NHS England

Clinical Priorities Advisory Group Summary Report

Agenda item	3.1
Date of Meeting	11/05/2026-13/05/2026
Title of the Proposition	Crizotinib for patients with relapsed or refractory ALK-positive anaplastic large cell lymphoma (ALCL) or ALK-positive unresectable inflammatory myofibroblastic tumour (IMT)
Unique Reference Number	2330
Programme of Care	Cancer
Clinical Reference Group	Children & Young People's Cancer Service
Service/treatment status	delegated

Action requested

Support the adoption of the policy proposition

Recommend its relative prioritisation.

Summary of the proposition:

Crizotinib is recommended to be available as a routine commissioning treatment option for ALK-positive anaplastic large cell lymphoma (ALCL) and ALK-positive inflammatory myofibroblastic tumour (IMT) within the criteria set out in the policy proposition.

ALCL and IMT are both rare types of cancer. ALCL is a blood cancer (non-Hodgkin lymphoma) that most commonly affects children and young adults. IMT forms on mucosal surfaces such as the eyes, mouth, lungs and mesentery (connects organs in the abdomen). In both types of cancer, the tumour cells may mutate to form a protein called anaplastic lymphoma kinase (ALK) on their surface. The ALK mutation drives the abnormal growth of cancer cells. Currently, ALK-positive ALCL is treated with chemotherapy however up to 30% of adult and paediatric ALCL patients' relapse. Surgery is the mainstay of treatment for IMT, however surgical resection is not always possible due to advanced disease or tumours being close to vital structures.

Crizotinib is an oral (tablet) chemotherapy drug that blocks the ALK mutation and causes cell death. This policy proposition has been restricted to ALCL patients aged 3 years and older, and IMT patients aged 2 years and older in line with the findings from the evidence review.

Clinical Panel recommendation:

The Clinical Panel recommended that the policy proposition progress as a routine commissioning policy.

Assurances

The committee is asked to receive the following assurance:		
1.	The Deputy Director of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of developmental and governance steps.	
2.	The Deputy Director of Cancer Programme confirms the proposition is supported by the following documentation (please tick the box where applicable)	
	Draft Clinical Commissioning policy proposition	☒
	Evidence Review	☒
	Public Health Evidence Report	☐
	Evidence to Decision Making (EtD) Summary	☒
	Equalities and Heath Inequalities Assessment (EHIA)	☒
	Prior Approval Form	☒
	Engagement Report	☒
	13Q Assessment and Patient & Public Voice Assurance	☒
	Clinical Panel Report	☒
	Policy Working Group membership	☒

	Other (please state if required)	☐
3.	The Deputy Director of Finance (Specialised Commissioning) confirms that the Impact Assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.	
4.	The Director of Clinical Commissioning (Specialised Commissioning) confirms that the Service and Operational Impact Assessments have been completed.	
5.	The Deputy Director of Quality and Nursing (Specialised Commissioning) confirms that the proposed quality indicators have been adequately defined (where applicable).	

Evidence Review Summary

Part A: ALCL

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

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Response to Treatment **Certainty of evidence:** Very low	Response rate is important to patients as it represents whether the treatment can improve disease burden. In total, three studies (three single-arm trials) provided evidence relating to response to treatment with crizotinib. *Best overall treatment response* **At 8 weeks post-treatment initiation**: One single-arm trial (Brugières et al 2023) (n=24) reported best overall response[1] of 9/24 complete response and 7/24 partial response. (**VERY LOW)** **Over duration of treatment (median duration 3.7 months (range 0.37 to 47.2 months))** One single-arm trial (Brugières et al 2023) (n=24) reported best overall response of 12/24 complete response and 4/24 partial response. (**VERY LOW)** **At unspecified duration of follow-up:**

