NHS England Evidence Review:

Dabrafenib for patients with $BRAF^{V600E}$ mutation positive histiocytic neoplasms where standard care has failed

NHS England URN: 2268

NHS England Evidence Review

Dabrafenib for patients with $BRAF^{V600E}$ mutation positive histiocytic neoplasms where standard care has failed

Completed: March 2023

Prepared by Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

This review examines the clinical effectiveness, safety and cost effectiveness of dabrafenib with or without best supportive care compared to best supportive care alone in patients with $BRAF^{V600E}$ mutation positive histiocytic neoplasms.

Histiocytic neoplasms are very rare, complex blood cancers that may lead to fatal illness or even death. They are caused by single mutations or fusions of mitogen activated protein kinase (MAPK) pathway genes. More than 50% of all histiocytic neoplasms are caused by the BRAFV600E mutation. The four main clinical syndromes shown to be caused by mutations to the MAPK pathway are

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

Dabrafenib is an oral BRAF inhibitor. It is NICE approved and commissioned by NHS England for the treatment of melanoma, which also frequently carries $BRAF^{V600E}$ mutation, but is more genetically diverse than histiocytic neoplasms which are driven only by single mutations. Dabrafenib may be given in the outpatient clinic with intermittent monitoring.

There are no standard treatments approved by NICE or NHS England for the treatment of histiocytic neoplasms. All drugs currently used are unlicensed for this indication. Treatment of histiocytic neoplasms is generally with escalating chemotherapy regimens empirically devised according to internationally agreed protocols and expert guidelines.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from dabrafenib more than the wider population of interest.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of dabrafenib with or without best supportive care compared to best supportive care alone in patients with $BRAF^{V600E}$ mutation positive histiocytic neoplasms. The searches for evidence published since January 2013 were conducted on 26 January 2023 and identified 175 references. These were screened using their titles and abstracts and 15 references potentially relating to the use of dabrafenib in $BRAF^{V600E}$ mutation positive histiocytic neoplasms were obtained in full text and assessed for relevance.

Four studies were identified for inclusion: one cohort study and three case series. The cohort study included 22 children, 12 of whom were treated with dabrafenib. A prospective case series followed 22 children and a retrospective case series examined the notes of 20 children. These studies were conducted at the same paediatric hospital and research centre, Beijing Children's Hospital and only included paediatric patients with Langerhans cell histiocytosis (LCH). One retrospective case series was conducted across 3 centres in the United States (2 centres) and Israel (1 centre). This study included 11 adult patients with Erdheim-Chester Disease $BRAF^{V600E}$ mutation positive or ECD/Langerhans Cell Histiocytosis (LCH) $BRAF^{V600E}$-mutation positive disease.

The cohort study compared oral dabrafenib with second-line chemotherapy in patients with $BRAF^{V600E}$ mutation positive histiocytic neoplasms. The case series presented evidence of dabrafenib treatment in patients with $BRAF^{V600E}$ mutation positive histiocytic neoplasms following first-line therapy.

No randomised controlled trial nor cost effectiveness evidence was identified.

In terms of clinical effectiveness:

- **Disease response (critical outcome)**
  - For patients that had first-line chemotherapy followed by oral dabrafenib, compared to patients that had first-line chemotherapy followed by second-line chemotherapy, one cohort study provided very low certainty evidence of a statistically significant improvement in disease state after one month of daily dabrafenib treatment compared to two cycles of second-line chemotherapy. One case series provided very low certainty non-comparative evidence that during dabrafenib treatment, all patients reached partial or complete metabolic response; no statistical analyses were conducted. Two case series provided very low certainty non-comparative evidence that at the end of treatment with dabrafenib, a higher proportion of patients were classed as AD/better and AD/stable than AD/worse; the data were not statistically compared.
- **Overall survival (critical outcome)**
  - One cohort study provided very low certainty evidence of no difference in mortality following dabrafenib treatment compared with second-line chemotherapy; the groups were not compared statistically. One case series, non-comparator data, provided very low certainty evidence of low mortality rates in patients with $BRAF^{V600E}$ mutation positive histiocytic neoplasms treated with dabrafenib.
- **Progression free survival (critical outcome)**
  - One cohort study provided very low certainty evidence of statistically significant improvement in progression free survival when comparing those that had first-line

chemotherapy followed by oral dabrafenib to patients that had first-line chemotherapy followed by second-line chemotherapy. One case series provided very low certainty non-comparative evidence that at the end of two years, patients with $BRAF^{V600E}$ mutation positive histiocytic neoplasms treated with dabrafenib had a progression free survival rate of almost 50%.

- **Quality of life (important outcome)**
  - No evidence was identified for quality of life.
- **Relapse rate (important outcome)**
  - One cohort study provided very low certainty evidence of no statistically significant difference in relapse / progression rate following dabrafenib treatment compared with second-line chemotherapy. Two case series, non-comparator data, provided very low certainty evidence of relapse rates of 32% and 50% in children with $BRAF^{V600E}$ mutation positive histiocytic neoplasms, specifically LCH, treated with dabrafenib.
- **Symptom alleviation (important outcome)**
  - No evidence was identified for symptom alleviation.
- **Organ specific disease response (important outcome)**
  - One cohort study provided very low certainty evidence of a statistically significant shorter time to improvement for the key disease markers of MAS-HLH (temperature, haemoglobin levels and platelet levels) in those treated with dabrafenib compared with those treated with second-line chemotherapy. The same study also provided very low certainty evidence of a statistically significantly smaller spleen size following one month of dabrafenib therapy compared with those receiving second-line chemotherapy. One case series provided very low certainty narrative evidence of improvements in liver, spleen and pituitary disease following dabrafenib therapy**.**

In terms of safety:

- **Adverse events**
  - One cohort study provided very low certainty evidence that there were fewer adverse events in those treated with dabrafenib compared with those treated with second-line chemotherapy; the groups were not statistically compared. The most common adverse event reported across all included studies was skin-related. These studies provide very low certainty evidence that many patients reported adverse events during dabrafenib treatment; however, most were not severe.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- Subgroup results by risk organ group from one retrospective case series reported the critical outcomes, disease response and progression free survival. Subgroup analysis was pre-planned in the cohort.
- The retrospective case series compared outcomes in patients treated with dabrafenib therapy stratified by risk organ group (RO+ve and RO-ve) and reported no statistically significant difference in the effectiveness of dabrafenib in terms of disease response or progression free survival.

In terms of dabrafenib dose:

- Evidence about dabrafenib dose came from one retrospective cohort study, one prospective case series and two retrospective case series.
- One retrospective case series treated adult patients with ECD or ECD/LCH with oral dabrafenib at doses ranging from 50mg, twice daily to 150mg, twice daily. Three studies of paediatric patients with LCH, used an oral dabrafenib dose of 2 mg/kg (twice daily).

Please see the results table (section 5) in the review for further details of outcomes and definitions

Limitations

All the outcomes reported were classified as very low certainty evidence. Limitations reducing certainty for the outcomes reported in the retrospective cohort study included uncertainty about the differences between the groups at baseline, lack of adjustment for potential confounding factors and uncertainty about how drug compliance was measured. Limitations reducing certainty in the outcomes reported in the prospective case series and one of the retrospective case series included uncertainty about whether the inclusion of participants was complete or consecutive and a lack of statistical analysis. A lack of events in one or both arms of an outcome led to serious imprecision for some outcomes; a lack of comparator was also a limitation across all three of the case series.

Conclusion

This evidence review includes one retrospective cohort study, one prospective case series and two retrospective case series. The cohort study compared dabrafenib following first-line chemotherapy with second-line chemotherapy following first-line chemotherapy for $BRAF^{V600E}$ mutation positive histiocytic neoplasms. Three of the four included studies only included paediatric patients with LCH; one study included adults with ECD or ECD/LCH.

There were observational data comparing dabrafenib with second-line chemotherapy in children with LCH for all the critical clinical effectiveness outcomes of interest. There was very low certainty evidence of a statistically significant improvement in those treated with dabrafenib compared with those treated with second-line chemotherapy in disease state (at one month follow-up) and in four-year progression free survival. There was very low certainty evidence of no statistically significant difference in mortality between children with LCH treated with dabrafenib compared to those treated with second-line chemotherapy. Non-comparative data were available for all the critical clinical effectiveness outcomes of interest.

Data for populations >18 years were only available for the outcome ‘disease response.’ There was very low certainty, non-comparative evidence that all adults with ECD or ECD/LCH treated with dabrafenib showed improvement in disease state, reaching partial or complete metabolic response whilst on treatment. No comparative data were available for populations >18 years.

There were also comparative observational data available for the important clinical effectiveness outcomes of relapse rate, organ specific disease response and safety. There was very low certainty evidence of a statistically significantly improved organ specific disease responses in those receiving dabrafenib therapy compared to those receiving second-line chemotherapy. These differences were particularly noted in MAS-HLH markers (body temperature, haemoglobin levels and platelet levels) and spleen size. Cohort data provided very low certainty evidence of no statistically significant difference in relapse rate and/or disease

progression in children treated with dabrafenib compared with those treated with second-line chemotherapy. No data were available for populations >18 years.

Safety outcomes, in the form of adverse events, were reported for those receiving dabrafenib therapy. One cohort study provided very low certainty evidence that there were fewer adverse events in those treated with dabrafenib compared with those treated with second-line chemotherapy. Adverse events were common in both adults and children; however, most were not severe (very low certainty evidence). The most common adverse event reported across all the studies was skin-related.

There was very low certainty evidence of no statistically significant difference in disease response and progression free survival following dabrafenib therapy in children with risk organ positive disease status compared with those with risk organ negative disease status. These results should be interpreted with caution as the subgroups were very small and may not have been large enough to reach statistical significance.

No evidence on cost effectiveness was identified.

The studies identified for this review, therefore, provide very low certainty evidence suggesting improved disease response in adults and children and progression free survival in children associated with dabrafenib with $BRAF^{V600E}$ mutation positive histiocytic neoplasms.

3. Methodology

Review questions

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

1. In patients with BRAF^{V600E} mutation positive histiocytic neoplasms where standard care has failed, what is the clinical effectiveness of dabrafenib with or without best supportive care compared with best supportive care alone?
2. In patients with BRAF^{V600E} mutation positive histiocytic neoplasms where standard care has failed, what is the safety of dabrafenib with or without best supportive care compared with best supportive care alone?
3. In patients with BRAF^{V600E} mutation positive histiocytic neoplasms where standard care has failed, what is the cost effectiveness of dabrafenib with or without best supportive care compared with best supportive care alone?
4. From the evidence selected, are there any subgroups of patients that may benefit from dabrafenib with or without best supportive care more than the wider population of interest?
5. From the evidence selected, what dose of dabrafenib was used in the research studies?

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 [insert date.

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

Four studies were identified for inclusion: one cohort study (Wang et al 2022) and three case series (Kieran et al 2019, Shi et al 2021 & Yang et al 2021). The cohort study compared oral dabrafenib with second-line chemotherapy in patients with $BRAF^{V600E}$ mutation positive histiocytic neoplasms. The case series presented evidence of dabrafenib treatment in patients with $BRAF^{V600E}$ mutation positive histiocytic neoplasms following first-line therapy. No randomised controlled trial evidence was identified.

Table 1 provides a summary of the included studies and full details are given in Appendix E.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported

Bhatia et al 2018
 	
Case series
 	
USA, Israel
	n=11
	
	Adults with $BRAF^{600E}$-mutated ECD or ECD/LCH
	
	No subgroups reported
		Intervention
		
		Oral dabrafenib
		
		Comparison
		
		No comparator
			Duration of dabrafenib therapy (range 4 to 43 months); median not reported
			
			Critical outcomes
			
			• Disease response
			
			Important outcomes
			
			• Safety
			  • Discontinuation
			  • Specific adverse events
			  • Adverse event grading

Shi et al 2021
 	
Case series
 	
China
	n=22
	
	Children with relapsed or refractory LCH with $BRAF^{V600E}$ mutation.
	
