



National Comprehensive  
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Histiocytic Neoplasms

Version 2.2024 — July 19, 2024

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ξ	Bone marrow transplantation
‡	Hematology/Hematology oncology
†	Internist/Internal medicine, including family practice, preventive management
†	Medical oncology
Ψ	Neurology/Neuro-oncology
φ	Nuclear medicine
≠	Pathology
¥	Patient advocacy
€	Pediatric oncology
§	Radiotherapy/radiation oncology
*	Discussion Writing Committee Member



### [NCCN Histiocytic Neoplasms Panel Members](#) [Summary of the Guidelines Updates](#)

#### Langerhans Cell Histiocytosis:

- [Workup/Evaluation \(LCH-1\)](#)
- [Tissue Biopsy Analysis for LCH \(LCH-2\)](#)
- [Unifocal LCH \(LCH-3\)](#)
- [Multisystem or Multifocal Single-System LCH or Unifocal LCH that Progresses on Local Therapy or Involves Critical Organs \(LCH-4\)](#)
- [Follow-Up, Treatment for Relapsed/Refractory Disease \(LCH-5\)](#)

#### Erdheim-Chester Disease:

- [Workup/Evaluation \(ECD-1\)](#)
- [Tissue Biopsy Analysis for ECD \(ECD-2\)](#)
- [Presentation \(ECD-3\)](#)

#### Rosai-Dorfman Disease:

- [Workup/Evaluation \(RDD-1\)](#)
- [Tissue Biopsy Analysis for RDD \(RDD-2\)](#)
- [Unifocal/Multifocal RDD \(RDD-3\)](#)

#### [Principles of Diagnostic Evaluation \(HIST-A\)](#)

#### [Characteristic Features of Histiocytic Neoplasms \(HIST-B\)](#)

#### [Principles of Pathology \(HIST-C\)](#)

#### [Principles of Systemic Therapy \(HIST-D\)](#)

#### [Principles of Supportive Care \(HIST-E\)](#)

#### [Abbreviations \(ABBR-1\)](#)

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**NCCN Categories of Evidence and Consensus:** All recommendations are category 2A unless otherwise indicated.

See [NCCN Categories of Evidence and Consensus](#).

**NCCN Categories of Preference:** All recommendations are considered appropriate.

See [NCCN Categories of Preference](#).

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2024.



**Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.**

**Updates in Version 2.2024 of the NCCN Guidelines for Histiocytic Neoplasms from Version 1.2024 include:**

### [HIST-D 1 of 6](#)

- Langerhans Cell Histiocytosis
  - ▶ Multisystem or single-system lung LCH and bone disease only, Useful in Certain Circumstances:
    - ◊ Regimen added: Repotrectinib for NTRK gene fusion

### [HIST-D 2 of 6](#)

- Langerhans Cell Histiocytosis
  - ▶ CNS lesions, Useful in Certain Circumstances:
    - ◊ Regimen added: Repotrectinib for NTRK gene fusion

**Updates in Version 1.2024 of the NCCN Guidelines for Histiocytic Neoplasms from Version 1.2023 include:**

### **Global**

- References updated throughout the guideline.

### [LCH-1](#)

- 3rd bullet modified: Pulmonary function tests (PFTs) ~~and with or without~~ high-resolution CT of the chest for suspected pulmonary Langerhans cell histiocytosis (LCH)
- 4th bullet modified: Laboratory evaluation (~~HIST-D and LCH-2~~)
- 5th bullet modified: Tissue biopsy (~~LCH-2~~)
  - ▶ Sub bullets deleted
    - ◊ BRAF V600E (VE1) immunohistochemistry
    - ◊ Targeted-capture, next-generation sequencing (NGS) in BRAF V600E wild-type or equivocal cases for mutations in the MAPK pathway (eg, ARAF, NRAS, KRAS, MAP2K1/2) and in other molecular pathways
    - ◊ Gene fusion assay
- Right column modified: *Tissue biopsy analysis and CBC abnormality (LCH-2) Treatment (LCH-3)*
- Footnote b modified: ~~Please see~~ Principles of Diagnostic Evaluation (HIST-A) for details on H&P and laboratory evaluation.
- Footnote c modified: Common sites of involvement include: bone, skin, lymph node, liver, spleen, oral mucosa, lung, and central nervous system (CNS). *See Characteristic features of Histiocytic Neoplasms (HIST-B).*

### [LCH-2](#)

- This page was extensively revised.

### [LCH-4](#)

- Footnote l modified: For neurodegenerative LCH, clinical findings may not be accompanied by imaging changes. Cognitive symptoms should be carefully *evaluated and* monitored, and early treatment should be considered *if cognitive decline is evident*.