	• One single-arm trial (Gambacorti-Passerini et al 2018) (n=17) reported a best overall response[2] of complete response: 47.1%; partial response: 5.9%; stable disease: 17.6%; objective progression: 17.6%; early death: 5.9%; indeterminate: 5.9%, after a median treatment duration of 35 months. **(VERY LOW)** • One single-arm trial (Mossé et al 2017) (n=26) reported a best overall response[3] for patients treated with crizotinib 165mg/m^2 for a median 2.79 years of complete response: 83%; partial response: 0%; stable disease: 17%; progressive disease: 0%; and for patients treated with crizotinib 280mg/m^2 for a median of 0.4 years of complete response: 80%; partial response: 10%; stable disease: 10%; progressive disease: 0%. **(VERY LOW)** *Objective response rate* **At 8 weeks post-treatment initiation**: One single-arm trial (Brugières et al 2023) (n=24) reported an objective response rate of 67% (95% CI 47% to 82%). (**VERY LOW)** **At unspecified duration of follow-up:** • One single-arm trial (Gambacorti-Passerini et al 2018) (n=17) reported an objective response rate of 52.9% (95% CI 27.8% to 77%) after a median treatment duration of 35 months. **(VERY LOW)** • One single-arm trial (Mossé et al 2017) (n=26) reported an objective response rate of 83% (95% CI 36% to 99.6%) for patients treated with crizotinib 165mg/m^2 for a median 2.79 years, and 90% (95% CI 68% to 99%) for patients treated with crizotinib 280mg/m^2 for a median of 0.4 years. **(VERY LOW)** *Duration of response* One single-arm trial (Brugières et al 2023) (n=24) reported a median duration of response of 43.4 months (95% CI 8.3 to not reached) after a median treatment duration of 3.7 months. (**VERY LOW)** • One single-arm trial (Gambacorti-Passerini et al 2018) (n=17) reported a median duration of response of 135.8 weeks (range 6 to 205.9 weeks) after a median treatment duration of 35 months**. (VERY LOW)** **One single-arm trial provided very low certainty evidence of a best overall response to treatment with crizotinib at 8 weeks after treatment initiation of 9/24 subjects with complete response and 7/24 with partial response. The same single-arm trial provided very low certainty evidence of a best overall response to treatment with crizotinib after a median duration of treatment of 3.7 months (range 0.37 to 47.2 months) of 12/24 complete response and 4/24 partial response. Two single-arm trials provided very low certainty evidence of a best overall response to treatment with crizotinib of between 47% and 83% complete response, 0% and 10% partial response, 10% and 18% stable disease and 0% and 18% progressive disease, at an unspecified duration of follow-up. Three single-arm trials provided**

	very low certainty evidence of an objective response to treatment of 67 % (8 weeks after treatment initiation) and between 53% and 90% (at unspecified duration of follow-up). Two single-arm trials provided very low certainty evidence that the median duration of response was between 136 weeks and 43.4 months.
Progression-free Survival **Certainty of evidence:** Very low	This outcome is important to patients because it represents the time for which their disease is not progressing. Stable disease might represent longer survival and disease stability may result in patients experiencing fewer symptoms from the disease itself. It can be determined sooner than overall survival outcome measures. In total, two studies (two single-arm trials) provided evidence relating progression-free survival (PFS). Both estimated survival using the Kaplan-Meier method. **At median follow-up 45 months (95% CI 28 to 50.9 months):** One single-arm trial (Brugières et al 2023) (n=24) reported 3-year PFS of 40% (95% CI 23% to 59%). **(VERY LOW)** One single-arm trial (Brugières et al 2023) (n=24) reported median PFS of 11.0 months (95% CI 1.7 to 47.6 months). **(VERY LOW)** **At unspecified duration of follow-up:** One single-arm trial (Gambacorti-Passerini et al 2018) (n=17) reported 2-year PFS of 63% (95% CI 35.3% to 81.4%). **(VERY LOW)** **Two single-arm trials provided very low certainty evidence of 2-year progression-free survival of 63% at unspecified duration of follow-up, and 3-year progression-free survival of 40% at median follow-up 45 months with a median progression-free survival of 11 months.**
Overall Survival **Certainty of evidence:** Very low	Overall survival is important to patients as individuals with relapsed or refractory ALK-positive ALCL have a high mortality rate due to advanced disease. Improved survival is an important marker of effective treatment. Overall survival does not give any indication of a patient's quality of life during this time. In total, one study (one single-arm trial) provided evidence relating to overall survival (OS), estimated using the Kaplan-Meier method. **At median follow-up 45 months (95% CI 28 to 50.9 months):** One single-arm trial (Brugières et al 2023) (n=24) reported 3-year OS of 63% (95% CI 43% to 79%). **(VERY LOW)** **One single-arm trial provided very low certainty evidence of 3-year overall survival of 63% at median follow-up 45 months.**
Important outcomes	
Quality of life **Certainty of evidence:** Not applicable	Quality of life is important to patients as it provides an indication of an individual's general health, their self-perceived well-being and their ability to participate in activities of daily living. Measurement of quality of life can help inform patient-centred decision making and inform health policy. **No evidence was identified for quality of life.**

