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Clinical Commissioning Policy:

# Dabrafenib for BRAF$^{V600E}$ mutation positive histiocytic neoplasms where standard care has failed (all ages) [2268]

## Summary

Dabrafenib is not recommended to be available off-label as a routine commissioning treatment option for BRAF$^{V600E}$ mutation positive histiocytic neoplasms where standard care has failed. This policy is for all ages in line with the findings from the evidence review.

## Committee discussion

Clinical Panel considered the evidence base and the recommendation was made to progress the policy as proposed. Please see Clinical Panel reports for full details of Clinical Panel's discussion.

The Clinical Priorities Advisory Group committee papers can be accessed here: Dabrafenib for BRAF (V600E) mutation positive histiocytic neoplasms where standard care has failed (all ages)

## What we have decided

NHS England has carefully reviewed the evidence to treat BRAF$^{V600E}$ mutation positive histiocytic neoplasms with dabrafenib where standard care has failed. NHS England recognises that the published evidence identifies that, at present, there is sufficient evidence to commission this treatment. However, following the relative prioritisation process undertaken in May 2024, NHS England has concluded that, balanced against other relative priorities that were also considered during this process, dabrafenib to treat BRAF$^{V600E}$ mutation positive histiocytic neoplasms where standard care has failed will not be funded at this time within the resources available.

The evidence review can be accessed here: Dabrafenib for BRAF (V600E) mutation positive histiocytic neoplasms where standard care has failed (all ages)

# Plain language summary

## About histiocytic neoplasms

Histiocytic neoplasms are very rare, complex blood cancers that may lead to fatal illness or even death. They can occur at any age and are fatal in 10% of children with high-risk disease at one year and in up to 70% of adults at 5 years (Liu et al, 2022).

Histiocytic neoplasms are characterised by an over production of a type of white blood cell called histiocytes. Although complex, histiocytic neoplasms are all caused by single changes (mutations or translocations) to genes that code for the mitogen activated protein kinase (MAPK) pathway. The MAPK pathway is a cell signalling pathway that is responsible for cell growth, creation, and survival. Mutations to the MAPK pathway results in hyperactivation of cells, in this case histiocytes, that enter organs from the blood stream leading to organ damage and the formation of inflammatory tumours.

Mutations and translocations can occur to the following genes: *CSF1*, *RAS*, *BRAF*, *MAP2K1 (MEK)*. More than 50% of all histiocytic neoplasms are caused by the $BRAF^{V600E}$ mutation. The MAPK pathway is mutated in many different types of cancer, such as melanoma. In histiocytic neoplasms, a single mutation to one gene in the pathway is sufficient to cause disease.

While there are many ultra-rare and less well-characterised types of histiocytic neoplasm, four main clinical syndromes are recognised that have been clearly shown to be caused by mutations to the MAPK pathway:

1. Langerhans Cell Histiocytosis (LCH)
2. Erdheim Chester Disease (ECD)
3. Juvenile Xanthogranuloma (JXG)
4. Rosai Dorman Disease (RDD)

There are also a few miscellaneous histiocytic neoplasms that do not have a named syndrome and are covered by the ICD11 codes 2B31.1, 2B31.Y and 2B31.Z. Histiocytic neoplasms are highly variable with clinical presentation ranging from single tumours to widespread, multisystem disease. Organs most affected include the skin, bones, brain, and blood forming (haematopoietic) organs but histiocytic neoplasms can affect almost any tissue including the heart, lungs, liver, gut, and soft tissues. A devastating neurodegenerative syndrome is a late complication in about 10% of patients (McClain et al, 2021).

Many patients with histiocytic neoplasms will respond to standard care with chemotherapy. However, standard care treatment fails in a small proportion of patients with high-risk disease (Appendix A).

## About current standard care

All drugs currently used are unlicensed for this indication and are not commissioned by NHS England or approved by NICE. Treatment of histiocytic neoplasms is generally with escalating chemotherapy regimens empirically devised according to internationally agreed protocols and expert guidelines.

Where first line chemotherapy has failed, patients with high-risk LCH disease will usually be initiated on an intensive salvage chemotherapy regime that includes a purine analogue (cytarabine, cladribine, or clofarabine). For patients with ECD, methotrexate and interferon alpha are used, usually once a week, at maximal tolerated doses. Responses to these

drugs are often slow and incomplete, leaving some patients with progressive disease despite treatment.

The only alternative intervention for LCH in children failing all conventional therapy is haematopoietic stem cell transplantation (HSCT), but this is an extremely risky and dangerous procedure and almost all children with high-risk LCH will be too unwell to undergo transplantation. In the case of neurodegeneration and pulmonary LCH, there is no current standard active treatment in children or adults and the patients' disease progresses until death.

In ECD there are no alternative treatments available and patients where standard care has failed, or with life-threatening complications are currently at risk of progression, long-term disability and death.

In JXG conventional therapy usually involves prednisolone, vinblastine, or methotrexate but occasionally these drugs fail to produce an adequate response.

