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HEALTH TECHNOLOGY BRIEFING
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Crizotinib for paediatric ALK-positive anaplastic large cell lymphoma or inflammatory myofibroblastic tumour

NIHRIO ID	30531	**NICE ID**	10574
Developer/Company	Pfizer Limited	**UKPS ID**	659713

Licensing and market availability plans	Currently in Phase I/II clinical trials.

SUMMARY

Anaplastic large cell lymphoma (ALCL) and inflammatory myofibroblastic tumour (IMT) are both rare conditions that usually affect children and young adults. ALCL is a type of cancer that occurs when T-cells, which contribute to the body's immune system, become abnormal. IMTs are most commonly non-cancerous (benign), however in some cases the tumour can become cancerous (malignant). Both conditions can be ALK-positive (ALK+), this means that the tumour cells have a mutation in anaplastic lymphoma kinase (ALK) resulting in uncontrolled cell replication. These conditions may not be able to be treated through surgical removal of the tumour (unresectable); they may also come back after treatment (relapse) or be resistant to current treatment options (refractory).

Crizotinib is an anticancer medication that can be taken up to twice daily, orally, as a capsule. This medication acts by blocking the growth and spread of tumorous cells that are ALK+. If licenced, crizotinib would be the first biomarker-driven therapy for paediatric ALK+ ALCL and IMT.

PROPOSED INDICATION

For the treatment of paediatric patients (aged ⩾6 years to <18 years of age, able to swallow the capsules) with relapsed or refractory systemic ALK+ anaplastic large cell lymphoma (ALCL), or with unresectable, recurrent, or refractory ALK+ inflammatory myofibroblastic tumour (IMT).[a]

TECHNOLOGY

DESCRIPTION

Crizotinib (Xalkori) is a selective small-molecule inhibitor of the ALK receptor tyrosine kinase (RTK) and its oncogenic variants.[1] ALK gene activation is involved in carcinogenesis of a number of cancers such as ALCL, lung cancer, inflammatory myofibroblastic tumours and neuroblastoma as a result of fusion with other oncogenes, gene amplification, mutation or protein overexpression.[2,3] ALK is a therapeutic target in cancers that are ALK+ and crizotinib inhibits ALK function.[2]

Crizotinib is in clinical development for paediatric patients with ALK+ ALCL or ALK+ IMT. In the phase I/II clinical trial (NCT00939770) participants were given crizotinib oral capsules twice daily at a dose of 100, 130, 165, 215, 280 or 365 mg/m^2.[4]

INNOVATION AND/OR ADVANTAGES

Crizotinib is not currently licenced for children, if licenced this would be the first biomarker-driven therapy (precision medicine, which uses a biological molecule that is an indicator of a specific condition[5]) for paediatric ALK+ ALCL.[6]

In the phase I/II study of patients aged 1 to 21 years with solid tumours and ALCL, the overall response rate for patients who were ALK+ was 88%. Response was maintained for up to six months in 39% of patients and up to twelve months in 22% of patients.[7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Crizotinib has US FDA Breakthrough Therapy designation (2018) and was granted priority review in September 2020.[6]

Crizotinib is indicated in the EU as a monotherapy for:[8]
- The first-line treatment of adults with ALK+ advanced non-small cell lung cancer (NSCLC)
- The treatment of adults with previously treated ALK+ advanced NSCLC
- The treatment of adults with ROS1-positive (ROS1+) advanced NSCLC

Crizotinib is currently marketed in the UK for ALK+ advanced NSCLC (specialist use only), and ROS1+ advanced NSCLC (specialist use only).[9]

Very common (may affect more than 1 in 10 people) side effects include vision changes (blurred vision, double vision and light flashes), vomiting, diarrhoea, nausea, oedema, constipation, decreased appetite, tiredness, dizziness, neuropathy, change in taste, abdomen pain, anaemia, skin rash, reduced heart rate, neutropenia, leukopenia and transaminitis (elevated transaminases).[10,11]

[a] Information provided by Pfizer Limited on UK PharmaScan.