### [HIST-D 3 of 6](#)

- Erdheim-Chester Disease
  - ▶ Useful in Certain Circumstances:
    - ◊ Regimen added: Repotrectinib for NTRK gene fusion

### [HIST-D 4 of 6](#)

- Rosai-Dorfman Disease
  - ▶ Useful in Certain Circumstances:
    - ◊ Regimen added: Repotrectinib for NTRK gene fusion

### [ECD-1](#)

- 3rd bullet modified: Laboratory evaluation (~~HIST-D and ECD-2~~)
- 4th bullet modified: Tissue biopsy (~~ECD-2~~)
  - ▶ Sub bullets removed
    - ◊ BRAF V600E (VE1) immunohistochemistry
    - ◊ Targeted-capture, next-generation sequencing (NGS) in BRAF V600E wild-type or equivocal cases for mutations in the MAPK pathway (eg, ARAF, NRAS, KRAS, MAP2K1/2) and in other molecular pathways
    - ◊ Gene fusion assay
- Right column modified: *Tissue biopsy analysis and CBC abnormality (ECD-2) Treatment (ECD-3)*
- Footnote c modified: Common sites of involvement include: long bones (bilateral and symmetric diaphyseal and metaphyseal osteosclerosis with subchondral sparing); orbits (retro-orbital mass with exophthalmos; xanthelasma); CNS (pituitary gland, posterior fossa); lungs (interstitial changes); vascular (periaortic infiltrate; pericardium, right atrium); retroperitoneal/perinephric or "hairy kidney" (mesentery). *See Characteristic features of Histiocytic Neoplasms (HIST-B).*
- Footnote e added: The presence of hairy kidney is highly suggestive of ECD and is present in 50% to 68% of patients. Periarterial infiltration involving the thoracic or abdominal aorta and other vessels is present in 56% to 85% of patients with ECD. Goyal G, et al. Mayo Clin Proc 2019;94:2054-2071.

### [ECD-2](#)

- This page was extensively revised.

**Continued**  
**UPDATES**

**Updates in Version 1.2024 of the NCCN Guidelines for Histiocytic Neoplasms from Version 1.2023 include:****RDD-1**

- 3rd bullet modified: Laboratory evaluation (~~HIST-D and RDD-2~~)
- 4th bullet modified: Tissue biopsy (~~RDD-2~~)
  - ▶ Sub bullets removed
    - ◊ Targeted-capture, next-generation sequencing (NGS) for mutations in the MAPK pathway (eg, ARAF, NRAS, KRAS, MAP2K1/2) and in other molecular pathways
    - ◊ Gene fusion assay
    - ◊ Germline mutations in SLC29A3 (if familial RDD is suspected)
- Right column modified: *Tissue biopsy (RDD-2)* ~~Treatment (RDD-3)~~
- Footnote c modified: Common sites of involvement include: peripheral lymphadenopathy, subcutaneous nodules, and extranodal sites (skin, soft tissue, upper respiratory tract, bone, retroperitoneum, orbits, spleen). See *Characteristic features of Histiocytic Neoplasms (HIST-B)*.

**RDD-2**

- 3rd column, 2nd bullet moved to a new 4th column.
- 4th column added: Molecular testing section and Germline mutations (optional).
- Footnote h modified: NGS sequencing studies are performed if clinically indicated, which may reveal ~~BRAF-RAS-RAF-MEK-ERK pathway~~ mutations in the MAPK pathway (eg, KRAS, MAP2K1/2) with or without additional somatic mutations also seen in myeloid neoplasia.

**HIST-A 1 of 2**

- Medical History and Physical Examination
  - ▶ 2nd bullet modified: HEENT (head, eyes, ears, nose, and throat): double or decreased vision, blurry vision, decreased hearing, mass, lymphadenopathy, retroorbital pain, xanthelasma, exophthalmos, retro-orbital pain, eyelids/lacrimal swelling, proptosis, nasal obstruction, epistaxis, hyposmia, oral ~~lesions sores~~ or pain, dysmorphic facies, ~~hearing abnormalities (familial RDD)~~, and enlarged tongue or tonsils

**HIST-B**

- New section added: Characteristic Features of Histiocytic Neoplasms

**HIST-D 1 of 6**

- Footnote b modified and moved to the page header: *Consider starting targeted agents at lower dose. See Principles of Supportive Care (HIST-E)* (Also for HIST-D 2, HIST-D 3, HIST-D 4)

**HIST-D 2 of 6**

- CNS lesions, 4th column
  - ▶ Relapsed/Refractory
    - ◊ Bullet removed: Allogeneic hematopoietic cell transplant (for highly select patients)

**HIST-D 3 of 6**

- Footnote e added: Peginterferon alfa-2a is the only peginterferon alfa available for clinical use in the United States and it may be substituted for peginterferon alfa-2b (Schiller M, et al. J Eur Acad Dermatol Venereol 2017;31:1841-1847; Patsatsi A, et al. J Eur Acad Dermatol Venereol 2022;36:e291-e293; Osman S, et al. Dermatologic Therapy 2023;2023:7171937).

**HIST-E**

- New section added to Principles of Supportive Care: Toxicities of Other Targeted Therapies
- Chronic Pain, Fatigue, Depression, Anxiety, and Poor Quality of Life
  - ▶ 7th bullet modified: It is important for clinicians to acknowledge these symptoms fully and refer the patients to appropriate specialties (eg, *palliative medicine*, ~~supportive care, fatigue clinic~~, psychiatry, psychology).



