NHS England

NHS ENGLAND SPECIALISED SERVICES

CLINICAL PANEL REPORT

Date: 15 May 2024

Intervention: Crizotinib

Indication: relapsed or refractory anaplastic lymphoma kinase-positive (ALK-positive) anaplastic large cell lymphoma (ALCL) or ALK-positive unresectable inflammatory myofibroblastic tumour (IMT)

URN: 2330

Gateway: 2, Round 1

Programme: Cancer

CRG: Children and Young People's Cancer Service

Information provided to the Panel

Policy Proposition

Two Evidence Reviews completed by Solutions for Public Health

Two Clinical Priorities Advisory Group (CPAG) Summary Reports

Evidence to Decision (EtD) Summary

Equalities and Health Inequalities (EHIA) Assessment

Patient Impact Assessment (PIA)

Blueteq® Form

Policy Working Group (PWG) Appendix

This Policy Proposition recommends the use of crizotinib for patients with relapsed or refractory ALCL or unresectable IMT which is validated as ALK-positive.

Panel members were presented with a summary of the proposed intervention and indication, and current lines of treatment. ALCL is a type of non-Hodgkin lymphoma (NHL) that most commonly affects children and young adults. It is a rare type of blood cancer where a genetic mutation means T-cells make a protein called ALK on their surface. The ALK mutation drives the abnormal growth of the cancer cells. IMT is a very rare type of tumour that can form on mucosal surfaces and mesentery. A diagnosis of IMT is confirmed by tumour biopsy which can also determine if the IMT is ALK-positive.

Surgical resection is the mainstay of IMT treatment where possible. There is no currently commissioned standard care treatment for adult or paediatric patients with unresectable IMT who may be offered chemotherapy, systemic corticosteroid therapy or non-steroidal anti-inflammatory drugs.

Crizotinib is an ALK inhibitor, which targets the ALK mutation found in ALK positive ALCL and ALK-positive IMT. Crizotinib is taken orally. It is licensed for use in paediatric patients (age ≥ 6 to < 18 years) with relapsed and refractory ALK positive ALCL and unresectable ALK positive IMT.

It is estimated that 30-35 new patients with ALK-positive relapsed or refractory ALCL and fewer than 5 patients with ALK-positive unresectable IMT would be eligible for this treatment per year in England.

The two evidence reviews were presented to Panel members.

For both reviews, the critical outcomes for clinical effectiveness were response to treatment, progression-free survival and overall survival. Important outcomes were quality of life, activities of daily living (ADLs), treatment-related hospitalisation, treatment adherence. No evidence relating to quality of life, ADLs, treatment-related hospitalisation or cost effectiveness were identified for either review. The evidence presented for all critical and important outcomes for both reviews was reported as very low using modified GRADE.

The first evidence review of crizotinib for relapsed or refractory ALK-positive ALCL included three single-arm, phase II trials. The available evidence demonstrated that following crizotinib treatment the majority of patients experienced at least a partial response to treatment and that disease progression and survival rates appeared favourable. Treatment adherence rates seemed reasonably high, despite common, but few serious, adverse events. It was noted that some patients would not be able to tolerate treatment and would not experience any benefit. Slightly more positive clinical effectiveness and safety results were noted for the second review of crizotinib for ALK-positive unresectable IMT which consisted of three studies, reported in four papers. One study was a retrospective case series, one a single-arm trial and the last was a phase II clinical trial.

Limitations of the studies presented were discussed including the lack of comparison with standard care, short duration of follow up for potentially lifelong treatment, lack of QoL evidence to further support the disease response and survival benefits seen, lack of statistical analyses and small numbers of study participants.

The proposition and supporting documents were considered and some amendments required.

Panel members discussed whether this treatment is used as a bridge to haemopoietic stem cell transplantation (HSCT) and questioned how many patients are likely to go on to receive HSCT. It is not clear from the studies or proposition.

The medicine's administration as described in the Summary of Product Characteristics (SmPC) was discussed and actual clinical practice regarding administration in younger children. Panel members agreed this should be clinical discretion.

EHIA – no amendments requested.

PIA – no amendments requested.

