: serious limitations due to a lack of blinding of patients and clinicians.
7 Risk of bias: very serious limitations due to both a lack of blinding of patients and clinicians and an unclear reporting of study participants (in relation to non-consecutive and/or incomplete inclusion).
8 Risk of bias: very serious limitations due to a lack of blinding of patients and clinicians, an unclear reporting of study participants (in relation to non-consecutive and/or incomplete inclusion) and a lack of any statistical analysis or summary statistic.
9 Indirectness: very serious indirectness due to lack of comparator group and a mixed ALK+/ALK- population which did not match the PICO (the PICO states patients with ALK-positive unresectable IMT).
10 Risk of bias: very serious limitations due to both a lack of blinding of patients and clinicians and a lack of any statistical analysis or summary statistic.

A Treatment response evaluated by RECIST: Response Evaluation Criteria in Solid Tumours v1.1. This uses defined criteria to categorise the treatment response as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD).
B Objective response rate (ORR). This composite measure was calculated as RECIST's CR + PR. Disease control rate (DCR). This composite measure was calculated as CR + PR + SD.
C Objective Response Rate (ORR): This composite measure is calculated as RECIST's CR + PR.
D K-M%: Kaplan-Meier survival statistic.
E Adverse events were assessed according to the International Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.
F Adverse events were assessed according to the National Cancer Institute-Common Terminology Criteria for Adverse Events v4.0.

a Includes ALK+ and ALK- IMT patients.

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).

Term	Definition
Prospective study	A research study in which the health or other characteristic of patients is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
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 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.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.

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