### INTRODUCTION

**These Guidelines describe treatment recommendations for adults with histiocytic neoplasms. In scenarios where there is little evidence in the adult population, recommendations are extrapolated from pediatric studies.**

**WORKUP / EVALUATION<sup>a</sup>****ESSENTIAL:**

- History and physical examination (H&P)<sup>b</sup> with attention to common sites of involvement<sup>c</sup>
- Whole-body fluorodeoxyglucose (FDG)-PET/CT scan including distal extremities (vertex to toes)
- Pulmonary function tests (PFTs) and high-resolution CT of the chest for suspected pulmonary Langerhans cell histiocytosis (LCH)
- Laboratory evaluation<sup>b</sup>
- Tissue biopsy<sup>d</sup>

**USEFUL UNDER CERTAIN CIRCUMSTANCES, BASED ON SYMPTOMS OR ORGAN INVOLVEMENT:**

- CT of the chest, abdomen, and pelvis with contrast
- MRI with and without contrast<sup>e</sup> for the following:
  - ▶ brain
  - ▶ spine
  - ▶ sella turcica ± pituitary (if diabetes insipidus suspected)
- Right heart catheterization if pulmonary hypertension is suspected
- Transthoracic echocardiogram (TTE) especially for pulmonary LCH
- Ultrasound (US) of the abdomen (liver/spleen)
- Endoscopic retrograde cholangiopancreatography (ERCP) (if LFTs abnormal or ducts dilated on CT/US)
- Endocrine evaluation (essential in detected endocrinopathy or pituitary hypothalamic involvement)\*
- Digital panoramic x-ray

Tissue biopsy  
analysis  
and CBC  
abnormality  
([LCH-2](#))

<sup>a</sup> Adapted with permission from Goyal G, et al. Blood 2022;139:2601-2621.

<sup>b</sup> [Principles of Diagnostic Evaluation \(HIST-A\)](#).

<sup>c</sup> Common sites of involvement include: bone, skin, lymph node, liver, spleen, oral mucosa, lung, and central nervous system (CNS). See [Characteristic features of Histiocytic Neoplasms \(HIST-B\)](#).

<sup>d</sup> [Principles of Pathology \(HIST-C\)](#).

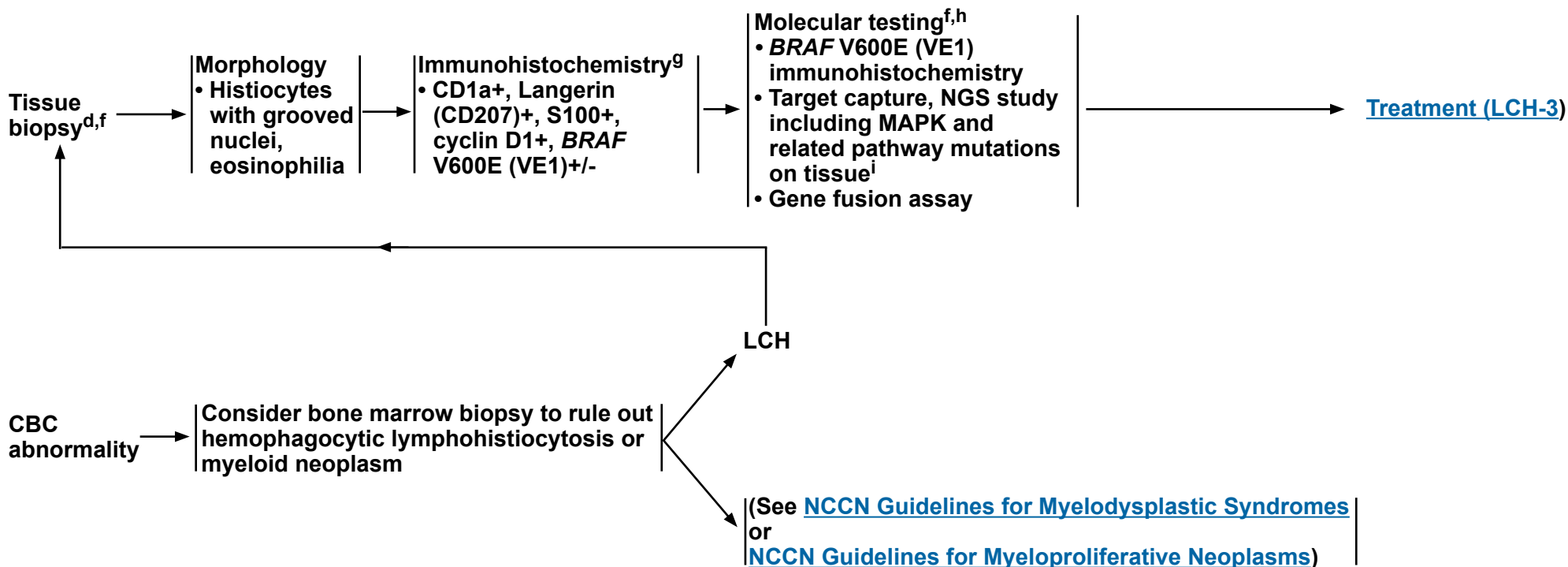
<sup>e</sup> It is recommended for imaging studies to be performed with contrast, unless contrast is contraindicated.