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

	which was considered 'possibly, probably, or definitely' related to the study drug. **(VERY LOW)** • One single-arm trial (Gambacorti-Passerini et al 2018) (n=44, including n=18 patients with ALCL and n=26 with other malignancies) reported that 88.6% of patients experienced any AE, with 36.4% experiencing a grade 3 AE, 13.6% experiencing a grade 4 AE and 4.5% experiencing a grade 5 AE. **(VERY LOW)** **At median follow-up 45 months (95% CI 28 to 50.9 months):** • One single-arm trial (Brugières et al 2023; n=24) reported that the most common Grade 3 or 4 AEs were neutropaenia (32%), anaemia (20%) and lymphopaenia (12%), while the most common AEs (all grades) were ALAT increase (72%), anaemia (68%), lymphopaenia (64%), neutropaenia (56%) and leucopaenia (56%). **(VERY LOW)** **At unspecified duration of follow-up:** • One single-arm trial (Mossé et al 2017) (n=26) reported that between 33% and 70% patients had at one neutrophil count decrease. **(VERY LOW)** • One single-arm trial (Gambacorti-Passerini et al 2018) (n=44, including n=18 patients with ALCL and n=26 with other malignancies) reported that the most common AEs (all grades) were diarrhoea (45.5%), vision disorder (45.5%), nausea (38.6%), elevated transaminases (34.1%), vomiting (34.1%) and neutropaenia (31.8%). **(VERY LOW)** **All three single-arm trials provided very low certainty evidence that the majority of patients with relapsed or refractory ALCL reported adverse events during crizotinib treatment. One trial reported 83% of patients treated with crizotinib 165mg/m^2 twice daily experienced at least one grade 3 or 4 AE, of which 33% were considered to be related to crizotinib therapy. 100% of those treated with higher dose crizotinib 280mg/m^2 twice daily experienced at least one grade 3 or 4 AE; 85% were considered to be related to crizotinib therapy. A second trial provided very low certainty evidence that around 55% of patients treated with crizotinib 250mg twice daily experienced a grade 3, 4 or 5 AE.**

Abbreviations
ADL: activities of daily living; AE: adverse event; ALAT: Alanine Transaminase; ALCL: anaplastic large cell lymphoma; ALK: anaplastic lymphoma kinase, BOR: Best Overall Response; CI: confidence interval; DOR: Duration of Response; ECOG: Eastern Cooperative Oncology Group (performance status), ORR: Objective Response Rate; OS: Overall Survival; PFS: Progression-free Survival; RECIST: Response evaluation criteria in solid tumours; WBC: white blood cell

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

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

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

Response to treatment	**At 8 weeks post-treatment initiation** One single-arm trial (Brugières et al 2023) (n=24) reported an objective response rate of 80% (95% CI 44% to 97%) in those aged ≤18 years (n=11) and 57% (95% CI 29% to 82%) in those aged >18 years (n=14).
Progression-free survival and overall survival	**At median follow-up 45 months (95% CI 28 to 50.9 months):** One single-arm trial (Brugières et al 2023) (n=24) reported 3-year progression-free survival of 64% (95% CI 35% to 85%) in those aged ≤18 years (n=11) and 21% (95% CI 8% to 48%) in those aged >18 years (n=14). One single-arm trial (Brugières et al 2023) (n=24) reported 3-year overall survival of 78% (95% CI 45% to 94%) in those aged ≤18 years) (n=11) and 50% (95% CI 27% to 73%) in those aged >18 years (n=14).