Crizotinib is currently in phase II clinical trials for lobular breast carcinoma, gastric cancer, haematological cancers, solid tumours, metastatic cancer, lung cancer, neurofibromatosis 2, progressive vestibular schwannoma, renal cell carcinoma, brain metastases, amongst others listed on ClinicalTrials.gov. Crizotinib is currently in phase III clinical trials for NSCLC, neoplasms and ganglioneuroblastoma.[12]

PATIENT GROUP

DISEASE BACKGROUND

Lymphoma is a cancer that starts in the lymph nodes or other areas of the lymphatic system. There are many types of lymph cancer which can be defined in two broad categories - Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). HL is characterised by the presence of Reed Sternberg cells, whereas in NHL these are absent.[13]

ALCL is a rare type of NHL, which occurs when T-cells (also known as T-lymphocytes) become abnormal. T-cells are white blood cells that are part of the body's immune response. ALCL can be ALK+, where the lymphoma cells have a protein called anaplastic lymphoma kinase, or ALK-negative (ALK-) where the cells do not have ALK.[14] ALK+ ALCL is the most common type of ALCL and is a fast-growing lymphoma.[15] Symptoms of ALK+ ALCL, include night sweats, fevers, and unexplained weight loss. When ALCL affects areas of the body outside the lymphoma nodes this can result in other symptoms, depending on the affected areas, such as loss of appetite, tiredness, diarrhoea, vomiting, shortness of breath, cough, rashes and anaemia.[14,15] The exact causes of ALCL are not known.[14] Most people with ALK+ ALCL are diagnosed at an advanced stage, meaning the lymphoma affects several areas of the body. A lymphoma is classed as refractory if it does not respond to treatment, or relapsed if it comes back after treatment.[15]

Inflammatory myofibroblast tumour (IMT) is a rare kind of soft tissue tumour, which is usually benign.[16,17] There are two types of cell that develop in an IMT: myofibroblasts and immune cells (as part of inflammatory response). Myofibroblasts ordinarily help maintain the shape of organs and are also part of wound healing. IMT usually starts in the lungs, but can also develop in the bladder, uterus, larynx, stomach, liver or intestine.[17,18] IMT can affect nearby tissue, which can be problematic if located in essential organs like the lung or stomach, and in rare cases it can spread (metastasise) to distant organs.[17] A tumour is defined as unresectable if it cannot be removed with surgery.[19] It is not clear what causes IMT, however ALK presence (ALK+) can indicate genetic changes characteristic of IMT.[18] There are associations between MIT and the following:[17]

- Infections, such as organising pneumonia, Epstein-Barr virus and E. coli
- Previous abdominal surgery
- Trauma
- Radiation therapy
- Steroid usage

Symptoms of IMT include fevers, night sweats, weight loss, feeling unwell and pain at the site of the tumour.[16]

CLINICAL NEED AND BURDEN OF DISEASE

ALK+ lung cancers make up 4% of lung cancer diagnoses, equating to approximately 3,400 patients in the UK with ALK+ lung cancer, this includes people with ALK+ ALCL.[20]

ALCL usually affects children and young adults, and affects males three times more than females.[14,15]

Fewer than 200 people a year are diagnosed with ALCL in the UK.[15] In 2019-20 in England there were 816 finished consultant episodes (FCE) for patients with a primary diagnosis of ALK+ ALCL (ICD-10 C84.6) totalling to 2,414 FCE bed days and 475 day cases.[21]

IMT is most common in children and young adults.[16,17] As IMT is a rare condition it does not have a designated ICD-10 code specifically associated to it.[22,23] This makes it difficult to estimate incidence, as diagnoses could be placed under the umbrella of different ICD-10 codes, such as "neoplasm of uncertain behaviour, unspecified" (ICD-10 D48.9).[24] This is further complicated by the fact IMT can be benign or malignant (though malignancy is rare).[17] IMT has an approximate prevalence ranging from 0.04% to 0.7%, and makes up around 1% of all lung tumours.[25]

Patients being ALK+ may be associated with a more favourable prognosis compared to those who are ALK-negative, as ALK+ is associated with localisation, with a study showing a higher percentage of patients with localised disease were ALK+ (around 60%). However this association needs to be validated with further studies.[17]

Malignant IMTs were included in Public Health England and Cancer52's research on rare and less common cancers. In England, between 2010 to 2013, there were four cases of IMT, myofibroblastic tumour or not otherwise specified (NOS) in the category of bone sarcoma. Whereas there were 61 cases of IMT, myofibroblastic tumour or NOS in the soft tissue sarcoma category.[22]

There were no definitive mortality statistics found for ALCL or IMT.