	No subgroups reported
		Intervention
		
		Oral dabrafenib
		
		Comparison
		
		No comparator
			Median follow-up 14.0 months (range 4.8 to 37.7)
			
			Critical outcomes
			
			• Disease response
			  • Disease state (AD/better) at 1, 3, 6, 9 & 12 months
			  • LCH Study group criteria at 1 month & 3 months
			• Progression free survival at 1 and 2 years
			
			Important outcomes
			
			• Relapse rate
			• Safety
			  • skin toxicity events

Wang et al 2022
 	
Cohort study
 	
China
	n=22
	
	Children diagnosed LCH and with a secondary MAS-HLH diagnosis carrying the $BRAF^{V600E}$ mutation. LCH and HLH remain uncontrolled following first-line chemotherapy.
	
	No subgroups reported
		Intervention
		
		Oral dabrafenib
		
		Comparison
		
		Second-line chemotherapy
			Median follow-up 28.9 months (range 10.0 to 60.8) v 19.9 months (range 0.8 to 62.8)
			
			Critical outcomes
			
			• Disease response
			  • Disease Activity Score (DAS)[a] at Month 1 / Week 5[b]
			  • Disease state (AD/better) at Month 1 / Week 5
			• Survival
			• Progression free survival at 4 years

Study	Population	Intervention and comparison	Outcomes reported

			Important outcomes
			• Organ specific disease response
			  • Recovery time of temperature, haemoglobin and platelets
			  • Size of spleen at 1 month
			• Safety
			  • Number of AEs
			  • Primary AEs for dabrafenib and chemotherapy

Yang et al 2021
 	
Case series
 	
China
	n=20
	
	Children diagnosed LCH with $BRAF^{V600E}$ mutation. Chemotherapy could not be tolerated, or LCH disease continued to progress following chemotherapy or pituitary lesion was not improved following first-line chemotherapy.
	
	Subgroups:
	• Risk Organs[c]: RO+, RO-
		Intervention
		
		Oral dabrafenib
		
		Comparison
		
		No comparator
			Median follow-up 30.8 months (range 18.9 to 43.6)
			
			Critical outcomes
			• Disease response
			  • Objective response rate at the end of treatment
			  • Disease control rate at the end of treatment
			  • LCH study group criteria at the end of treatment
			  • LCH study group criteria during follow-up at 1, 3, 6, 9 & 12 months
			• Survival
			
			Important outcomes
			• Relapse rate
			• Organ specific disease response
			  • HLH patients
			  • Disease of the liver and spleen
			  • Disease of pituitary
			• Safety
			  • Number of AEs
			  • Grade 3 AEs
			  • Primary AEs

Abbreviations
AD: active disease; AE: adverse events; DAS: Disease Activity Score; ECD: Erdheim-Chester disease; HLH: hemophagocytic lymphohistiocytosis; LCH: Langerhans cell histiocytosis; MAS-HLH: Macrophage activation syndrome-hemophagocytic lymphohistiocytosis; n: number; RO: risk organs; UK: United Kingdom; US: United States of America; v: versus

a LCH disease activity score (DAS) is a 15 domain scale with scores ranging from 0-35 (35 being very poor health). Scores 0-2 are considered low, 3-6 moderate, ≥7 high
b Comparison of DAS after one month of dabrafenib and five weeks (two therapeutic courses) of second-line chemotherapy
c RO+ indicates a high-risk group, a subgroup of interest. The authors do not further define this group.

5. Results

In people with BRAF^{V600E} mutation positive histiocytic neoplasms where standard care has failed, what is the clinical effectiveness and safety of oral dabrafenib with or without best supportive care compared with best supportive care alone?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Disease response **Certainty of evidence:** Very low	This outcome is important to patients because it can reflect the benefits the treatment may have for a patient. This can be important to control the symptomatic burden of the disease and/or reflect subgroups who may configure additional response benefits, allowing the treatment protocol to be individualised. In total, one retrospective cohort study, one prospective case series and two retrospective case series provided evidence relating to disease response in patients with BRAF^{V600E} mutation positive histiocytic neoplasms. The cohort study compared dabrafenib following first-line chemotherapy with second-line chemotherapy following first-line chemotherapy. Disease response was evaluated using the International LCH Study Group Criteria[1], the LCH Disease Activity Score (DAS),[2] and the PET Response Evaluation Criteria in Solid Tumours (PERCIST)[3]. At 1 month: • One cohort study (Wang et al 2022) reported a *statistically significant lower* DAS in those that received dabrafenib compared with those that received second-line chemotherapy (2.5 v 8.5, p=0.002). The same cohort study also showed a *statistically significant difference* in those reporting to be AD/better on the LCH Study Group Criteria at one month between those that received dabrafenib (n=12, 100%) and those receiving second-line chemotherapy (n=3, 37.5%; p=0.004). **(VERY LOW)** • One prospective case series (Shi et al 2021) reported that 86.4% of those on dabrafenib (n=19) were AD/better at one month follow-up. No statistical comparison was reported. **(VERY LOW)** During follow-up: • One prospective case series (Shi et al 2021) reported that amongst the group receiving dabrafenib over 12 months, the proportion with an AD/better score decreased from 86.4% at one month follow-up (n=19) to 64.3% at nine months follow-up (n=9). The results were not compared statistically. **(VERY LOW)** • One retrospective case series (Bhatia et al 2018) reported that for 11 adults with ECD and ECD/LCH achieved either partial or complete metabolic response on dabrafenib treatment (total cases=11, PMR=8, CMR=3); dabrafenib treatment ranged from four to 43 months; median not reported. No statistical analyses were reported. **(VERY LOW)** At the end of treatment:

[1] International LCH Study Group Criteria, Disease State: non-active disease (NAD); active disease (AD)/better; AD/intermediate; AD/worse

[2] LCH disease activity score (DAS) is a 15 domain scale with scores ranging from 0-35 (35 being very poor health). Scores 0-2 are considered low, 3-6 moderate and ≥7 high

[3] Modified PET Response Criteria in Solid Tumours (PERCIST): up to 5 lesions were selected, SUVs were normalized for body weight, and the FDG avidity of each lesion was calculated as $SUV_{max\ lesion} - SUV_{max\ liver\ background} = SUV_{corrected\ for\ background}$, or simply "SUV." For brain lesions, brain background was used *in lieu* of liver background. Values less than zero were treated as 0, which allowed the FDG avidity of a lesion to be considered as the excess avidity above background. Complete metabolic response (CMR) was defined as all lesions decreased to or below background; partial metabolic response (PMR) was defined as a 50% or greater decrease from baseline in the sum SUV of all target lesions; progressive metabolic disease (PMD) was defined as a 50% or greater increase from the nadir in the sum of SUV all target lesions or the appearance of new evaluable lesions; stable metabolic disease (SMD) was when the response did not meet other criteria

Outcome	Evidence statement
	• One retrospective case series (Yang et al 2021) reported that at the end of dabrafenib treatment, 65% of patients were AD/better (n=13), 10% AD/stable (n=2), 5% AD/mixed (n=1) and 20% AD/worse (n=4). The DCR rate[4] in those treated with dabrafenib was 75%. No statistical comparison was reported. **(VERY LOW)** • One prospective case series (Shi et al 2021) reported that at 12 months follow-up and treatment completion, 100% of the patients still taking dabrafenib were classed as AD/better (n=11). **(VERY LOW)** **For patients that had first-line chemotherapy followed by oral dabrafenib, compared to patients that had first-line chemotherapy followed by second-line chemotherapy, one cohort study provided very low certainty evidence of a statistically significant improvement in disease state after one month of daily dabrafenib treatment compared to two cycles of second-line chemotherapy. One case series provided very low certainty non-comparative evidence that during dabrafenib treatment, all patients reached partial or complete metabolic response; no statistical analyses were conducted. Two case series provided very low certainty non-comparative evidence that at the end of treatment with dabrafenib, a higher proportion of patients were classed as AD/better and AD/stable than AD/worse; the data were not statistically compared.**
Overall survival **Certainty of evidence:** Very low	Overall survival is important to patients as individuals with refractory histiocytic neoplasms have a high mortality rate due to progression of cancer. Improved survival is an important marker of effective treatment. In total, one retrospective cohort study and one retrospective case series provided evidence relating to overall survival in children with $BRAF^{V600E}$ mutation positive histiocytic neoplasms. The cohort study compared dabrafenib following first-line chemotherapy with second-line chemotherapy following first-line chemotherapy. • One cohort study (Wang et al 2022) reported that during follow-up (median: 28.9 months, range 10.0 to 60.8 months), no patients died in either the dabrafenib group or the chemotherapy comparator group. **(VERY LOW)** • One retrospective case series (Yang et al 2021) reported that during 30.8 months of follow-up (range 18.9 to 43.6 months), no patients died. **(VERY LOW)** **One cohort study provided very low certainty evidence of no difference in mortality following dabrafenib treatment compared with second-line chemotherapy; the groups were not compared statistically. One case series, non-comparator data, provided very low certainty evidence of low mortality rates in patients with $BRAF^{V600E}$ mutation positive histiocytic neoplasms treated with dabrafenib.**
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, one retrospective cohort study and one prospective case series provided evidence relating to progression free survival in children with $BRAF^{V600E}$ mutation positive histiocytic neoplasms. The cohort study compared dabrafenib following first-line chemotherapy with second-line chemotherapy following first-line chemotherapy. *Progression free survival (PFS) rate* • One cohort study (Wang et al 2022) reported a *statistically significant higher* PFS in those that received dabrafenib (74% ± 12.5%) compared with those that received second-line chemotherapy (14.6% ± 13.5%) at four years follow-up (p=0.034). **(VERY LOW)**

[4] DCR: disease control rate; the percentage of all patients AD/better and AD/stable at the end of treatment

Outcome	Evidence statement
	• One prospective case series (Shi et al 2021) reported a PFS of 47.9% (95% CI 31.3% to 64.5%) at 2 years and a PFS of 63.9% (95% CI 51.7% to 76.1%) at one year in those treated with dabrafenib. **(VERY LOW)** **One cohort study provided very low certainty evidence of statistically significant improvement in progression free survival when comparing those that had first-line chemotherapy followed by oral dabrafenib to patients that had first-line chemotherapy followed by second-line chemotherapy. One case series provided very low certainty non-comparative evidence that at the end of two years, patients with $BRAF^{V600E}$ mutation positive histiocytic neoplasms treated with dabrafenib had a progression free survival rate of almost 50%.**
Important outcomes	
Quality of Life **Certainty of evidence:** N/A	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.**
Relapse rate **Certainty of evidence:** Very low	This outcome is important to patients because it can indicate that their condition may not be adequately controlled by their current treatment, impacting on quality of life and patient treatment decisions. In total, one retrospective cohort study, one prospective case series and one retrospective case series provided evidence relating to relapse rate in children with $BRAF^{V600E}$ mutation positive histiocytic neoplasms. The cohort study compared dabrafenib following first-line chemotherapy with second-line chemotherapy following first-line chemotherapy. • One cohort study (Wang et al 2022) reported that during follow-up (median: 28.9 months, range 10.0 to 60.8 months), three patients in the dabrafenib group (n=12, 25.0%) and six patients in the chemotherapy comparator group (n=8, 75.0%) had disease progression or relapse; the difference between the groups was *not statistically significant*. **(VERY LOW)** • One prospective case series (Shi et al 2021) reported that during 14.0 months of follow-up (range 4.8 to 37.7 months), seven patients had disease relapse or progression (n=7, 31.8%). **(VERY LOW)** • One retrospective case series (Yang et al 2021) reported that during 30.8 months of follow-up (range 18.9 to 43.6 months), 50% of the children suffered relapse or LCH progression following cessation of dabrafenib treatment (10 of 20). **(VERY LOW)** **One cohort study provided very low certainty evidence of no statistically significant difference in relapse / progression rate following dabrafenib treatment compared with second-line chemotherapy. Two case series, non-comparator data, provided very low certainty evidence of relapse rates of 32% and 50% in children with $BRAF^{V600E}$ mutation positive histiocytic neoplasms, specifically LCH, treated with dabrafenib.**
Symptom alleviation **Certainty of evidence:** N/A	This outcome is important to patients because reduction of symptoms directly improves the patient's quality of life. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment. **No evidence was identified for symptom alleviation.**
Organ specific disease response **Certainty of evidence:** Very low	This outcome is important to patients as objective measures of functioning of affected organs. Given the progressive nature of pulmonary and neurodegenerative histiocytosis, disease activity results might not be expected to return to normal following treatment, however, stabilisation may indicate treatment has successfully limited disease progression.