Treatment of RDD is completely empirical and supported only by anecdotal evidence (Abla et al, 2018). Conventional therapy involves empiric sequencing of prednisolone, vinblastine or methotrexate followed by sirolimus, imatinib and lenalidomide. Occasionally these drugs fail to produce an adequate response.

### About dabrafenib

The proposed intervention is off-label use of dabrafenib, an oral BRAF inhibitor. Dabrafenib is NICE approved and commissioned by NHS England for the treatment of melanoma, which also frequently carries $BRAF^{V600E}$, but is more genetically diverse than histiocytic neoplasms which are driven only by single mutations (Dabrafenib | Guidance | NICE). Dabrafenib offers a potentially life-saving line of therapy for those with high-risk disease where standard care has failed.

The main clinical side effects of dabrafenib include fevers; rash; keratosis (adults only); arthralgia; fatigue; alopecia; pain. However, compared with the harmful and unintended consequences of conventional chemotherapy, or untreated progressive disease, the risks of dabrafenib are very low.

Dabrafenib is an oral treatment that is out-patient based, in contrast to standard lines of salvage therapy that require close supervision, recurrent injections or inpatient admission, including the insertion of indwelling central venous catheters, support for bone marrow suppression, and emergency treatment of infections and sepsis.

## Epidemiology and needs assessment

Histiocytic neoplasms are rare, with an incidence of ~2 per million people a year and a prevalence of ~10 per million in the UK. There is little epidemiological data available for histiocytic neoplasms given the rarity. LCH is the most common type of histiocytic neoplasm and whilst it can affect all ages, it is significantly more common in children with a peak of 11 per million in infants. The incidence of LCH is also significantly higher in deprived areas of the UK (deprivation quintiles 4 and 5) (Liu et al, 2022). ECD is the second most common manifestation and has a higher incidence in adult males and is very rare in children. JXG and RDD are very rare manifestations. JXG is primarily a disorder of infancy and childhood, whilst RDD predominantly affects young adults.

Most patients with histiocytic neoplasms will respond to standard of care treatment. However, based on data from the National Congenital Anomaly and Rare Disease Registration Service and anecdotal clinical data, there are an estimated 15 new patients per year with high-risk disease where standard care has failed (Liu et al, 2022). This

corresponds with real-world experience of an independent Histiocytosis Advisory Panel which has recommended treatment for 68 patients with high-risk disease in the last 5 years.

For patients with high-risk disease where one or more standard treatments have failed, dabrafenib offers an additional line of salvage therapy.

These patients currently have limited alternative treatment options and will often progress to life-threatening disease or even death without alternative salvage treatment.

## Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

## Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

## Definitions

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| Mutation | A change or alternation to genetic material. Mutations can result in altered function of the gene which can be harmful or beneficial. In cancer the mutations are usually harmful. |
| Neurodegenerative disease | Neurodegenerative diseases are thought to be caused by damage to neurons in the brain. Neurons make up the nervous system which includes your brain and spinal cord. Unlike some parts of the body, when a neuron gets damaged, it's unable to replace itself. |
| The National Institute for Health and Care Excellence (NICE) | NICE provides national guidance and advice to improve health and social care.<br><br>NICE is an executive non-departmental public body, sponsored by the Department of Health and Social Care. |

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| Salvage therapy | Salvage therapy, also known as rescue therapy, is a form of therapy given after a condition does not respond to standard therapy. Salvage therapy drugs or drug combinations have, in general, much more severe side effects than the standard line of therapy. |
| Translocation | A genetic problem in which material from a chromosome moves to another chromosome or is exchanged with material from it. |

# References


Abla O, Jacobsen E, Picarsic J, Krenova Z, Jaffe R, Emile JF, Durham BH, Braier J, Charlotte F, Donadieu J, Cohen-Aubart F, Rodriguez-Galindo C, Allen C, Whitlock JA, Weitzman S, McClain KL, Haroche J, Diamond EL. Consensus recommendations for the diagnosis and clinical management of Rosai-Dorfman-Destombes disease. Blood. 2018 Jun 28;131(26):2877-2890. doi: 10.1182/blood-2018-03-839753. Epub 2018 May 2. PMID: 29720485; PMCID: PMC6024636.

Liu, H, Stiller, CA, Crooks, CJ, Rous, B, Bythell, M, Broggio, J, et al. Incidence, prevalence and survival in patients with Langerhans cell histiocytosis: A national registry study from England, 2013–2019. Br J Haematol. 2022; 199: 728– 738. https://doi.org/10.1111/bjh.18459

McClain, K.L., Bigenwald, C., Collin, M., Haroche, J., Marsh, R.A., Merad, M., Picarsic, J., Ribeiro, K.B. & Allen, C.E. (2021) Histiocytic disorders. Nat Rev Dis Primers, 7, 73.