**Note: All recommendations are category 2A unless otherwise indicated.**





### TISSUE BIOPSY ANALYSIS FOR LCH



Immunophenotype key: +/-: positive or negative; +: positive; -: negative

<sup>d</sup> [Principles of Pathology \(HIST-C\)](#).

<sup>f</sup> For patients with suspected LCH or histiocytosis and biopsy is not possible because of location or risk factors, mutational analysis of the peripheral blood is an option.

<sup>g</sup> A minimal panel would include CD1a, S100, and Langerin; cyclin D1 and *BRAF* V600E (VE1) immunohistochemistry is recommended.

<sup>h</sup> Molecular testing for somatic mutations and fusions can be performed in a stepwise manner or in parallel, depending on clinical need and institutional protocols. The frequency of suspected molecular lesions should drive the order of testing if a stepwise algorithm is chosen. Allele-specific polymerase chain reaction (PCR) for *BRAF* V600E mutations can be the first step if *BRAF* V600E (VE1) immunohistochemistry is not available or is equivocal. Somatic mutation NGS panel testing should cover the common MAPK pathway mutations. RNA-based molecular panel including fusion testing should cover *BRAF*, *ALK*, *RET*, and *NTRK1* rearrangements. If there is clinical concern for *ALK* rearrangement, or if fusion panel testing is not available, *ALK* immunohistochemistry and fluorescence in situ hybridization (FISH) studies may be performed.

<sup>i</sup> Fresh or paraffin-embedded tissue is used for NGS study; peripheral blood may be informative in multisystem disease. The NGS panel should cover the common MAPK pathway mutations (*BRAF*, *ARAF*, *NRAS*, *KRAS*, *MAP2K1/2*) and other related pathway mutations (eg, *PIK3CA*, *CSF1R*).

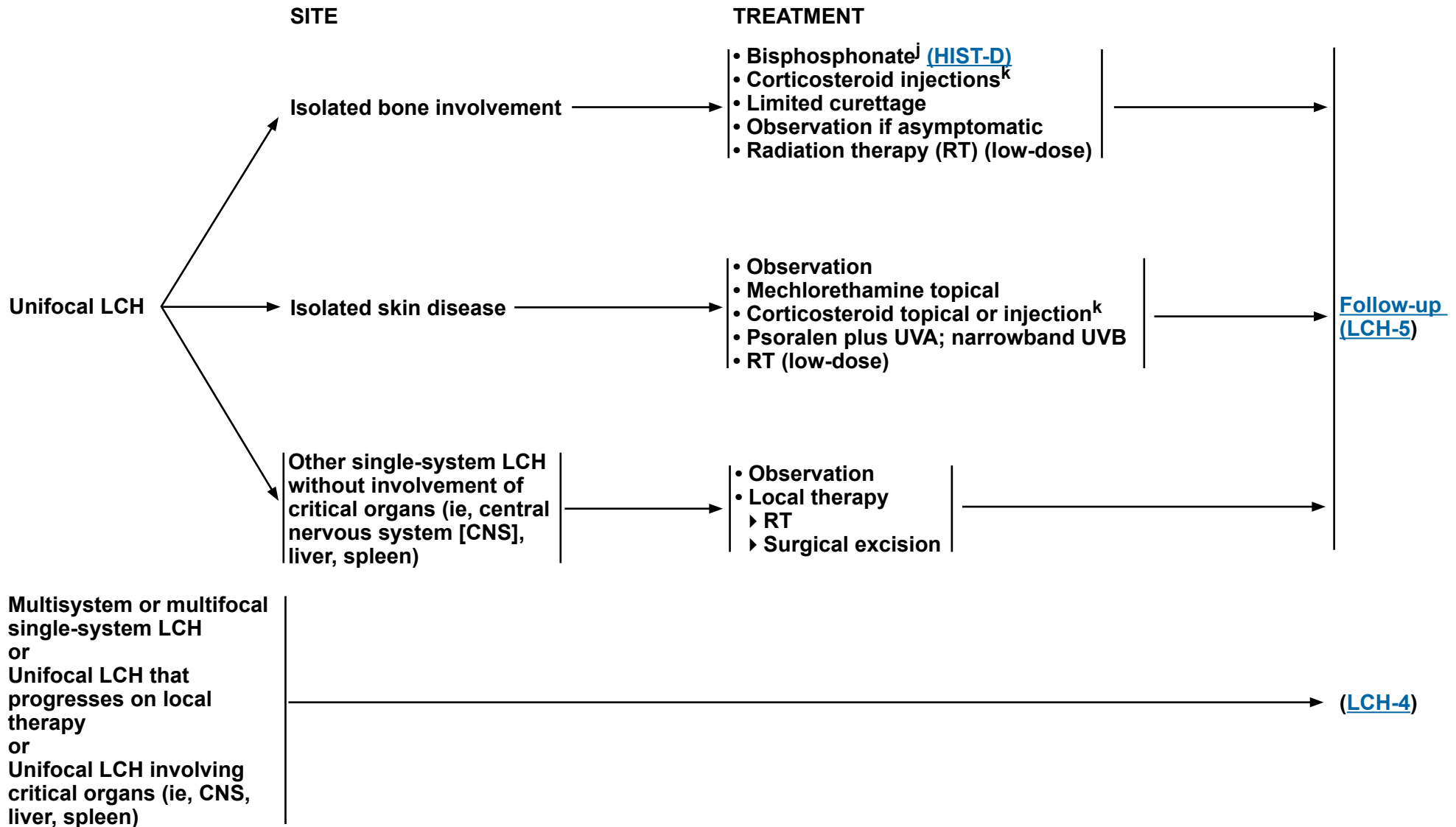
**Note: All recommendations are category 2A unless otherwise indicated.**