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

As with other types of NHL ALK+ ALCL treatment is coordinated by a multidisciplinary team (MDT) who work with the patient and their family to come up with a plan of best possible care depending on disease stage and progression.[26] Potential treatment includes surgery to remove the tumour, chemotherapy, radiotherapy, monoclonal antibody therapy, stem cell therapy and steroids.[26,27]

IMT treatment is similarly organised using an MDT, with treatment options including surgery, radiotherapy, chemotherapy, immunotherapy, steroids, stem cell therapy and other targeted therapies (e.g. enzyme inhibitors).[16,28]

CURRENT TREATMENT OPTIONS

Pharmacological treatments for paediatric patients with ALK+ ALCL, as per recommendations from the international protocol for the treatment of childhood anaplastic large cell lymphoma (ALCL 99), are as follows:[29-31]

- Alternating multiagent chemotherapy, including dexamethasone, methotrexate, ifosfamide, cytarabine, etoposide, cyclophosphamide, doxorubicin
- Vinblastine – may be suitable for lower risk patients to have alone, or in combination with multiagent chemotherapy
- Folinic acid

Pharmacological treatments for soft tissue sarcomas (like ALK+ IMT) are:[32]

- Chemotherapy regimen of ifosfamide and doxorubicin

- Low-dose chemotherapy, such as methotrexate and vinblastine

PLACE OF TECHNOLOGY

If licenced, crizotinib would be the first biomarker-driven therapy for children with ALK+ ALCL or ALK+ IMT.

CLINICAL TRIAL INFORMATION

Trial	NCT01121588; A Phase 1B Open-label Study of the Safety and Clinical Activity of Crizotinib (PF-02341066) in Tumors with Genetic Events Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus **Phase IB** – Active, not recruiting **Location(s):** EU (not including UK), USA and others **Study completion date:** December 2022
Trial design	Open-label, non-randomized interventional treatment.
Population	N=44 (with two paediatric patients with ALK+ IMT and three paediatric patients with ALK+ ALCL[b]); aged 15 years or older; ALK-positive malignancy.
Intervention(s)	Patients receive 250mg crizotinib orally, twice daily, on a continuous dosing schedule.
Comparator(s)	N/A
Outcome(s)	Primary outcomes: • Number of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs);Type, incidence, severity, seriousness and relationship to study medication of adverse events and any laboratory abnormalities [Time Frame: 36 Months] • Overall Response Rate [Time Frame: 36 months] See trial record for a full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT00939770; A Phase 1/2 Study of Crizotinib, an Oral Small Molecule Inhibitor of Anaplastic Lymphoma Kinase (ALK) and C-Met, in Children With Relapsed/Refractory Solid Tumors and Anaplastic Large Cell Lymphoma **Phase I/II** – Completed **Location(s):** USA and Canada **Study completion date:** December 2018
Trial design	Open-label sequential assignment.

[b] Information provided by Pfizer Limited

Population	N=122; aged 1 to 21 years; ALK-positive patients with relapsed or refractory ALCL; ALK-positive patients with relapsed or refractory IMT.
Intervention(s)	Patients receive crizotinib orally, twice daily on days 1-28. Treatment repeats every 28 days in the absence of disease progression or unacceptable toxicity. Dose levels studied were 100, 130, 165, 215, 280 and 365 mg/m^2 twice daily.[4]
Comparator(s)	N/A
Outcome(s)	Primary outcomes: • Maximum-tolerated Dose and Recommended Phase 2 Dose of Crizotinib [Time Frame: 28 days] • Number of Participants With Toxicities of Crizotinib [Time Frame: Up to 30 days post-treatment] • Steady State C Max of Crizotinib [Time Frame: Cycle 1 (day 15- 28) pre-dose, 1, 2,4, 6-8 hours post dose] • Steady State C Average of Crizotinib [Time Frame: Cycle 1 (day 15-28) pre-dose, 1, 2, 4, 6-8 hours post-dose] • Steady State AUC of Crizotinib [Time Frame: Cycle 1 (day 15-28) pre-dose, 1, 2, 4, 6-8 hours post-dose] • Steady State Clearance of Crizotinib [Time Frame: Cycle 1 (day 15-28) pre-dose, 1, 2, 4, 6-8 hour post-dose] See trial record for a full list of other outcomes.
Results (efficacy)	See trial record.
Results (safety)	See trial record.

ESTIMATED COST

The NHS indicative price for crizotinib 200mg and 250mg, for 60 capsules (prescription-only medicine), is £4,689.00 (hospital only).[33]

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance identified.

OTHER GUIDANCE

- European Paediatric Soft Tissue Sarcoma Study Group (EPSSG). A protocol for Localized Non-Rhabdomyosarcoma Soft Tissue Sarcomas (Version 1.1). September 2009[32]

- Stichting Nederlandse Werkgroep Leukemie bij Kinderen (Foundation of the Dutch Working Group on Leukemia in Children). ALCL 99 - International protocol for the treatment of childhood anaplastic large cell lymphoma. July 2000[29]

ADDITIONAL INFORMATION

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