Outcome	Evidence statement
	One retrospective cohort study and one retrospective case series provided evidence relating to organ specific disease response in children with $BRAF^{V600E}$ mutation positive histiocytic neoplasms. The cohort study compared dabrafenib following first-line chemotherapy with second-line chemotherapy following first-line chemotherapy. *MAS-HLH disease: recovery time of temperature, haemoglobin and platelets* • One cohort study (Wang et al 2022) reported *statistically significant fewer* days until reduction of fever to normal body temperature in those children treated with dabrafenib (n=12, median 2.0 days) compared with those treated with second-line chemotherapy (n=8, median 18.0 days; p<0.001). **(VERY LOW)** • The same study reported *statistically significant fewer* days until normal levels of haemoglobin were reached in those children treated with dabrafenib (n=12, median 7.0 days) compared with those treated with second-line chemotherapy (n=8, median 30.5 days; p<0.001). **(VERY LOW)** • The cohort study also reported *statistically significant fewer* days until normal levels of platelets were reached in those children treated with dabrafenib (n=12, median 7.0 days) compared with those treated with second-line chemotherapy (n=8, median 27.0 days; p<=0.013). **(VERY LOW)** *Liver and Spleen* • One cohort study (Wang et al 2022) reported *statistically significant smaller* spleen size following one month of dabrafenib therapy (n=12) compared with those treated with second-line chemotherapy (n=8) for two rounds (p=0.047). **(VERY LOW)** • One retrospective case series (Yang et al 2021) stated that five patients showed improvement in all lesions except hepatic cirrhosis following a median of 11.4 months of dabrafenib treatment (range 3.1 to 19.2 months). Two additional patients with symptoms of hepatosplenomegaly and liver damage (but no cirrhosis-related manifestations) reported a reduction in symptoms. Clinical measurements were not reported. **(VERY LOW)** *Pituitary* • One retrospective case series (Yang et al 2021) stated that seven patients with pituitary lesions showed no further progression of disease following a median of 11.4 months of dabrafenib treatment (range 3.1 to 19.2 months). One of three patients with diabetes insipidus had an improvement of symptoms. Clinical measurements were not reported. **(VERY LOW)** **One cohort study provided very low certainty evidence of a statistically significant shorter time to improvement for the key disease markers of MAS-HLH (temperature, haemoglobin levels and platelet levels) in those treated with dabrafenib compared with those treated with second-line chemotherapy. The same study also provided very low certainty evidence of a statistically significantly smaller spleen size following one month of dabrafenib therapy compared with those receiving second-line chemotherapy. One case series provided very low certainty narrative evidence of improvements in liver, spleen and pituitary disease following dabrafenib therapy.**
Safety	
Adverse events **Certainty of evidence:** Very low	These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment. In total, one retrospective cohort study, one prospective case series and two retrospective case series provided evidence relating to safety in patients with $BRAF^{V600E}$ mutation positive histiocytic neoplasms. The cohort study compared dabrafenib following first-line chemotherapy with second-line chemotherapy following first-line chemotherapy.

Outcome	Evidence statement
	Number of adverse events (AEs) • One cohort study (Wang et al 2022) reported fewer adverse events in those children treated with dabrafenib (4, 33.3%) compared with those treated with second-line chemotherapy (12, 92.3%); the groups were not statistically compared. **(VERY LOW)** • One retrospective case series (Yang et al 2021) reported 17 AEs in nine patients over a median of 11.4 months of dabrafenib treatment (range 3.1 to 19.2 months). None of the AEs were reported to be severe. **(VERY LOW)** • One retrospective case series (Bhatia et al 2018) reported AEs in eight out of 11 adults over a range of 4 to 43 months of treatment with dabrafenib. One patient reported Grade 3 fever; all other AEs were Grade 1 or 2. **(VERY LOW)** *Specific AEs* • One cohort study (Wang et al 2022) stated that the primary AEs for dabrafenib patients were skin-related toxicity (75%), diarrhoea, vomiting, fatigue, joint pain and transient myocardium enzyme rising; whilst the most common AEs for those receiving second-line chemotherapy were myelosuppression and pancytopenia. **(VERY LOW)** • One retrospective case series (Yang et al 2021) reported that over a median of 11.4 months of dabrafenib treatment (range 3.1 to 19.2 months) the most common AE was maculopapular rash with eight events (47.1%). **(VERY LOW)** • One prospective case series (Shi et al 2021) reported that during 14.0 months of follow-up (range 4.8 to 37.7 months), 13 children had skin toxicity due to dabrafenib treatment (56.5%). **(VERY LOW)** • One prospective case series (Bhatia et al 2018) reported skin toxicities to be the most common (panniculitis, keratoacanthoma, keratosis pilaris and skin; n=4) followed by fever (n=3), fatigue (n=2) and arthralgia (n=2) during dabrafenib treatment (range 4 to 43 months; median not reported). **(VERY LOW)** **One cohort study provided very low certainty evidence that there were fewer adverse events in those treated with dabrafenib compared with those treated with second-line chemotherapy; the groups were not statistically compared. The most common adverse event reported across all included studies was skin-related. These studies provide very low certainty evidence that many patients reported adverse events during dabrafenib treatment; however, most were not severe.**
Abbreviations AD: active disease; AE: adverse events; CI: confidence interval; CMR: complete metabolic response; DAS: Disease Activity Score; DCR: disease control rate; ECD: Erdheim-Chester Disease; LCH: Langerhans cell histiocytosis; MAS-HLH: Macrophage activation syndrome-hemophagocytic lymphohistiocytosis; n: number; ORR: objective response rate; PERCIST: Modified PET Response Criteria in Solid Tumours; PFS: progression free survival; PMR: partial metabolic response; v: versus	

In people with BRAF^{V600E} mutation positive histiocytic neoplasms where standard care has failed, what is the cost effectiveness of oral dabrafenib with or without best supportive care compared with best supportive care alone?

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 oral dabrafenib with or without best supportive care more than the wider population of interest?

Outcome	Evidence statement
Subgroups	Subgroup results by risk organ (RO) group[5] from one retrospective case series reported the critical outcomes, disease response and progression free survival. Subgroup analysis was pre-planned in the cohort. **Disease Response** • One case series (Yang et al 2021) reported a higher treatment response following dabrafenib therapy in those from RO+ve group (n=14, 78.6%) compared to those that were RO-ve (n=6, 33.3%). The results were *not statistically significant.* (p=0.122) **Progression free survival** • One retrospective case series (Yang et al 2021) showed *no statistically significant difference* in the 2-year progression free survival rate in those in the RO+ve group compared to those in the RO-ve group after dabrafenib treatment (X^2=0.062, p=0.804). **One retrospective case series compared outcomes in paediatric patients treated with dabrafenib therapy stratified by risk organ group (RO+ve and RO-ve) and reported no statistically significant difference in the effectiveness of dabrafenib in terms of disease response or progression free survival.**
Abbreviations n: number; RO: risk organ group; RO+ve: risk organ positive, LCH disease involved risk organs; RO-ve: risk organ negative, LCH disease did not involve risk organs	

From the evidence selected, what dose of dabrafenib was used in the research studies?

Outcome	Evidence statement
Dabrafenib dose	Evidence about dabrafenib dose came from one retrospective cohort study, one prospective case series and two retrospective case series. • One cohort study (Wang et al 2022) treated children with poorly controlled LCH and MAS-HLH with oral dabrafenib at a dose of 2 mg/kg, twice daily for 12 months. • The two additional case series (Shi et al 2021 and Yang et al 2021), used the same dosing regimens for their paediatric patients with LCH: oral dabrafenib, 2 mg/kg, twice daily. • One retrospective case series (Bhatia et al 2018) treated adults with ECD or ECD/LCH with oral dabrafenib at the following doses (all twice daily): 50mg, 75mg, 100mg, 150mg. Treatment ranged from 4 to 43 months and was ongoing for n=9 patients at the time of follow-up; median follow-up time was not reported. **One retrospective case series treated adult patients with ECD or ECD/LCH with oral dabrafenib at doses ranging from 50mg, twice daily to 150mg, twice daily. Three studies of paediatric patients with LCH, used an oral dabrafenib dose of 2 mg/kg (twice daily).**
Abbreviations ECD: Erdheim-Chester Disease; LCH: Langerhans cell histiocytosis; MAS-HLH: Macrophage activation syndrome-hemophagocytic lymphohistiocytosis; mg: milligram; kg: kilogram; n: number	

[5] The authors do not further define this group.

6. Discussion

This evidence review examines the clinical effectiveness, safety and cost effectiveness of dabrafenib with or without best supportive care compared to best supportive care alone in patients with $BRAF^{V600E}$ mutation positive histiocytic neoplasms. The critical outcomes of interest were disease response, overall survival and progression free survival. Important outcomes of interest were quality of life, relapse rate, symptom alleviation, organ specific disease response and safety. Evidence on cost effectiveness was also sought.

Evidence was available from one retrospective cohort study, one prospective case series and two retrospective case series. The cohort study compared dabrafenib following first-line chemotherapy with second-line chemotherapy following first-line chemotherapy. No randomised controlled studies were identified comparing dabrafenib with or without best supportive care to best supportive care alone in people with $BRAF^{V600E}$ mutation positive histiocytic neoplasms.

One retrospective case series was conducted across three centres in the United States (2 centres) and Israel (1 centre). This study included 11 adult patients with Erdheim-Chester Disease (ECD) or ECD/Langerhans cell histiocytosis (LCH) $BRAF^{V600E}$ mutation positive histiocytic neoplasms.

Three of the studies (Wang et al 2022, Shi et al 2021, Yang et al 2021) were conducted at the same paediatric hospital and research centre, Beijing Children's Hospital and only included paediatric patients with LCH. The cohort study (Wang et al 2022) included 20 patients (n=12 treated with dabrafenib), Shi et al followed 22 children and Yang et al retrospectively examined the notes of 20 LCH patients. The recruitment dates for the three studies overlap and it is likely that some of the patients appear in more than one of the included studies; there is insufficient information to ascertain the extent of the overlap.

The duration of dabrafenib treatment and follow-up of individual patients within the included studies varied considerably. Dabrafenib therapy was offered for 12 months in studies reported by Wang et al (2022) and Shi et al (2021) and for six to 12 months in Yang et al (2021). In contrast, Bhatia et al (2018) reported a range of four to 43 months of oral dabrafenib treatment for the eleven adults included in the case series. Median follow-up ranged from one year to 2.5 years from dabrafenib commencement for the paediatric studies; median follow-up time was not reported for Bhatia et al (2018).

Evidence was identified for all the critical clinical outcomes of interest for this review; however, evidence was not identified for the important outcomes 'quality of life' and 'symptom alleviation.' It is possible that some of the outcome measures reported in other PICO categories may be useful for these important outcomes, but they were determined to be a better fit for one of the other PICO categories listed. The text provided in the PICO was used to determine which category was the best fit for the outcome measures available. The outcomes reported were primarily objective or assessed using standardised assessment tools. Some outcomes around organ specific disease response and safety were reported as narrative descriptions. The use of standardised outcome measures allows some interpretation of the level of function associated with specific scores; however, it was not always clear how clinically significant the changes observed on some scales were. No specific detail about what the minimal clinically important thresholds or differences might be was reported for the outcomes considered.