# Appendix A

High risk disease would be defined by the following clinical scenarios:

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| **Risk Organ Positive Multi-System Langerhans Cell Histiocytosis (LCH)** (RO+MS-LCH) failing high-dose purine analogues or presenting with critical illness. | • LCH is a disorder occurring at all ages but with much higher incidence in young children. LCH may cause single bone lesions or isolated diabetes insipidus but is well recognised for its high-risk form in infants <1 year old.<br>• Risk organs are the bone marrow, liver, and spleen. LCH involving these organs is a serious condition requiring intensive chemotherapy.<br>• It is staged by a multi-point 'Disease Activity Score (DAS)' ranging from 0-35. Treatment response is indicated by a reduction in the score: through Active Disease Better (ADB) to No Active Disease (NAD).<br>• Treatment failure is defined by failure of the score to decrease: Active Disease Intermediate (ADI) or Active Disease Worse (ADW). These definitions are established through several international prospective clinical trials including the current LCH IV protocol.<br>• Conventional chemotherapy is arduous requiring long inpatient stays and not infrequent admissions to intensive care. Salvage regimes all involve high dose purine analogues such as cytarabine, cladribine or clofarabine.<br>• Most patients in the UK will receive cytarabine and cladribine according to the LCH IV International Trial Protocol salvage arm, Stratum III. The mortality for infants in this condition who fail to respond or become intolerant of chemotherapy, is above 50% and accounts for nearly all LCH-related deaths in children. |
| **Risk Organ Negative Multi-System LCH** (RO-MS-LCH) failing high-dose purine analogues. | • A particularly aggressive form affecting the skin, cranial bones, and posterior pituitary (causing diabetes insipidus) is known to confer a high risk of late neurodegeneration.<br>• This form of 'chronic relapsing LCH' overlaps with the historical syndrome Hand-Schuller-Christian disease.<br>• Patients in second or higher relapse accumulate disease and treatment-related morbidity including bone deformity, destruction of the mandible and loss of teeth, hearing loss, multiple endocrine dysfunctions, visual disturbance and neurodegeneration. |
| **Life-threatening pulmonary LCH** (pLCH) | • Isolated pulmonary LCH (pLCH) can also occur. This occurs in two settings:<br>1. Children with recurrent pneumothoraces requiring ventilation or ECMO when the response to alternative therapy is too slow and there is a high risk of death from infection. Children with pLCH can become extremely ill very quickly requiring mechanical ventilation or even extra-corporeal membrane oxygenation (ECMO).<br>2. Non-smoking adults with progressive respiratory decline (FEV1<70% or DLCO <70% or pulmonary hypertension). These patients have usually failed purine analogues or alternative therapy is precluded because there is a high risk of death from infection. |
| **Neurodegenerative LCH** (ND-LCH) | • A devastating late neurodegenerative syndrome can occur in approximately 10% of older children with multi-system LCH. |

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| | • Typically, ND-LCH begins with a cerebellar syndrome and progresses to physical disability, cognitive decline, and death.<br>• The clinical syndrome is invariably accompanied by diffuse signal changes in the cerebellum and pons on MRI scan.<br>• ND-LCH is a late effect and most patients will have received (and therefore failed) at least one line of prior therapy.<br>• There is no standard of care therapy for ND-LCH. |
| **Erdheim Chester Disease (ECD) with high-risk features** (cardiovascular, respiratory, CNS or end organ damage) | • ECD is a disorder with predominance in older males and is very rare in children.<br>• Improved recognition of ECD reveals a much higher annual incidence than previously thought, now estimated at 1 per million (approximately half as common as LCH).<br>• In more than 50% of cases, there is life-threatening involvement of the cardiovascular, respiratory, and nervous systems that is poorly responsive to any conventional treatment. Neuroinflammatory lesions are also often compounded by neurodegeneration.<br>• Although alternative therapy with methotrexate or interferon alpha can reverse low risk skeletal and soft tissue lesions over months and years, high risk disease requires rapid reversal to avert a fatal outcome. |
| **Juvenile Xanthogranuloma (JXG) in high-risk sites** | • JXG is primarily a disorder of infancy and childhood where it most frequently causes superficial lesions that spontaneously regress, respond to local therapy, or require low intensity treatment with prednisolone, vinblastine, or methotrexate.<br>• A small proportion of patients (approximately 10%) develop progressive systemic JXG involving high risk sites in the nervous system, lung, liver, kidney, or bone.<br>• This can be life threatening when conventional therapy fails. |
| **Rosai Dorman Disease (RDD) in high-risk sites** | • A classical form of RDD affects young adults and is known as ‘sinus histiocytosis with massive lymphadenopathy’. When confined to the lymph nodes it may involute spontaneously or resolve with corticosteroids.<br>• However, about half of cases have extra-nodal disease that may be lethal when it involves the nervous system, pleural cavity, lungs, and other vital organs.<br>• This can be life threatening when conventional therapy fails. |
| **International Classification of Diseases (ICD)11 codes: 2B31.1, 2B31.Y and 2B31.Z** | • These ICD codes cover a miscellany of very rare disorders that may have $BRAF^{V600E}$ mutation and require treatment with inhibitors in exceptional circumstances where life is at risk. |