Recommendation

Clinical Panel recommends that this proposition progresses as a routine commissioning policy proposition. The Panel members, though, asked for clarification from the Policy Working Group

(PWG) regarding the use and then frequency of use of crizotinib as a bridging treatment for relapsed or refractory ALK-positive ALCL, its proposed line of treatment and prescribed use for ALK-positive unresectable IMT and its administration for both conditions, before this progresses.

Why the panel made these recommendations

The evidence and reported outcomes were considered carefully. Panel members discussed the very low certainty of the evidence but agreed that the evidence base supported the proposition. Further assurance from the PWG is required regarding the use and administration of crizotinib. It was agreed that the amendments requested would be considered via Chair's action.

Documentation amendments required

Policy Proposition:

- Clarification required from the PWG regarding the use of this treatment as a bridging therapy; and amendments to the proposition would be needed, including footnotes, as required to make this position clear. The PWG to clarify what proportion of patients would be expected to go on to HSCT.
- Clarification required regarding the wording in the treatment's marketing authorisation (MA) and whether the treatment as proposed is within its MA or off-label.
- Inclusion criteria: removal of the last bullet point and related footnote four.
- Dosing section, page six, dosing information for paediatric patients requires amending to remove reference to swallowing capsules.
- Governance section, page 10 - the capitalisation of crizotinib needs amending to be lower case.

Blueteq® Form:

- Removal of criterion five.

Declarations of Interest of Panel Members: One received.

Panel Chair: Anthony Kessel, Deputy National Medical Director, Specialised Services

<u>Post-Panel Amendments</u>

Suggest Post-Panel Amendment	PWG Response	Page number (if applicable)
Policy Proposition		
• Clarification required from the PWG regarding the use of this treatment as a bridging therapy; and amendments to the proposition would be needed, including	It is the opinion of the Clinical Lead that an estimated 80% of patients with ALK-positive ALCL will use crizotinib as a bridging therapy to HSCT. HSCT is a potentially curative treatment. This has been clarified on p.6 (footnote) of the policy document (below):	p.6

footnotes, as required to make this position clear. The PWG to clarify what proportion of patients would be expected to go on to HSCT.	*Clinical consensus suggests that approximately 80% of paediatric patients with ALK-positive ALCL will use crizotinib as a bridging therapy to allo-HSCT. Patients with ALK-positive ALCL who have received successful treatment with crizotinib (e.g. no disease progression whilst on treatment) and who have subsequently gone on to have allo-HSCT would not be exempt from receiving further treatment with crizotinib if their disease were to relapse following transplant and they met the eligibility criteria outlined in this NHS England Policy.*	
• Clarification required regarding the wording in the treatment's marketing authorisation (MA) and whether the treatment (for IMT) as proposed is within its MA or off-label.	The MA for crizotinib use in IMT states: *'The treatment of paediatric patients (age ≥ 6 to < 18 years) with recurrent or refractory anaplastic lymphoma kinase (ALK)-positive unresectable inflammatory myofibroblastic tumour (IMT)'* The wording regarding the indication for crizotinib use in IMT used in the policy proposition is *ALK-positive unresectable IMT*. The Clinical Lead has confirmed that the indication for crizotinib use for unresectable IMT as outlined in the NHS England policy is off-label. The policy document and Blueteq form have been updated to reflect this.	p.6, p.10 Blueteq amended
• Inclusion criteria: removal of the last bullet point and related footnote four.	This age limit for this policy has been restricted in line with the independent evidence review and the SmPC for crizotinib 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.' A footnote has been added to p.6 which states that *crizotinib is currently only commercially available in the*	p.5

	form of oral capsules which must be swallowed whole. Preparation of crizotinib as an oral suspension is off-label. If, following an informed discussion between the treating clinician, patient and/or parent, manipulation of the delivery method of crizotinib is felt to be appropriate, this is undertaken at the risk and discretion of the treating clinician. The inclusion criterion on p.5 relating to the ability to swallow capsules has been removed.	
• Dosing section, page six, dosing information for paediatric patients requires amending to remove reference to swallowing capsules.	As above.	p.6
• Governance section, page 10 - the capitalisation of crizotinib needs amending to be lower case.	Amended.	p.10
Blueteq® Form		
• Removal of criterion five.	As above.	Amended