All the outcomes reported were classified as very low certainty evidence. Limitations reducing certainty for the outcomes reported in the retrospective cohort study included uncertainty about the differences between the groups at baseline, lack of adjustment for potential confounding factors and uncertainty about how drug compliance was measured. Limitations reducing

certainty in the outcomes reported in the prospective case series (Shi et al 2021) and one of the retrospective case series (Bhatia et al 2018) included uncertainty about whether the inclusion of participants was complete or consecutive and a lack of statistical analysis. A lack of events in one or both arms of an outcome led to serious imprecision for some outcomes; a lack of comparator was also a limitation across all three of the case series.

One retrospective case series reported results for patient subgroups. Patients were divided into two groups: RO+ (risk organ-involved group) and RO- (risk organ-noninvolved). Disease response and progression free survival were presented by this risk group designation; no significant difference was found following dabrafenib treatment between the groups.

No evidence on cost effectiveness was identified.

7. Conclusion

This evidence review includes one retrospective cohort study, one prospective case series and two retrospective case series. The cohort study compared dabrafenib following first-line chemotherapy with second-line chemotherapy following first-line chemotherapy for $BRAF^{V600E}$ mutation positive histiocytic neoplasms. Three of the four included studies only included paediatric patients with LCH; one study included adults with ECD or ECD/LCH.

There were observational data comparing dabrafenib with second-line chemotherapy in children with LCH for all the critical clinical effectiveness outcomes of interest. There was very low certainty evidence of a statistically significant improvement in those treated with dabrafenib compared with those treated with second-line chemotherapy in disease state (at one month follow-up) and in four-year progression free survival. There was very low certainty evidence of no statistically significant difference in mortality between children with LCH treated with dabrafenib compared to those treated with second-line chemotherapy. Non-comparative data were available for all the critical clinical effectiveness outcomes of interest.

Data for populations >18 years were only available for the outcome 'disease response.' There was very low certainty, non-comparative evidence that all adults treated with dabrafenib showed improvement in disease state, reaching partial or complete metabolic response whilst on treatment. No comparative data were available for populations >18 years.

There were also comparative observational data available for the important clinical effectiveness outcomes of relapse rate, organ specific disease response and safety. There was very low certainty evidence of a statistically significantly improved organ specific disease responses in those receiving dabrafenib therapy compared to those receiving second-line chemotherapy. These differences were particularly noted in MAS-HLH markers (body temperature, haemoglobin levels and platelet levels) and spleen size. Cohort data provided very low certainty evidence of no statistically significant difference in relapse rate and/or disease progression in children treated with dabrafenib compared with those treated with second-line chemotherapy. No data were available for populations >18 years.

Safety outcomes, in the form of adverse events, were reported for those receiving dabrafenib therapy. One cohort study provided very low certainty evidence that there were fewer adverse events in those treated with dabrafenib compared with those treated with second-line chemotherapy. Adverse events were common in both adults and children; however, most were not severe (very low certainty evidence). The most common adverse event reported across all the studies was skin-related.

There was very low certainty evidence of no statistically significant difference in disease response and progression free survival following dabrafenib therapy in children with risk organ positive disease status compared with those with risk organ negative disease status. These results should be interpreted with caution as the subgroups were very small and may not have been large enough to reach statistical significance.

Limitations reducing certainty for the outcomes reported in the retrospective cohort study included uncertainty about the differences between the groups at baseline, lack of adjustment for potential confounding factors and uncertainty about how drug compliance was measured. Limitations reducing certainty in the outcomes reported in the two of the case series included uncertainty about whether the inclusion of participants was complete or consecutive and a lack of statistical analysis. A lack of events in one or both arms of an outcome led to serious imprecision for some outcomes; a lack of comparator was also a limitation across all three of the case series.

No evidence on cost effectiveness was identified.

The studies identified for this review, therefore, provide very low certainty evidence suggesting improved disease response in adults and children and progression free survival in children associated with dabrafenib with $BRAF^{V600E}$ mutation positive histiocytic neoplasms.

Appendix A PICO document

The review questions for this evidence review are:

1. In patients with BRAF^{V600E} mutation positive histiocytic neoplasms where standard care has failed, what is the clinical effectiveness of dabrafenib with or without best supportive care compared with best supportive care alone?
2. In patients with BRAF^{V600E} mutation positive histiocytic neoplasms where standard care has failed, what is the safety of dabrafenib with or without best supportive care compared with best supportive care alone?
3. In patients with BRAF^{V600E} mutation positive histiocytic neoplasms where standard care has failed, what is the cost effectiveness of dabrafenib with or without best supportive care compared with best supportive care alone?
4. From the evidence selected, are there any subgroups of patients that may benefit from dabrafenib with or without best supportive care more than the wider population of interest?
5. From the evidence selected, what dose of dabrafenib was used in the research studies?

P –Population and Indication	People with BRAF^{V600E} mutation positive histiocytic neoplasms where standard care has failed. Subgroups of interest are patients with high-risk disease. [Histiocytic neoplasm includes any patients with a diagnosis of: 1. Langerhans Cell Histiocytosis (LCH) 2. Erheim Chester Disease (ECD) 3. Juvenile Xanthogranuloma (JXG) 4. Rosai Dorman Disease (RDD)] [High risk disease would be defined by the following clinical scenarios: 1. Risk Organ Positive Multi-System LCH (RO+MS-LCH) 2. Risk Organ Negative Multi-System LCH (RO- MS-LCH) 3. Life-threatening pulmonary LCH (pLCH) 4. Neurodegenerative LCH (ND-LCH) 5. ECD with high-risk features (cardiovascular, respiratory, CNS or end organ damage) 6. JXG in high-risk sites 7. RDD in high-risk sites 8. ICD11 codes: 2B31.Y and 2B31.Z] [Where standard care has failed would include patients whose disease has progressed despite current standard care or patients with life threatening high-risk disease who cannot receive standard care due to: • slow or incomplete treatment response • inability to tolerate side effects of standard care • contraindications to standard care due to co-morbidities.] [Standard care is usually first line chemotherapy/ immunomodulation/ SACT and could include:

	• LCH - Intensive salvage chemotherapy regime that includes a purine analogue (cytarabine, cladribine, or clofarabine) • ECD - Methotrexate and interferon alpha • JXG - Prednisolone, vinblastine, or methotrexate • RDD - Prednisolone, vinblastine or methotrexate followed by sirolimus, imatinib and lenalidomide. • 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.]
I – Intervention	Oral dabrafenib +/- best supportive care. [Dabrafenib may be given as tablet or liquid form.] [Best supportive care involves symptom relief including management of any infections or complications from treatment for example treatment with corticosteroids.]
C – Comparator	Best supportive care alone.
O – Outcomes	**<u>Clinical Effectiveness</u>** Unless stated for the outcome, the minimum clinically important difference (MCID) is unknown. <u>*Critical to decision-making:*</u> - **Disease response** *This outcome is important to patients because it can reflect the benefits the treatment may have for a patient. This can be important to control the symptomatic burden of the disease and/or reflect subgroups who may configure additional response benefits, allowing the treatment protocol to be individualised.* [For example, but not limited to: - Clinical response, improvement in performance score, lower pain threshold, disease state, objective response rate. Risk Organ Positive Multi-System LCH - reduction in Disease Activity Score (DAS) at 8 weeks - Risk Organ Negative Multi-System LCH - improvement in Response Evaluation Criteria in Solid Tumours (RECIST V1.1) or PET Response Evaluation Criteria in Solid Tumours (PERCIST V1.0) at 3-6 months - High risk ECD - improvement in Response Evaluation Criteria in Solid Tumours (RECIST V1.1) or PET Response Evaluation Criteria in Solid Tumours (PERCIST V1.0) at 6-12 months - JXG, RDD and Others - improvement in Response Evaluation Criteria in Solid tumours (RECIST V1.1) or PET Response Evaluation Criteria in Solid tumours (PERCIST V1.0) at 6-12 months] - **Overall Survival** *Overall survival is important to patients as individuals with refractory histiocytic neoplasms have a high mortality rate due to progression of cancer. Improved survival is an important marker of effective treatment.* - **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. *<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 QLQ-OV28, QLQ-C30 and the EQ-5D.] - **Relapse rate** *This outcome is important to patients because it can indicate that their condition may not be adequately controlled by their current treatment, impacting on quality of life and patient treatment decisions.* [Relapse rate from treatment of histiocytic neoplasms is best measured over six months, during which time most relapses will occur.] - **Symptom alleviation** *This outcome is important to patients because reduction of symptoms directly improves the patient's quality of life. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment.* [Other terms used to describe or indicate symptom alleviation include but are not limited to symptoms, symptomatic response, alleviating disease symptoms.] - ***Organ specific disease response*** *This outcome is important to patients as objective measures of functioning of affected organs. Given the progressive nature of pulmonary and neurodegenerative histiocytosis, disease activity results might not be expected to return to normal following treatment, however, stabilisation may indicate treatment has successfully limited disease progression.* [For example, but not limited to: - Life-threatening pulmonary LCH - stabilisation or improvement of FEV1; reduction in cystic lung changes on high resolution CT; or improvement in symptom score at 3-6 months.

	- Neurodegenerative LCH (ND-LCH) - stabilisation or improvement of neurocognitive and ataxia rating scales; reduction abnormal signals on MRI brain at 3-6 months.] **<u>Safety</u>** *These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment.* **<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, Cochrane, PubMed and TRIP were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints, guidelines, case studies and resource utilisation studies were excluded.

Search date: 1 January 2013 to 26 January 2023

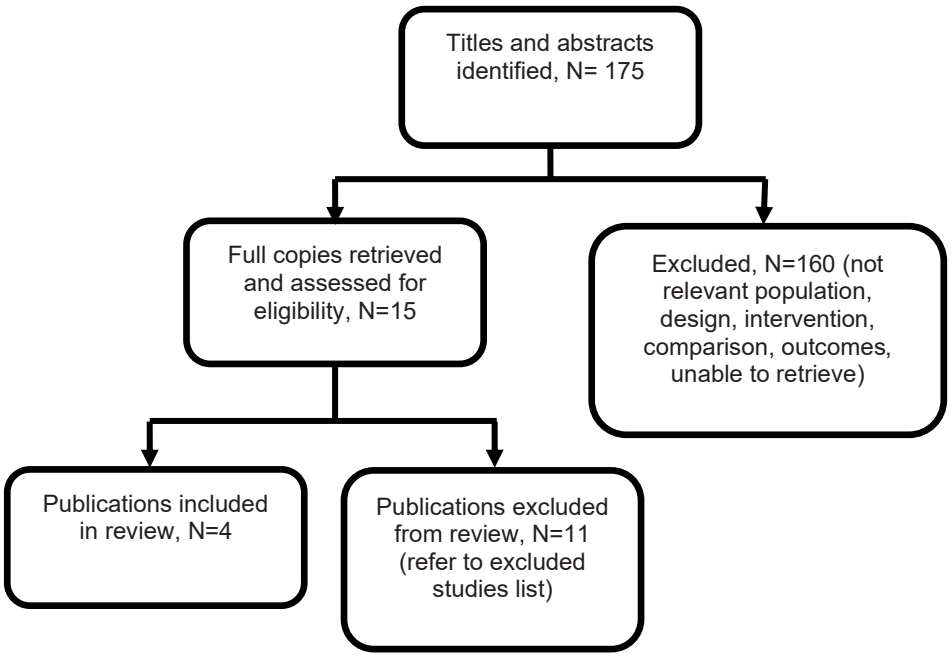
Medline search strategy:

1 exp Histiocytosis/
2 (histiocytosis or langerhans cell or erheim chester disease or juvenile xanthogranuloma? or rosai droman disease).ti,ab,kf.
3 1 or 2
4 Oximes/
5 (dabrafenib or tafinlar).ti,ab,kf.
6 4 or 5
7 3 and 6
8 limit 7 to (english language and yr="2013 -Current")

Appendix C Evidence selection

The literature searches identified 175 references. These were screened using their titles and abstracts and 15 references were obtained in full text and assessed for relevance. Of these, 4 references are included in the evidence summary. The remaining 11 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection - decision and rationale if excluded
Yang Y, Wang D, Cui L, Ma HH, Zhang L, Lian HY, et al. Effectiveness and Safety of Dabrafenib in the Treatment of 20 Chinese Children with BRAFV600E-Mutated Langerhans Cell Histiocytosis. Cancer Res Treat. 2021;53(1):261-9.	Included
Bhatia A, Ulaner G, Rampal R, Hyman DM, Abdel-Wahab O, Durham BH, et al. Single-agent dabrafenib for BRAF(V600E)-mutated histiocytosis. Haematologica. 2018;103(4):e177-e80.	Included at the request of NHS England.
Hazim AZ, Ruan GJ, Ravindran A, Abeykoon JP, Scheckel C, Vassallo R, et al. Efficacy of BRAF-Inhibitor Therapy in BRAF(V600E) -Mutated Adult Langerhans Cell Histiocytosis. Oncologist. 2020;25(12):1001-4.	n=1 dabrafenib. Case study design excluded by PICO.