# NCCN Guidelines Version 2.2024

## Langerhans Cell Histiocytosis



<sup>j</sup> Bone lesions not amenable to local therapies due to size and location.

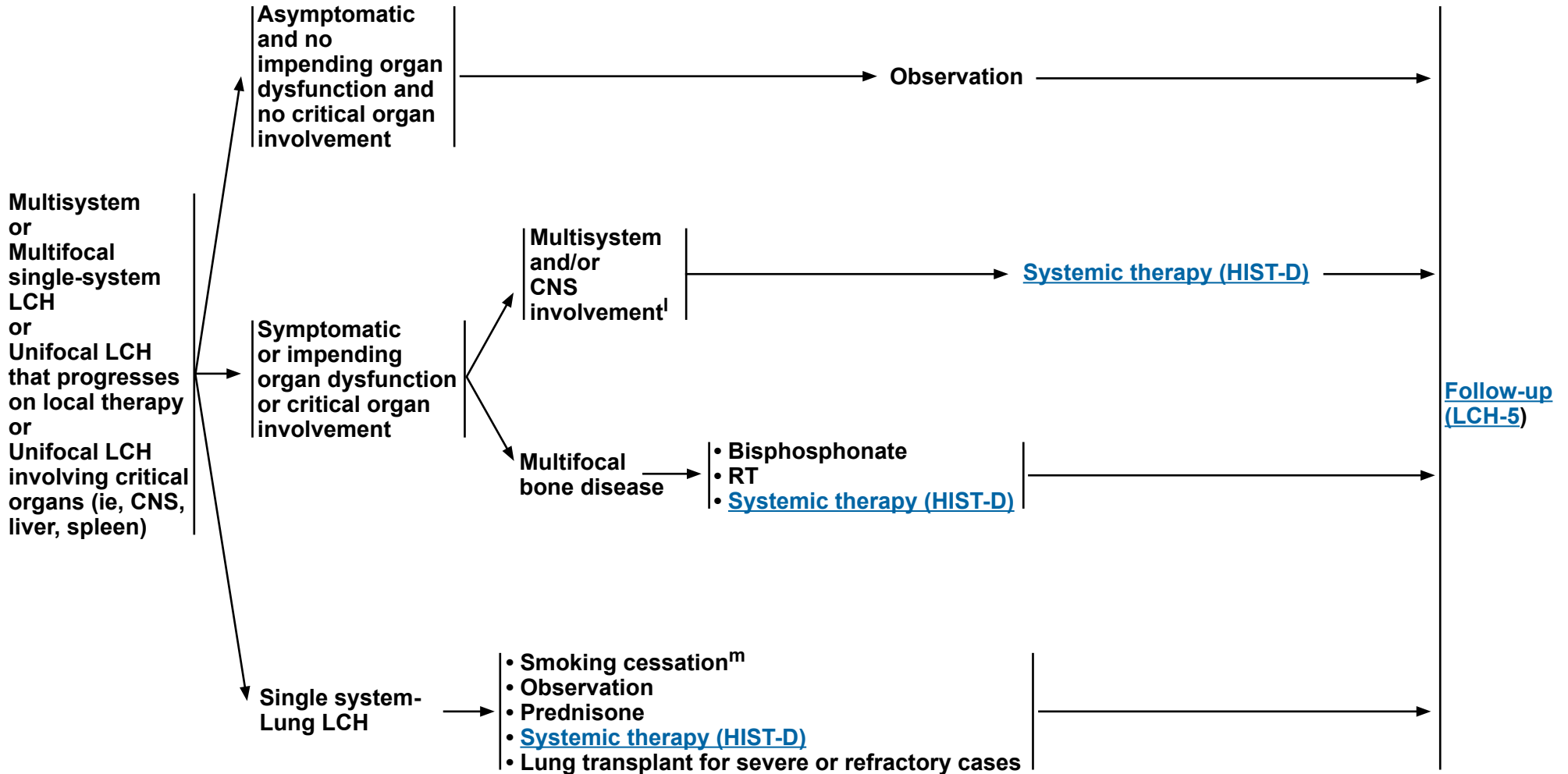
<sup>k</sup> Triamcinolone injection or equivalent corticosteroid.

**Note: All recommendations are category 2A unless otherwise indicated.**



### PRESENTATION

### TREATMENT



<sup>l</sup> For neurodegenerative LCH, clinical findings may not be accompanied by imaging changes. Cognitive symptoms should be carefully evaluated and monitored, and early treatment should be considered if cognitive decline is evident.