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

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

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

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

Part B: IMT

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)** *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:**	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

Very low	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 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. 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: 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	

Patient Impact assessment

Patient Impact Summary
The condition has the following impacts on the patient's everyday life: • **mobility:** Patients may be unable to walk about • **ability to provide self-care:** Patients are unable to wash or dress • **undertaking usual activities:** Patients are unable to do their daily activities • **experience of pain/discomfort:** Patients have pain or discomfort • **experience of anxiety/depression:** Patients are extremely anxious or depressed
Further details of impact upon patients: ALCL cancer diagnosis is devastating; children are worried about body image, hair loss, not able to see friends, feeling isolated, and fearing death. Side effects from range from

nausea and vomiting to mucositis, which can be life threatening. The treatment is intense and can make children very distressed, anxious, angry. This can lead to lack of adherence to treatment regimes. Children can be left for days, unable to move and feeling unwell. Crizotinib provides another treatment option for patients after chemotherapy has failed and can either help slow disease progression or act as a bridge to stem cell transplant.

IMT tumours can cause pain, fever, night sweats or other unpleasant symptoms depending on their location. If surgery is not possible because the tumour is too big or has spread, there is no standard care treatment for patients, which can cause worry and anxiety. Crizotinib provides a treatment for unresectable disease and has shown to slow disease progression.

Further details of impact upon carers: A diagnosis of ALCL can be incredibly scary for parents or carers. Feeling helpless, having to watch the pain, discomfort and disability cancer brings to child's life, financial worries, emotional and mental exhaustion, anxiety, sleepless nights, PTSD, relationship strains.

Patients with IMT or ALCL may need different levels of care depending on the progress of their disease.

Considerations

Equality and Health Inequalities Impact Assessment (EHIA)	
Summary of any potential impacts of the proposal	This policy proposition aims to make crizotinib available for all patients with ALK-positive relapsed or refractory ALCL and ALK-positive unresectable IMT if clinically eligible. It is not thought to adversely impact on any other individuals from protected characteristic groups. The proposition could provide an alternative treatment option for patients who are currently experiencing the consequences of ALK-positive relapsed or refractory ALCL and a first-line treatment option for patients with ALK-positive unresectable IMT which has currently limited or no treatment options to control the disease. This policy proposition is informed by the evidence base and the clinical expertise of the policy working group. A national commissioned policy proposition will reduce variation in clinical practice promoting an equity of care nationally for those in which this intervention is indicated. At present some trusts have agreed to fund the treatment for the occasional patient but other trusts have not agreed to do so.
13Q Assessment	

PPVAG outcome	No consultation required
Were PPVAG assured of the level of stakeholder testing?	Yes

Rare Disease Advisory Group

Not Applicable

Pharmaceutical

Yes

The Clinical Commissioning Policy proposition recommends crizotinib as a treatment option for patients with relapsed or refractory ALK-positive anaplastic large cell lymphoma (ALCL) or ALK-positive unresectable inflammatory myofibroblastic tumour (IMT). The proposition includes the following patient groups:

- Paediatric patients aged 3 years of age to less than 18 years of age with relapsed or refractory ALK-positive ALCL after first-line chemotherapy; use in children aged less than 6 years is outside of crizotinib's marketing authorisation
- Adult patients (aged ≥18 years) with relapsed or refractory ALK-positive ALCL following first-line and/or second-line treatment with brentuximab vedotin; this recommendation is outside of crizotinib's marketing authorisation
- Paediatric patients aged 2 years of age to less than 18 years of age with ALK-positive IMT not suitable for complete surgical resection; this recommendation is outside of crizotinib's marketing authorisation
- Adult patients (aged ≥18 years) with ALK-positive IMT not suitable for complete surgical resection; this recommendation is outside of crizotinib's marketing authorisation

These recommendations have been informed by the independent evidence review and crizotinib's Summary of Product Characteristics, which states that '*no safety or efficacy data are available for crizotinib treatment in ALK-positive ALCL paediatric patients below 3 years of age or ALK-positive IMT paediatric patients below 2 years of age*.'

Crizotinib is included on the NHS Payment Scheme Annex A, so is considered a high-cost drug.

National Programme of Care

The proposal received the full support of the Cancer National Programme of Care Assurance Group.