Appendix D Excluded studies table

Study reference	Reason for exclusion
Boull CL, Gardeen S, Abdali T, Li E, Potts J, Rubin N, et al. Cutaneous reactions in children treated with MEK inhibitors, BRAF inhibitors, or combination therapy: A multicenter study. Journal of the American Academy of Dermatology. 2021;84(6):1554-61.	54% (n=24) of the BRAF study population (n=44) were treated with dabrafenib. The remaining BRAF population were treated with vemurafenib or dabrafenib and trametinib. No results were reported for the dabrafenib treatment group.
Brodie J, Zhou S, Makkuni D, Beadsmoore C, Mukhtyar C, Saada J, et al. Erdheim-Chester Disease: Two cases from an ophthalmic perspective. Am J Ophthalmol Case Rep. 2020;20:100984.	n=1 dabrafenib. Case study design excluded by PICO.
Estrada-Veras JI, O'Brien KJ, Boyd LC, Dave RH, Durham B, Xi L, et al. The clinical spectrum of Erdheim-Chester disease: an observational cohort study. Blood Adv. 2017;1(6):357-66.	Only 3/60 patients reported in the study were treated with dabrafenib. No results specific to the patients treated with dabrafenib were reported.
Hazim AZ, Ruan GJ, Ravindran A, Abeykoon JP, Scheckel C, Vassallo R, et al. Efficacy of BRAF-Inhibitor Therapy in BRAF(V600E) -Mutated Adult Langerhans Cell Histiocytosis. Oncologist. 2020;25(12):1001-4.	n=1 dabrafenib. Case study design excluded by PICO.
Hubert G, Bittencourt H, Laverdiere C, Teira P, Cellot S, Langlois S, et al. Clinical response to dabrafenib and chemotherapy in clonally-related histiocytosis and acute lymphoblastic leukemia. Haematologica. 2022;17.	n=1 dabrafenib. Case study design excluded by PICO.
Lee LH, Gasilina A, Roychoudhury J, Clark J, McCormack FX, Pressey J, et al. Real-time genomic profiling of histiocytoses identifies early-kinase domain BRAF alterations while improving treatment outcomes. JCI insight. 2017;2(3):e89473.	No results reported for the outcomes specified in the PICO.
Lee LH, Krupski C, Clark J, Wunderlich M, Lorsbach RB, Grimley MS, et al. High-risk LCH in infants is serially transplantable in a xenograft model but responds durably to targeted therapy. Blood Adv. 2020;4(4):717-27.	n=4 dabrafenib. Case series with 20 or more patients have already been selected for inclusion. No additional in scope outcomes were reported.
Kieran MW, Geoerger B, Dunkel IJ, Broniscer A, Hargrave D, Hingorani P, et al. A Phase I and Pharmacokinetic Study of Oral Dabrafenib in Children and Adolescent Patients with Recurrent or Refractory BRAF V600 Mutation-Positive Solid Tumors. Clin Cancer Res. 2019;25(24):7294-302.	n=27 children but only n=2 with LCH; other study subjects did not have a diagnosis of histiocytic neoplasm. Case series with 20 or more patients have already been selected for inclusion. No additional in scope outcomes were reported.
Saunders IM, Goodman AM, Kurzrock R. Real-World Toxicity Experience with BRAF/MEK Inhibitors in Patients with Erdheim-Chester Disease. Oncologist. 2020;25(2):e386-e90.	n=3 dabrafenib. Case series with 20 or more patients have already been selected for inclusion. No additional in scope outcomes were reported.
Yang Y, Wang D, Li N, Ma H, Lian H, Cui L, et al. Improvement in Pituitary Imaging After Targeted Therapy in Three Children with BRAF-Mutated Langerhans Cell Histiocytosis with Pituitary Involvement. Onco Targets Ther. 2020;13:12357-63.	n=3 dabrafenib. Case series with 20 or more patients have already been selected for inclusion. No additional in scope outcomes were reported.

Study reference	Reason for exclusion
Yao JF, Wang D, Ma HH, Lian HY, Zhang L, Wang TY, et al. Characteristics and Treatment Outcomes of Pediatric Langerhans Cell Histiocytosis with Thymic Involvement. J Pediatr. 2022;244:194-202.e5.B3:C8	Retrospective case series of 19 patients, 6 of which are in scope (BRAF-mutation positive with a second line treatment). Case series with 20 or more patients have already been selected for inclusion. No additional in scope outcomes were reported.

Appendix E Evidence table

For abbreviations see list after table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Bhatia A, Ulaner G, Rampal R, Hyman DM, Abdel-Wahab O, Durham BH, et al. Single-agent dabrafenib for BRAF(V600E)-mutated histiocytosis. Haematologica. 2018;103(4):e177-e80. **Study location** Israel, USA **Study type** Retrospective case series **Study aim** Report a series of patients treated with single-agent dabrafenib for ECD (Erdheim Chester Disease) or ECD/LCH (Langerhans cell histiocytosis)	Patients with ECD or ECD/LCH treated with single-agent dabrafenib **Inclusion criteria** • Diagnosis of ECD or ECD/LCH • Treated with dabrafenib as: 1) initial histiocytosis therapy 2) following failure of chemotherapy or radiation 3) following discontinuation of vemurafenib therapy because of toxicity or intolerance. • $CD68^{+}/CD1a^{-}$ histiocytic infiltration of skeletal abnormalities,	**Interventions** Oral dabrafenib, dose range 50mg to 150mg, twice daily Duration of therapy ranged from 4 to 43 months. 2/11 patients discontinued therapy due to toxicity. **Comparators** No comparator	Duration of dabrafenib therapy ranged from 4 to 43 months (median not reported). **Critical outcomes** **Disease response** *PERCIST*,[6,7] n (% - SPH calculated) • Complete metabolic response (CMR): 3 (27)[8] • Partial metabolic response (PMR): 8 (73)[9] • Stable metabolic disease (SMD): 0 (0) • Progressive metabolic disease (PMD): 0 (0) **Important outcomes** **Safety** Toxicity leading to discontinuation, n 2 *Specific adverse events*, n[10]	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. Unclear 5. Unclear 6. No 7. Yes 8. Yes 9. No 10. Not applicable **Other comments:** This retrospective case series described the effectiveness and safety outcomes following treatment with dabrafenib for 11 adults with ECD or ECD/LCH and the $BRAF^{V600E}$-mutation with vemurafenib intolerance. Three hospitals participated in the case review (n=2 USA, n=1 Israel); the

[6] Modified PET Response Criteria in Solid Tumors (PERCIST): up to 5 lesions were selected, SUVs were normalized for body weight, and the FDG avidity of each lesion was calculated as $SUV_{max\ lesion} - SUV_{max\ liver\ background} = SUV_{corrected\ for\ background}$, or simply "SUV." For brain lesions, brain background was used *in lieu* of liver background. Values less than zero were treated as 0, which allowed the FDG avidity of a lesion to be considered as the excess avidity above background. Complete metabolic response (CMR) was defined as all lesions decreased to or below background; partial metabolic response (PMR) was defined as a 50% or greater decrease from baseline in the sum SUV of all target lesions; progressive metabolic disease (PMD) was defined as a 50% or greater increase from the nadir in the sum of SUV all target lesions or the appearance of new evaluable lesions; stable metabolic disease (SMD) was when the response did not meet other criteria

[7] PERCIST scores were reported at variable times of follow-up, ranging from 4 to 43 months; 9/11 patients were on on-going dabrafenib therapy at follow-up.

[8] One of three patients demonstrated a complete metabolic response following relapsed disease due to vemurafenib discontinuation (toxicity)

[9] 3/11 patients maintained PMR from vemurafenib; one patient achieved PMR following relapsed disease due to vemurafenib discontinuation (toxicity).

[10] Multiple adverse events could have been experienced by one patient

Study details	Population	Interventions	Study outcomes	Appraisal and funding

Study dates
January 2014 to October 2017
	demonstrated through tissue biopsy
	• At least one additional manifestation of ECD
	
	Exclusion Criteria
	No exclusion criteria described
	
	Total sample size
	n=11
	
	Baseline characteristics
	Age years, median (range): 59 (31 to 77)
	Male, n (%): 7 (64%)
	Cancer diagnosis, n:
	• ECD: 7
	• ECD/LCH: 4
	Prior therapies, n:
	• radiation: 1
	• cytarabine: 1
	• prednisone: 3
	• vinblastine: 1
	• vemurafenib: 6
	• interferon-α: 2
	• methotrexate: 1
	• anakinra: 1
	• none: 1
			• arthralgia: 2
			• fatigue: 2
			• fever: 3
			• hypophosphatemia: 1
			• skin (related): 4
			  ○ keratoacanthoma: 1
			  ○ keratosis pilaris: 1
			  ○ panniculitis: 1
			  ○ skin (not further detailed): 1
			• periorbital swelling: 1
			• none: 3
			
			Adverse event grading
			Fever, n (% - SPH calculated):
			• Grade 1: 1 (9)
			• Grade 2: 1 (9)[11]
			• Grade 3: 1 (9)[12]
			
			Fatigue, n (% - SPH calculated):
			• Grade 1: 0 (0)
			• Grade 2: 2 (18)[13]
			• Grade 3: 0 (0)
			
			Arthralgia, n (% - SPH calculated):
			• Grade 1: 1 (9)
			• Grade 2: 1 (9)
			• Grade 3: 0 (0)
				authors do not state if all patients eligible were included in the review.
				
				Limited demographic information was presented (only age and sex) and no co-morbidities were reported. No further subgroup analyses were attempted; no summary analyses or statistical tests were presented.
				
				The outcomes for each patient were objective or used standardised assessment measures, such as the PERCIST tool to define disease response and the Common Terminology Criteria for Adverse Events for adverse event grading. No summary statistics for clinical outcomes were reported.
				
				The data was collected retrospectively using case notes and imaging, leading to a greater potential for recall bias; however, no questionnaires or self-reported measures were used.
				
				Results only presented graphically or through images were not extracted.
				