<sup>m</sup> Provide resources for smoking cessation. See NCCN Guidelines for Smoking Cessation.

**Note: All recommendations are category 2A unless otherwise indicated.**



### FOLLOW-UP

Imaging of involved sites to evaluate treatment response (FDG-PET/CT scan [preferred], CT/MRI)

- After 2–3 cycles of systemic therapy and at completion
- After completion of surgical curettage
- After RT

### Surveillance

- H&P and labs as clinically indicated
- Imaging: FDG-PET/CT scan (preferred), CT/MRI
  - ▶ Every 3–6 months for the first 2 years post completion of treatment
  - ▶ >2 years: no more than annually
  - ▶ For patients who are asymptomatic with a single-site bone lesion, imaging surveillance can potentially end after year 1, with continued tracking of symptoms
- Monitor PFTs every 3–6 months for at least 2 years for pulmonary LCH
- Bone marrow evaluation in the presence of cytopenias or other blood count abnormalities (to rule out associated myeloid neoplasm)
- For patients with:
  - ▶ BRAF inhibitors, regular skin examination and echocardiogram<sup>n,o</sup>
  - ▶ MEK inhibitors, regular skin examination, retinal examination, and echocardiogram<sup>n,o</sup>
- Monitor every 1–2 years for pituitary hormone abnormalities

### TREATMENT FOR RELAPSED/ REFRACTORY DISEASE

#### [Systemic therapy \(HIST-D\)](#)

- If duration of response >1 year, consider same regimen; otherwise use a regimen not used for first-line

<sup>n</sup> [Principles of Supportive Care \(HIST-E\)](#).

<sup>o</sup> See Management of Toxicities Associated with Targeted Therapy (ME-K) in the NCCN Guidelines for Melanoma: Cutaneous.

**Note: All recommendations are category 2A unless otherwise indicated.**

**WORKUP / EVALUATION<sup>a</sup>****ESSENTIAL:**

- H&P<sup>b</sup> with attention to common sites of involvement<sup>c</sup>
- Whole-body FDG-PET/CT scan including distal extremities (vertex to toes)
- Laboratory evaluation<sup>b</sup>
- Tissue biopsy<sup>d</sup>

**USEFUL UNDER CERTAIN CIRCUMSTANCES, BASED ON SYMPTOMS OR ORGAN INVOLVEMENT:**

- CT of the following:
  - chest, abdomen, and pelvis with contrast<sup>e</sup>
  - sinuses with contrast
  - chest (high-resolution)
- MRI with and without contrast<sup>f</sup> for the following:
  - brain
  - orbit
  - spine
  - sella turcica ± pituitary (if diabetes insipidus suspected)
- PFTs
- TTE (especially for suspected pulmonary ECD)
- Renal artery US
- Testicular US
- Technetium-99<sup>m</sup> MDP bone scintigraphy

Tissue biopsy  
analysis  
and CBC  
abnormality  
([ECD-2](#))

<sup>a</sup> Adapted with permission from Goyal G, et al. Blood 2020;135:1929-1945.

<sup>b</sup> Please see [Principles of Diagnostic Evaluation \(HIST-A\)](#) for details on H&P and laboratory evaluation.

<sup>c</sup> Common sites of involvement include: long bones (bilateral and symmetric diaphyseal and metaphyseal osteosclerosis with subchondral sparing); orbits (retro-orbital mass with exophthalmos; xanthelasma); CNS (pituitary gland, posterior fossa); lungs (interstitial changes); vascular (periaortic infiltrate; pericardium, right atrium); retroperitoneal/perinephric or "hairy kidney" (mesentery). See [Characteristic features of Histiocytic Neoplasms \(HIST-B\)](#).

<sup>d</sup> [Principles of Pathology \(HIST-C\)](#).