				Source of funding:
				This research was supported by the Erdheim-Chester Disease Global Alliance and National Institutes of Health/National Cancer Institute Core Grant awarded to Sloan

[11] Grade 2 fever led to dabrafenib dosing decrease
[12] Grade 3 fever led to dabrafenib dosing decrease
[13] Grade 2 fatigue led to dabrafenib dosing decrease for one patient and dabrafenib cessation for another

Study details	Population	Interventions	Study outcomes	Appraisal and funding
				Kettering Cancer Center. The authors declared no conflict of interest.
Shi H, He H, Cui L, Kvedaraite E, Bian Z, Huang T, et al. Transcriptomic landscape of circulating mononuclear phagocytes in Langerhans cell histiocytosis at the single-cell level. Blood. 2021;138(14):1237-48. **Study location** Beijing, China **Study type** Prospective case series **Study aim** The study focused on mononuclear myeloid cells in LCH and combined immune-phenotyping and clinical observations with single-cell transcriptomics to understand how they may be affected in newly diagnosed patients and in response to BRAF inhibition. **Study dates** May 2018 to December 2019	Children with relapsed or refractory LCH, with $BRAF^{V600E}$ mutation, who were treated with dabrafenib (sub-sample of children in the study) **Inclusion criteria** • Newly diagnosed LCH • Aged <18 years • Admitted to Beijing Children's Hospital from May 2018 to Dec 2019 • Relapsed or refractory LCH, defined as meeting one of the following: 1) No improvement in risk organs (RO) or pituitary or had disease progression/relapse after at least one intensified course of second-line cytarabine and/or cladribine 2) No improvement in RO, pituitary or disease progression/relapse after at least one	**Interventions** Oral dabrafenib (2 mg/kg, twice daily) for 12 months 3/22 patients did not complete 12 months of dabrafenib therapy due to progression/relapse (dabrafenib administration: 3 to 10 months) 9/22 patients ended dabrafenib therapy at 12 months 8/22 patients continued dabrafenib after the initial 12 month period **Comparators** No comparator	Median (range) follow-up since dabrafenib administration: 14.0 months (4.8 to 37.7) **Critical outcomes** **Disease response** *Disease State*[15] AD/better, n (%) • 1 month: 19 (86.4) • 3 months: 19 (86.4) • 6 months: 15 (83.3) • 9 months: 9 (64.3) • 12 months: 11 (100) *1 month post-dabrafenib*, n (%): AD/better: 19 (86.4) AD/intermediate: 3 (13.6) *3 months post-dabrafenib*, n (%): AD/better: 19 (86.4) AD/intermediate: 2 (9.0) AD/worse: 1 (4.5) **Progression free survival (PFS), %** • 1-year: 63.9 (95% CI 51.7 to 76.1) • 2-year: 47.9 (95% CI 31.3 to 64.5) **Important outcomes** **Relapse rate** n (%): 7 (31.8)	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. Yes 5. No 6. Yes 7. Unclear 8. Yes 9. Yes 10. Yes **Other comments:** This was a prospective case study focussed on immune-phenotyping and clinical observations in children newly diagnosed with LCH. All patients referred to the paediatric department in Beijing, meeting the inclusion criteria, were included in the cohort. Data in this case series, form a sub-sample of children with relapsed or refractory LCH, with $BRAF^{V600E}$ mutation, who were treated with dabrafenib. The outcomes were objective or used standardised assessment measures. Loss to follow-up was significant, for disease response (50% at one year). Details were not given as to the

[15]Treatment response was evaluate using the International LCH Study Group Criteria, Disease State: non-active disease (NAD); active disease (AD)/better; AD/intermediate; AD/worse

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	course of induction therapy (vindesine and prednisone) and could not tolerate second-line treatment 3) Bone marrow or thymus involvement that could be directly treated with targeted therapy or had no improvement in bone marrow or thymus after ≥2 weeks of induction therapy **Exclusion Criteria** • Admitted to the hospital prior to May 2018 • Negative for $BRAF^{V600E}$ in biopsy tissue before treatment to dabrafenib • Did not have available plasma samples for $cfBRAF^{V600E}$ analysis following one-month of dabrafenib treatment • Had previously received other BRAF inhibitors, hematopoietic stem cell transplantation or an investigational		**Safety** *Skin toxicity events*, n (%): 13 (56.5)	reason for the lack of clinical information at one year. Denominators for not given for other outcome variables. Results only presented graphically were not extracted. **Source of funding:** The research was supported by grants from the National Key Research and Development of China, Stem Cell and Translational Research, The National Natural Science Foundation of China, the Program for Guangdong Introducing Innovative and Entrepreneurial Teams, the Key Research and Development Program of Guangdong Province and the China Postdoctoral Science Foundation. The authors declare no competing financial interest.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	agent before dabrafenib • History of myocardial infarction, unstable angina, peripheral vascular disease, familial QTc prolongation, abnormal cardiac valve morphology • Patients who are unable to comply during the trial / follow-up phase **Total sample size** n=233 in total cohort n=22 treated with dabrafenib **Baseline characteristics** Male, n (%): 13 (59.1) Age years, median (range): 1.2 (0.2 to 4.2) MS-high risk, n (%): 17 (77.3) Treatment before dabrafenib, n (%): • First-line therapy: 9 (40.9) • Second-line therapy: 2 (9.1)[14] • First-line + Second-line therapy: 5 (22.7)			

[14] Some patients did not have a full course of first-line therapy as they were unable to tolerate the treatment or had no improvement in their bone marrow or thymus after two weeks. Two of these patients moved onto second-line therapy; the other six moved directly onto targeted therapy (dabrafenib).

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	• No chemotherapy: 6 (27.3)			
Wang D, Chen XH, Wei A, Zhou CJ, Zhang X, Ma HH, et al. Clinical features and treatment outcomes of pediatric Langerhans cell histiocytosis with macrophage activation syndrome-hemophagocytic lymphohistiocytosis. Orphanet J Rare Dis. 2022;17(1):151. **Study location** Beijing, China **Study type** Retrospective cohort study **Study aim** Difference in the treatment outcomes between second-line chemotherapy and targeted therapy (dabrafenib) for $BRAF^{V600E}$-positive Langerhans cell histiocytosis (LCH) children with a macrophage	**Inclusion criteria** Children (age <18 years) referred to Beijing Children's Hospital with LCH, and fulfilling ≥5 of 8 of secondary HLH criteria[16] **Exclusion Criteria** • patients with controlled LCH and HLH following first-line chemotherapy (n=2) • patients not assessable for BRAF status (n=3) • patients $BRAF^{V600E}$-mutation negative (n=3) **Total sample size** LCH with MAS-HLH: n=28 LCH with MAS-HLH and $BRAF^{V600E}$-mutation:	All patients began with first line therapy and maintenance therapy, for a total period of 12 months. Those that with poorly controlled MAS-HLH were subsequently treated with either second-line chemotherapy or dabrafenib. 1) First-line vindesine-steroid therapy, one or two six-week courses of induction therapy: • vindesine 3 mg/m^2/day IV bolus, once weekly, 6 weeks • prednisone 40 mg/m^2/day orally, daily for 4 weeks, then weekly reduction for 2 weeks 2) Maintenance therapy: • vindesine 3 mg/m^2/day IV bolus, every 3 weeks • prednisone 40 mg/m^2/day orally, day 1-5, every 3 weeks	Dabrafenib v chemotherapy Median (range) follow up, since beginning of secondary therapy: 28.9 months (10.0 to 60.8) v 19.9 (0.8 to 62.8); p=0.238 **Critical outcomes** **Disease response** *Disease Activity Score (DAS)[18]* • dabrafenib: n=12, second-line chemotherapy: n=8 • Day 1: 12.5 v 12.0; p=0.734 • Month 1 / Week 5[19]: 2.5 v 8.5; p=0.002 *Treatment response[20]* AD/better at Month 1 / Week 5, n (%): 12 (100) v 3 (37.5); p=0.004 **Overall survival** n (%): 0 (0) v 0 (0) **Progression free survival (PFS)** *4-year PFS* (dabrafenib: n=12, second-line chemotherapy: n=8)	This study was appraised using the JBI checklist for cohort studies. 1. Unclear 2. Yes 3. No 4. No 5. No 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes 11. Yes **Other comments:** This was a retrospective cohort study evaluating the safety and effectiveness of dabrafenib compared with second-line chemotherapy in children with LCH and secondary MAS-HLH. All patients referred to the paediatric department in Beijing, meeting the inclusion criteria, were included in the cohort. The demographic and clinical characteristics of those receiving

[16] MAS-HLH is categorised as secondary HLH associated with rheumatologic conditions. It is diagnosed using 8 diagnostic criteria in the 2004 HLH protocol: fever, splenomegaly, cytopenia in ≥2 cell lineages, hypertriglyceridemia or hypofibrinogenemia, hyperferritinaemia, elevated soluble CD25, hemophagocytosis in bone marrow or other tissue, low or absent NK-cell cytotoxicity.
[18] LCH disease activity score (DAS) is a 15 domain scale with scores ranging from 0-35 (35 being very poor health). Scores 0-2 are considered low, 3-6 moderate, and ≥7 high
[19] Comparison of DAS after one month of dabrafenib and five weeks (two therapeutic courses) of second-line chemotherapy
[20] Treatment response was evaluate using the International LCH Study Group Criteria: 1) non-active disease (NAD) = complete resolution; 2) active disease (AD)/better = continuous regression of disease; 3) AD/intermediate = unchanged disease; 4) AD/worse = disease progression or appearance of new lesions. Patients that responded to therapy were those designated as NAD or AD/better

Study details	Population	Interventions	Study outcomes	Appraisal and funding
activation syndrome-hemophagocytic lymphohistiocytosis (MAS-HLH). **Study dates** January 2016 to December 2019	n=22 **No. of participants in each treatment group** First-line chemotherapy only: n=2 Second-line chemotherapy (comparator): n=8 Dabrafenib (treatment): n=12 **Baseline characteristics** All baseline characteristics are for full cohort of 28 MAS-HLH patients as characteristics are not summarised by second-line treatment. Male, n (%): 15 (53.6%) Age • <2, n (%): 28 (100%) • median (range): 1.0 (0.20 to 1.78) $BRAF^{V600E}$, n (%)[17]: 22 (88.0%)	• 6-mercaptopurine 50 mg/m^2/day, orally, daily **Interventions** Oral dabrafenib, 2 mg/kg twice a day for 12 months **Comparators** Second-line chemotherapy comprised of 4 courses of treatment arm A, 4 courses of treatment arm B and maintenance treatment 1) Treatment arm A, administered every 4 weeks over 5 days: • cytarabine 150 mg/m^2/day IV guttae within 2 hr, day 1-5 • cladribine 9 mg/m^2/day IV guttae, day 2-4 • vindesine 3 mg/m^2/day IV bolus within 2 hr, day 1 • dexamethasone 6 mg/m^2/day, IV or orally, day 1-5 2) Treatment arm B, administered every 3 weeks, over 5 days: • cytarabine 150 mg/m^2/day IV guttae within 2 hr, day 1-5 • vindesine 3 mg/m^2/day IV bolus within 2 hr, day 1	• 75%±12.5% v 14.6%±13.5%; p=0.034 **Important outcomes** **Relapse rate** n (%) • 3 (25.0) v 6 (75.0); p=0.065 **Organ specific disease response** *Recovery time of temperature, haemoglobin and platelets* Days, median • temperature: 2.0 v 18.0; p < 0.001 • haemoglobin: 7.0 v 30.5; p < 0.001 • platelets: 7.0 v 27.0; p=0.013 *Size of spleen* only p-value was reported • Day 0: p=0.305 • Month 1: p=0.047 **Safety** *Adverse Events (AEs)*[21] • n (%): 4/12 (33.3) v 12/13 (92.3) • Primary AEs for dabrafenib patients: skin-related toxicity (75%), diarrhoea, vomiting, fatigue, joint pain and transient myocardium enzyme rising • Primary AEs for chemotherapy patients: myelosuppression and pancytopenia • All AEs were grade 1 or 2	second-line chemotherapy compared with those receiving dabrafenib were not described. If these groups were significantly different at baseline, it could have significant impact on the interpretation of results. Given the nature of the intervention, oral drugs compared with IV chemotherapy, it was not possible to blind participants and those delivering the intervention to treatment allocation. The paper does not report whether outcome assessors were blinded. The outcomes were objective or used standardised assessment measures. Statistical comparison between the groups was not reported for safety outcomes and was not available for overall survival as there were no events in either group. Results only presented graphically were not extracted. **Source of funding:** The study was funded by the National Natural Science Foundation of China, the Capital's Funds for Health Improvement and Research, the Special Fund of the Paediatric Medical Coordinated Development Center of Beijing Hospitals Authority and Funding for Reform and

[17] Samples available for 22/25 patients
[21] All AEs were defined and graded using the Common Terminology Criteria for Adverse Events CTCAE grade 3-4

Study details	Population	Interventions	Study outcomes	Appraisal and funding
		• dexamethasone 6 mg/m^2/day, IV or orally, day 1-5 3) Maintenance therapy: • vindesine 3 mg/m^2/day IV bolus, every 3 weeks • prednisone 40 mg/m^2/day orally, day 1-5, every 3 weeks • 6-mercaptopurine 50 mg/m^2/day, orally, daily		Development of Beijing Municipal Health Commission. The authors did not declare any competing interests.
Yang Y, Wang D, Cui L, Ma HH, Zhang L, Lian HY, et al. Effectiveness and Safety of Dabrafenib in the Treatment of 20 Chinese Children with BRAFV600E-Mutated Langerhans Cell Histiocytosis. Cancer Res Treat. 2021;53(1):261-9. **Study location** Beijing, China **Study type** Retrospective case series **Study aim** Determine the effectiveness and safety of dabrafenib in treating 20 children with LCH and the BRAF^{V600E}-mutation **Study dates** November 2016 to June 2020	**Inclusion criteria** • Diagnosed with LCH according to clinical features; positive staining of CD1a and/or Langerin of biopsy tissue • BRAF^{V600E} detected in peripheral blood or affected tissue at disease onset • Chemotherapy could not be tolerated OR disease continued to progress following chemotherapy OR pituitary lesion was not improved after chemotherapy • Aged <18 years • Admitted to Beijing Children's Hospital from 1 Nov 2016 to 30 Nov 2018	**Interventions** Oral dabrafenib 2 mg/kg, every 12 hours for 6-12 months Treatments prior to dabrafenib *First-line therapy*, n=20 1) Induction therapy A, six weeks: • vindesine 3 mg/m^2/day IV bolus, once weekly, 6 weeks • Prednisone 40 mg/m^2/day orally, daily for 4 weeks, then weekly reduction for 2 weeks 2) Induction therapy B, six weeks: • vindesine 3 mg/m^2/day IV bolus, once weekly, 6 weeks	Median (range) follow up: 30.8 months (18.9 to 43.6) **Critical outcomes** **Disease response** *Disease State* ORR[23] = 65% DCR[24] = 75% At the end of dabrafenib treatment, n (%) • AD/better: 13 (65) • AD/stable: 2 (10) • AD/mixed: 1 (5) • AD/worse: 4 (20) *Disease state at 3 monthly follow-ups* 1 month follow-up, n (%) • AD/better: 15 (75) • AD/stable: 2 (10) • AD/mixed: 3 (15) • AD/worse: 0 (0) • drug withdrawal: 0 (0) 3 months follow-up, n (%)	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes **Other comments:** This was a retrospective case series to determine the effectiveness and safety of dabrafenib in treating children with LCH and the BRAF^{V600E}-mutation. All patients referred to the paediatric department in Beijing, meeting the inclusion criteria, were included in the cohort. The case series included 20 children with LCH treated with dabrafenib. Further subgroup analyses were

[23] ORR: objective response rate; the percentage of all patients AD/better at the end of treatment
[24] DCR: disease control rate; the percentage of all patients AD/better and AD/stable at the end of treatment

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Exclusion Criteria Other BRAF kinase inhibitors had been used previously **Total sample size** n=20 *Subgroup, high risk*[22] RO+=14 (70%) RO-=7 (30%) **Baseline characteristics** Male, n (%): 14 (70%) Age, years; median (range) • at diagnosis: 1 (0.1 to 5.1) • at dabrafenib initiation: 2.3 (0.6 to 6.5) Disease state – LCH study group criteria; n (%) • AD/Better: 0 (0) • AD/Stable: 5 (25) • AD/Mixed: 1 (5) • AD/Worse: 14 (70)	• Prednisone 40 mg/m^2/day orally, days 1-3 each week 3) Maintenance therapy: • vindesine 3 mg/m^2/day IV bolus, every 3 weeks • prednisone 40 mg/m^2/day orally, day 1-5, every 3 weeks • 6-mercaptopurine 50 mg/m^2/day, orally, daily • methotrexate 50 mg/m^2, weekly *Second-line therapy*, n=12 1) Treatment, 4 courses, every 4 weeks: • cladribine 5 mg/m^2/day IV guttae, days 2-6 • cytarabine 100 mg/m^2/day IV guttae, days 1-5 • vindesine 1.5 mg/m^2/day (max 2 mg) IV bolus, day 1 • dexamethasone 6 mg/m^2/day IV/oral, days 1-5 2) Maintenance therapy: • vindesine 1.5 mg/m^2/dose (max 2 mg) IV bolus, every 3 weeks • prednisone 40 mg/m^2/day orally, day 1-5, every 3 weeks	• AD/better: 13 (65) • AD/stable: 2 (10) • AD/mixed: 2 (10) • AD/worse: 3 (15) • drug withdrawal: 0 (0) 6 months follow-up, n (%) • AD/better: 13 (65) • AD/stable: 2 (10) • AD/mixed: 1 (5) • AD/worse: 1 (5) • drug withdrawal: 3 (15) 9 months follow-up, n (%) • AD/better: 7 (35) • AD/stable: 1 (5) • AD/mixed: 2 (10) • AD/worse: 2 (10) • drug withdrawal: 8 (40) 12 months follow-up, n (%) • AD/better: 6 (30) • AD/stable: 1 (5) • AD/mixed: 1 (5) • AD/worse: 1 (5) • drug withdrawal: 11 (55) **Overall survival** n (%): 0 (0) **Important outcomes** **Relapse rate** n (%): 10 (50) **Organ specific disease response** *HLH patients* (n=5) • 4/5 (80%) experienced disease improvement	attempted; none were statistically significant. The outcomes were objective or used standardised assessment measures, such as the International LCH Study Group Criteria to define disease states and the Common Terminology Criteria for Adverse Events for adverse event grading. The data was collected retrospectively using case notes and imaging, leading to a greater potential for recall bias; however, no questionnaires or self-reported measures were used. Results only presented graphically were not extracted. **Source of funding:** The study was funded through grants from the Capital's Funds for Health Improvement and Research, the Special Fund of the Paediatric Medical Coordinated Development Center of Beijing Hospitals Authority, the National Natural Science Foundation of China, the National Science and Technology Key Projects, Beijing University & Capital Medical University Advanced Innovation Center for Big Data-Based Precision Medicine Plan, and Funding for Reform and Development of Beijing Municipal Health Commission. The authors did not declare any competing interests.

[22] RO: risk organ involved group; RO+ indicates a high-risk group, a subgroup of interest. The authors do not further define this group.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
		• 6-mercaptopurine 50 mg/m^2/day, orally, daily • methotrexate 20 mg/m^2, weekly **Comparators** No comparator	• comparable response in those with and without HLH (80% v 60%; p=0.613) *Disease of liver and spleen* (n=7) • 5/7 (71.4%) experienced improvement in all lesions except hepatic cirrhosis • symptoms of hepatosplenomegaly and liver damage were alleviated *Disease of pituitary* (n=7) • No progression of disease following dabrafenib • 1/3 with diabetes insipidus had improvement of symptoms **Safety** *Adverse Events (AEs)*[25] • 17 events in n=9 patients (45%) • Maculopapular rash was the most common AE (8 events, 47.1%) • Grade 3 events: n=1; maculopapular rash • Grade 2 events: n=6; maculopapular rash, skin pain, eye swelling and conjunctival petechia • Severe adverse events (squamous cell carcinoma, keratoacanthoma) were not observed **Subgroups** **Disease Response**	

[25] All AEs were defined and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), v5.0

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Treatment response[26] RO+ v RO-, %: 78.6 v 33.3; p=0.122 **Progression free survival** RO+ v RO-, 24 month PFS: X^2=0.062, p=0.804	

Abbreviations
AD: active disease; AE: adverse events; CTCAE: Common Terminology Criteria for Adverse Events; DAS: Disease Activity Score; DCR: disease control rate; HGG: high grade glioma; IV: intravenous; kg: kilogram; HLH: hemophagocytic lymphohistiocytosis; LCH: Langerhans cell histiocytosis; MAS-HLH: Macrophage activation syndrome-hemophagocytic lymphohistiocytosis; m: metres; mg: milligram; MS: multiple system; n: number; ORR: objective response rate; PFS: progression free survival; pLGG: paediatric low-grade glioma; RO: risk organs; UK: United Kingdom; US: United States of America; v: versus

[26] The authors do not state if this is the objective response rate (ORR) or the disease control rate (DCR)

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Cohort Studies

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow-up time reported and sufficient to be long enough for outcomes to occur?
9. Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?
10. Were strategies to address incomplete follow-up utilized?
11. Was appropriate statistical analysis used?

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

In people with BRAFV600E mutation positive histiocytic neoplasms where standard care has failed, what is the clinical effectiveness and safety of oral dabrafenib with or without best supportive care compared with best supportive care alone?

For abbreviations and footnotes see end of tables.