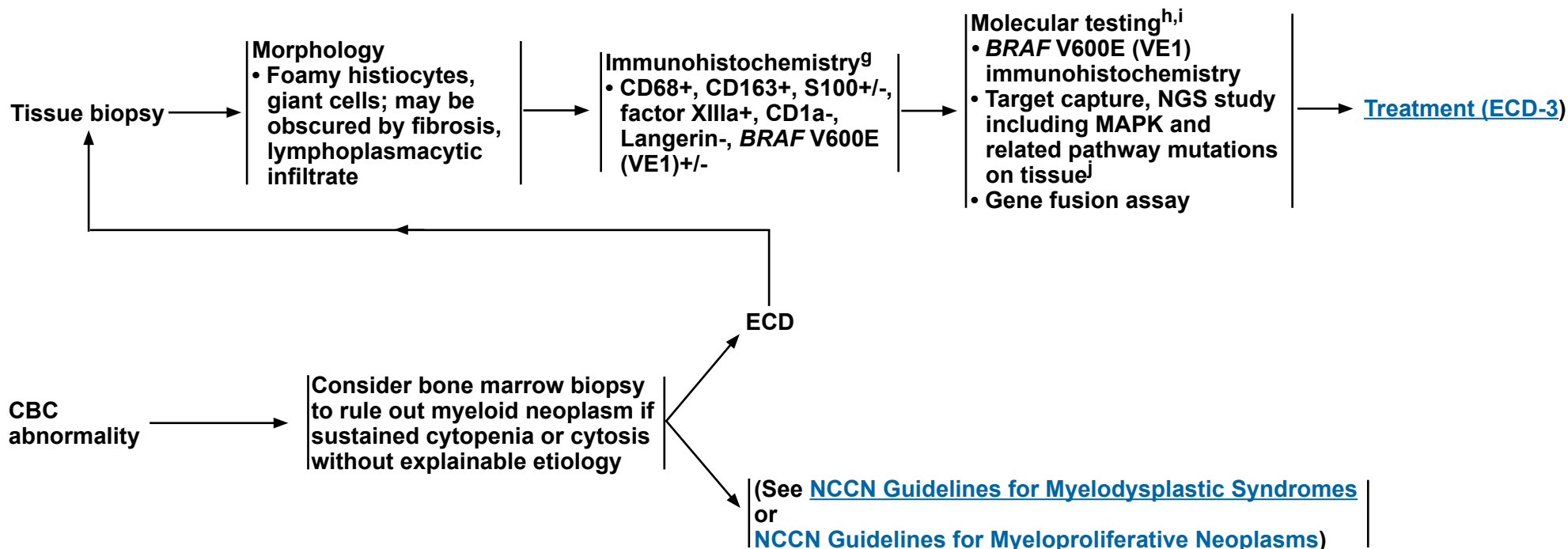
<sup>e</sup> The presence of hairy kidney is highly suggestive of ECD and is present in 50% to 68% of patients. Periarterial infiltration involving the thoracic or abdominal aorta and other vessels is present in 56% to 85% of patients with ECD. Goyal G, et al. Mayo Clin Proc 2019;94:2054-2071.

<sup>f</sup> It is recommended for imaging studies to be performed with contrast, unless contrast is contraindicated.

**Note: All recommendations are category 2A unless otherwise indicated.**



### TISSUE BIOPSY ANALYSIS OF ECD



Immunophenotype key: +/-: positive or negative; +: positive; -: negative

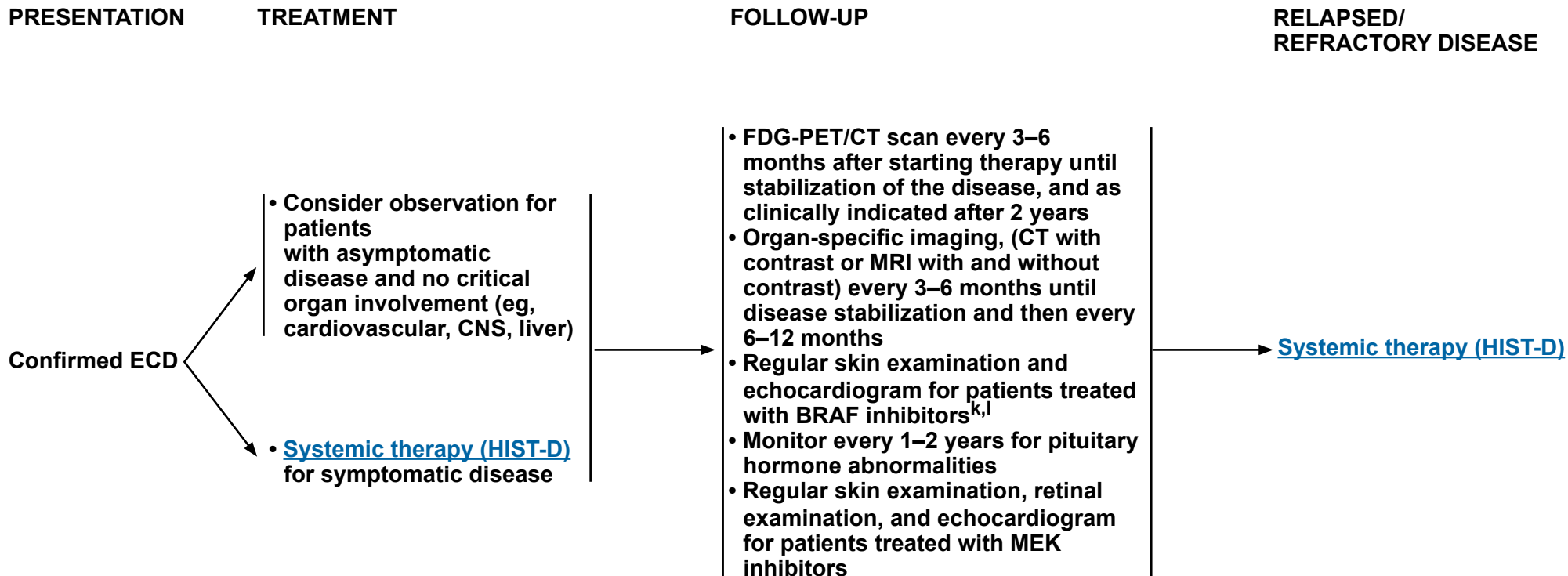
<sup>g</sup> A minimal panel would include CD68 or CD163, factor XIIIa, S100, or CD1a; *BRAF* V600E (VE1) immunohistochemistry is recommended.