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Dabrafenib	Best supportive care	Result		
Disease Response (1 cohort study, 3 case series)									
Disease Activity Score (DAS)[A], Day 1 and Month 1 / Week 5[B] (benefit is indicated by lower score)									
1 cohort study Wang et al 2022	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	12	8	• Day 1: 12.5 v 12.0; p=0.734 • Month 1 / Week 5: 2.5 v 8.5; p=0.002	Critical	Very low
Treatment Response[C], AD/better at Month 1 / Week 5; n (%)									
1 cohort study Wang et al 2022	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	12	8	12 (100) v 3 (37.5); p=0.004	Critical	Very low
Disease State[C], AD/better at 1, 3, 6, 9 and 12 months; n (%)									
1 case series Shi et al 2021	Serious limitations[2]	Serious indirectness[3]	Not applicable	Not calculable	1 month: 22 3 months: 22 6 months: 18 9 months: 14 12 months: 11	None	• 1 month: 19 (86.4) • 3 months: 19 (86.4) • 6 months: 15 (83.3) • 9 months: 9 (64.3) • 12 months: 11 (100)	Critical	Very low
Disease Response, PERCIST[D], during follow-up, range of treatment 4 to 43 months; n (% - SPH calculated)									
1 case series Bhatia et al 2018	Very series limitations[4]	Serious indirectness[3]	Not applicable	Serious imprecision[5]	11	None	• Complete metabolic response (CMR): 3 (27) • Partial metabolic response (PMR): 8 (73) • Stable metabolic disease (SMD): 0 (0) • Progressive metabolic disease (PMD): 0 (0)	Critical	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Dabrafenib	Best supportive care	Result		
Treatment Response[C], Objective Response Rate[E] and Disease Control Rate[F] at the end of dabrafenib treatment, median (range) time of treatment 11.4 months (3.1 to 19.2 months); %									
1 case series Yang et al 2021	No serious limitations	Serious indirectness[3]	Not applicable	Not calculable	20	None	ORR = 65% DCR = 75%	Critical	Very low
Disease State[C], at the end of dabrafenib treatment, median (range) time of treatment 11.4 months (3.1 to 19.2 months); n (%)									
1 case series Yang et al 2021	No serious limitations	Serious indirectness[3]	Not applicable	Not calculable	20	None	• AD/better: 13 (65) • AD/stable: 2 (10) • AD/mixed: 1 (5) • AD/worse: 4 (20)	Critical	Very low
Disease State[C], at 12 months follow-up; n (%)									
1 case series Yang et al 2021	No serious limitations	Serious indirectness[3]	Not applicable	Not calculable	20	None	• AD/better: 6 (30) • AD/stable: 1 (5) • AD/mixed: 1 (5) • AD/worse: 1 (5) • drug withdrawal: 11 (55)	Critical	Very low
Disease State[C], at 9 months; n (%)									
1 case series Yang et al 2021	No serious limitations	Serious indirectness[3]	Not applicable	Not calculable	20	None	• AD/better: 7 (35) • AD/stable: 1 (5) • AD/mixed: 2 (10) • AD/worse: 2 (10) • drug withdrawal: 8 (40)	Critical	Very low
Disease State[C], at 6 months; n (%)									
1 case series Yang et al 2021	No serious limitations	Serious indirectness[3]	Not applicable	Not calculable	20	None	• AD/better: 13 (65) • AD/stable: 2 (10) • AD/mixed: 1 (5) • AD/worse: 1 (5) • drug withdrawal: 3 (15)	Critical	Very low
Disease State[C], at 3 months; n (%)									
1 case series Yang et al 2021	No serious limitations	Serious indirectness[3]	Not applicable	Not calculable	20	None	• AD/better: 13 (65) • AD/stable: 2 (10) • AD/mixed: 2 (10) • AD/worse: 3 (15) • drug withdrawal: 0 (0)	Critical	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Dabrafenib	Best supportive care	Result		
Disease State[C], at 1 month; n (%)									
1 case series Yang et al 2021	No serious limitations	Serious indirectness[3]	Not applicable	Serious imprecision[5]	20	None	• AD/better: 15 (75) • AD/stable: 2 (10) • AD/mixed: 3 (15) • AD/worse: 0 (0) • drug withdrawal: 0 (0)	Critical	Very low
Overall Survival (1 cohort study, 1 case series)									
Died during follow up, median (range) follow-up 28.9 months (10.0 to 60.8); n (%)									
1 cohort study Wang et al 2022	Very serious limitations[1]	No serious indirectness	Not applicable	Serious imprecision[6]	12	8	0 (0) v 0 (0)	Critical	Very low
Died during follow up, median (range) follow-up 30.8 months (18.9 to 43.6); n (%)									
1 case series Yang et al 2021	No serious limitations	Serious indirectness[3]	Not applicable	Serious imprecision[5]	20	None	Died: 0 (0)	Critical	Very low
Progression free survival (1 cohort study, 1 case series)									
Progression free survival at 4 years; %±SE									
1 cohort study Wang et al 2022	Very serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	12	8	74±12.5 v 14.6±13.5; p=0.034	Critical	Very low
Progression free survival at 2 years; % (95% CI)									
1 case series Shi et al 2021	Serious limitations[7]	Serious indirectness[3]	Not applicable	Not calculable	22	None	47.9 (31.3 to 64.5)	Critical	Very low
Progression free survival at 1 year; % (95% CI)									
1 case series Shi et al 2021	Serious limitations[7]	Serious indirectness[3]	Not applicable	Not calculable	22	None	63.9 (51.7 to 76.1)	Critical	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Dabrafenib	Best supportive care	Result		
Relapse rate (1 cohort study, 2 case series)									
Relapse rate, during median 28.9 months follow-up (range 10.0 to 60.8); n (%)									
1 cohort study Wang et al 2022	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	12	8	3 (25.0) v 6 (75.0); p=0.065	Important	Very low
Relapse rate, during median 14.0 months follow-up (range 4.8 to 37.7); n (%)									
1 case series Shi et al 2021	Serious limitations[7]	Serious indirectness[3]	Not applicable	Not calculable	22	None	7 (31.8)	Important	Very low
Relapse rate, during median (range) follow-up 30.8 months (18.9 to 43.6); n (%)									
1 case series Yang et al 2021	No serious limitations	Serious indirectness[3]	Not applicable	Not calculable	20	None	10 (50)	Important	Very low
Organ specific disease response (1 cohort study, 1 case series)									
Recovery time of temperature, haemoglobin, platelets; median days (benefit is indicated by lower result)									
1 cohort study Wang et al 2022	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	12	8	• temperature: 2.0 v 18.0; p < 0.001 • haemoglobin: 7.0 v 30.5; p < 0.001 • platelets: 7.0 v 27.0; p=0.013	Important	Very low
Size of spleen; Day 0 and Month 1; p-value only									
1 cohort study Wang et al 2022	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	12	8	• Day 0: p=0.305 • Month 1: p=0.047	Important	Very low
Disease of the pituitary, at the end of dabrafenib treatment, median (range) time of treatment 11.4 months (3.1 to 19.2 months)									
1 case series	No serious limitations	Serious indirectness[3]	Not applicable	Not calculable	7	None	The authors stated that none of the seven patients with pituitary lesions showed no further progression of disease. One of	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Dabrafenib	Best supportive care	Result		
Yang et al 2021							three patients with diabetes insipidus had an improvement of symptoms.		
Disease of the liver and spleen, at the end of dabrafenib treatment, median (range) time of treatment 11.4 months (3.1 to 19.2 months)									
1 case series Yang et al 2021	No serious limitations	Serious indirectness[3]	Not applicable	Not calculable	7	None	The authors stated that 5 (71.4%) of patients with liver lesions showed improvement following dabrafenib treatment. Two patients with no liver lesions, but with symptoms of hepatosplenomegaly and liver damage reported a reduction in symptoms.	Important	Very low
Safety (1 cohort study, 3 case series)									
Adverse Events (AEs), – Grade 1 or 2 median follow-up 28.9 months, range (5.6 to 148.7); n (%)									
1 cohort study Wang et al 2022	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	12	13	• 4 (33.3) v 12 (92.3) • Primary AEs for dabrafenib patients: skin-related toxicity (75%), diarrhoea, vomiting, fatigue, joint pain and transient myocardium enzyme rising • Primary AEs for chemotherapy patients: myelosuppression and pancytopenia.	Important	Very low
Adverse Events (AEs) – Grade 1 or 2, treatment range 4 to 43 months; n									
1 case series Bhatia et al 2018	Very series limitations[4]	Serious indirectness[3]	Not applicable	Not calculable	11	None	• Total AEs: 11[a] • AEs leading to drug dose reduction: 2 • AEs leading to drug discontinuation: 2	Important	Very low
Adverse Events (AEs) – Grade 3, treatment range 4 to 43 months; n									
1 case series Bhatia et al 2018	Very series limitations[4]	Serious indirectness[3]	Not applicable	Not calculable	11	None	• Total AEs: 1 • AEs leading to drug dose reduction: 1 AEs leading to drug discontinuation: 0	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Dabrafenib	Best supportive care	Result		
Adverse Events reported during treatment (dabrafenib), treatment range 4 to 43 months); n									

1 case series
 	
Bhatia et al 2018
	Very series limitations[4]	Serious indirectness[3]	Not applicable	Not calculable	11	None	• arthralgia: 2
							• fatigue: 2
							• fever: 3
							• hypophosphatemia: 1
							• skin (related): 4
							  ○ keratoacanthoma: 1
							  ○ keratosis pilaris: 1
							  ○ panniculitis: 1
							  ○ skin (not further detailed): 1
							• periorbital swelling: 1
							• none: 3
								Important	Very low

Adverse Events (AEs), median treatment 11.4 months (3.1 to 19.2 months); n (%)									
1 case series Yang et al 2021	No serious limitations	Serious indirectness[3]	Not applicable	Not calculable	20	None	• 17 events in n=9 patients • Most common AE, maculopapular rash: 8 events (47.1%) • No severe adverse events	Important	Very low
Skin toxicity, median follow-up 14.0 months, range (4.8 to 37.7); n (%)									
1 case series Shi et al 2021	Serious limitations[7]	Serious indirectness[3]	Not applicable	Not calculable	22	None	13 (56.5)	Important	Very low

Abbreviations
AD: active disease; AE: adverse events; CI: confidence interval; CMR: complete metabolic response; DAS: Disease Activity Score; DCR: disease control rate; LCH: Langerhans cell histiocytosis; n: number; ORR: objective response rate; PERCIST: PET Response Criteria in Solid Tumors; PMD: progressive metabolic disease; PMR: partial metabolic response; SE: standard error; SMD: stable metabolic disease; v: versus

A LCH disease activity score (DAS) is a 15 domain scale with scores ranging from 0-35 (35 being very poor health). Scores 0-2 are considered low, 3-6 moderate, and ≥7 high
B Comparison of DAS after one month of dabrafenib and five weeks (two therapeutic courses) of second-line chemotherapy
C Treatment response was evaluate using the International LCH Study Group Criteria: 1) non-active disease (NAD) = complete resolution; 2) active disease (AD)/better = continuous regression of disease; 3) AD/intermediate = unchanged disease; 4) AD/worse = disease progression or appearance of new lesions. Patients that responded to therapy were those designated as NAD or AD/better
D Modified PET Response Criteria in Solid Tumors (PERCIST): up to 5 lesions were selected, SUVs were normalized for body weight, and the FDG avidity of each lesion was calculated as $SUV_{max\ lesion} - SUV_{max\ liver\ background} = SUV_{corrected\ for\ background}$, or simply "SUV." For brain lesions, brain background was used *in lieu* of liver background. Values less than zero were treated as 0, which allowed the FDG avidity of a lesion to be considered as the excess avidity above background. Complete metabolic response (CMR) was defined as all lesions decreased to or below background; partial metabolic response (PMR) was defined as a 50% or greater decrease from baseline in the sum SUV of all target lesions; progressive metabolic disease (PMD) was defined as a 50% or greater increase from the nadir in the sum of SUV all target lesions or the appearance of new evaluable lesions; stable metabolic disease (SMD) was when the response did not meet other criteria

E ORR: objective response rate; the percentage of all patients AD/better at the end of treatment
F DCR: disease control rate; the percentage of all patients AD/better and AD/stable at the end of treatment

1 Risk of bias: very serious limitations due to potential selection bias (randomisation and allocation), lack of adjustment for confounding factors and a lack of blinding of patients and clinicians.
2 Risk of bias: serious limitations due to loss to follow up.
3 Indirectness: serious indirectness due to lack of comparator.
4 Risk of bias: very serious limitations due to unclear reporting of study participants (in relation to non-consecutive and/or incomplete inclusion) and a lack of any statistical analysis or summary statistic.
5 Imprecision: serious imprecision due to 0 events in the intervention arm.
6 Imprecision: serious imprecision due to 0 events in both treatment and comparator groups.
7 Risk of bias: serious limitations due to unclear follow up.

a Multiple adverse events could be reported for more than one individual. Three of eleven cases reported no AEs

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.
Comparative cohort study	An observational study with two or more groups (cohorts) of people with similar characteristics. One group has a treatment, is exposed to a risk factor or has a particular symptom and the other group does not.
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).
Control group	A group of people in a study who do not have the intervention or test being studied. Instead, they may have the standard intervention. The results for the control group are compared with those for a group having the intervention being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the intervention group, to make it as easy as possible to detect any effects due to the intervention.
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.

Term	Definition
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).
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.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment or other intervention. One group (the experimental group) has the intervention being tested, the other (the comparison or control group) has an alternative intervention, a dummy intervention (placebo) or no intervention at all. The groups are followed up to see how effective the experimental intervention was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
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.

References

Included studies

- Bhatia A, Ulaner G, Rampal R, Hyman DM, Abdel-Wahab O, Durham BH, et al. Single-agent dabrafenib for BRAF(V600E)-mutated histiocytosis. Haematologica. 2018;103(4):e177-e80.
- Shi H, He H, Cui L, Kvedaraite E, Bian Z, Huang T, et al. Transcriptomic landscape of circulating mononuclear phagocytes in Langerhans cell histiocytosis at the single-cell level. Blood. 2021;138(14):1237-48.
- Wang D, Chen XH, Wei A, Zhou CJ, Zhang X, Ma HH, et al. Clinical features and treatment outcomes of pediatric Langerhans cell histiocytosis with macrophage activation syndrome-hemophagocytic lymphohistiocytosis. Orphanet J Rare Dis. 2022;17(1):151.
- Yang Y, Wang D, Cui L, Ma HH, Zhang L, Lian HY, et al. Effectiveness and Safety of Dabrafenib in the Treatment of 20 Chinese Children with BRAFV600E-Mutated Langerhans Cell Histiocytosis. Cancer Res Treat. 2021;53(1):261-9.

NHS England
Wellington House
133-155 Waterloo Road
London
SE1 8UG