<sup>h</sup> For patients with suspected ECD or histiocytosis and biopsy is not possible because of location or risk factors, mutational analysis of the peripheral blood is an option. Janku F, et al. *Mol Cancer Ther* 2019;18:1149-1157.

<sup>i</sup> Molecular testing for somatic mutations and fusions can be performed in a stepwise manner or in parallel, depending on clinical need and institutional protocols. The frequency of suspected molecular lesions should drive the order of testing if a stepwise algorithm is chosen. Allele-specific PCR for *BRAF* V600E mutations can be the first step if *BRAF* V600E (VE1) immunohistochemistry is not available or is equivocal. Somatic mutation NGS panel testing should cover the common MAPK pathway mutations. RNA-based molecular panel including fusion testing should cover *BRAF*, *ALK*, *RET*, and *NTRK1* rearrangements. If there is clinical concern for *ALK* rearrangement, or if fusion panel testing is not available, *ALK* immunohistochemistry and FISH studies may be performed.

<sup>j</sup> Fresh or paraffin-embedded tissue is used for the NGS study; peripheral blood testing may be informative in multisystem disease. The NGS panel should cover the common MAPK pathway mutations (*BRAF*, *ARAF*, *NRAS*, *KRAS*, *MAP2K1/2*) and other related pathway mutations (eg, *PIK3CA*, *CSF1R*). If clinically indicated in cases without the usual MAPK pathway mutations, FISH for *BRAF*, *ALK*, *RET*, or *NTRK1* fusions may be performed.

**Note: All recommendations are category 2A unless otherwise indicated.**



<sup>k</sup> See Management of Toxicities Associated with Targeted Therapy (ME-K) in the NCCN Guidelines for Melanoma: Cutaneous.  
<sup>l</sup> [Principles of Supportive Care \(HIST-E\)](#).

**Note: All recommendations are category 2A unless otherwise indicated.**



### WORKUP / EVALUATION<sup>a</sup>

#### **ESSENTIAL:**

- H&P<sup>b</sup> with attention to common sites of involvement<sup>c</sup>
- Whole-body FDG-PET/CT scan including distal extremities (vertex to toes)
- Laboratory evaluation<sup>b</sup>
- Tissue biopsy<sup>d</sup>

#### **USEFUL UNDER CERTAIN CIRCUMSTANCES, BASED ON SYMPTOMS OR ORGAN INVOLVEMENT:**

- CT of the following:
  - ▶ chest, abdomen, and pelvis with contrast
  - ▶ sinuses with contrast
  - ▶ chest (high-resolution)
- MRI with and without contrast<sup>e</sup> for the following:
  - ▶ brain
  - ▶ orbit
  - ▶ spine
  - ▶ sella turcica ± pituitary (if diabetes insipidus suspected)
- PFTs
- TTE (especially for suspected pulmonary RDD)
- Thyroid US
- Testicular US

Tissue  
biopsy  
([RDD-2](#))

<sup>a</sup> Adapted with permission from Abla O, et al. Blood 2018;131:2877-2890.

<sup>b</sup> Please see [Principles of Diagnostic Evaluation \(HIST-A\)](#) for details on H&P and laboratory evaluation.

<sup>c</sup> Common sites of involvement include: peripheral lymphadenopathy, subcutaneous nodules, and extranodal sites (skin, soft tissue, upper respiratory tract, bone, retroperitoneum, orbits, spleen). See [Characteristic features of Histiocytic Neoplasms \(HIST-B\)](#).

<sup>d</sup> [Principles of Pathology \(HIST-C\)](#).

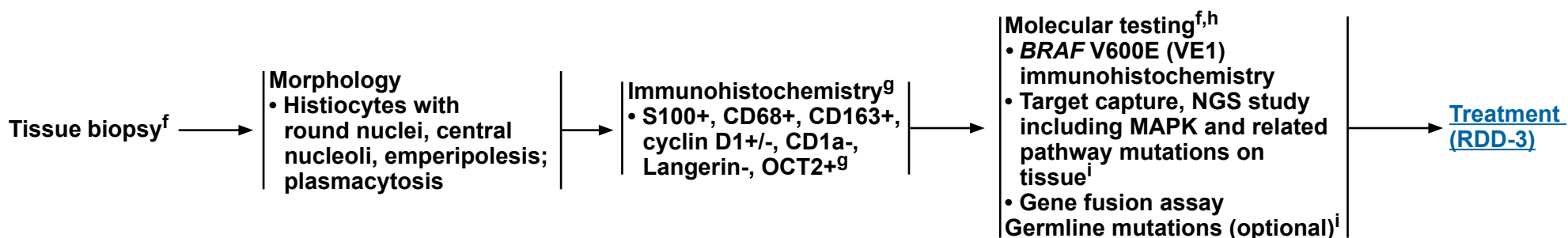
<sup>e</sup> It is recommended for imaging studies to be performed with contrast, unless contrast is contraindicated.

**Note: All recommendations are category 2A unless otherwise indicated.**





**TISSUE BIOPSY ANALYSIS OF RDD**



Immunophenotype key: +/-: positive or negative; +: positive; -: negative

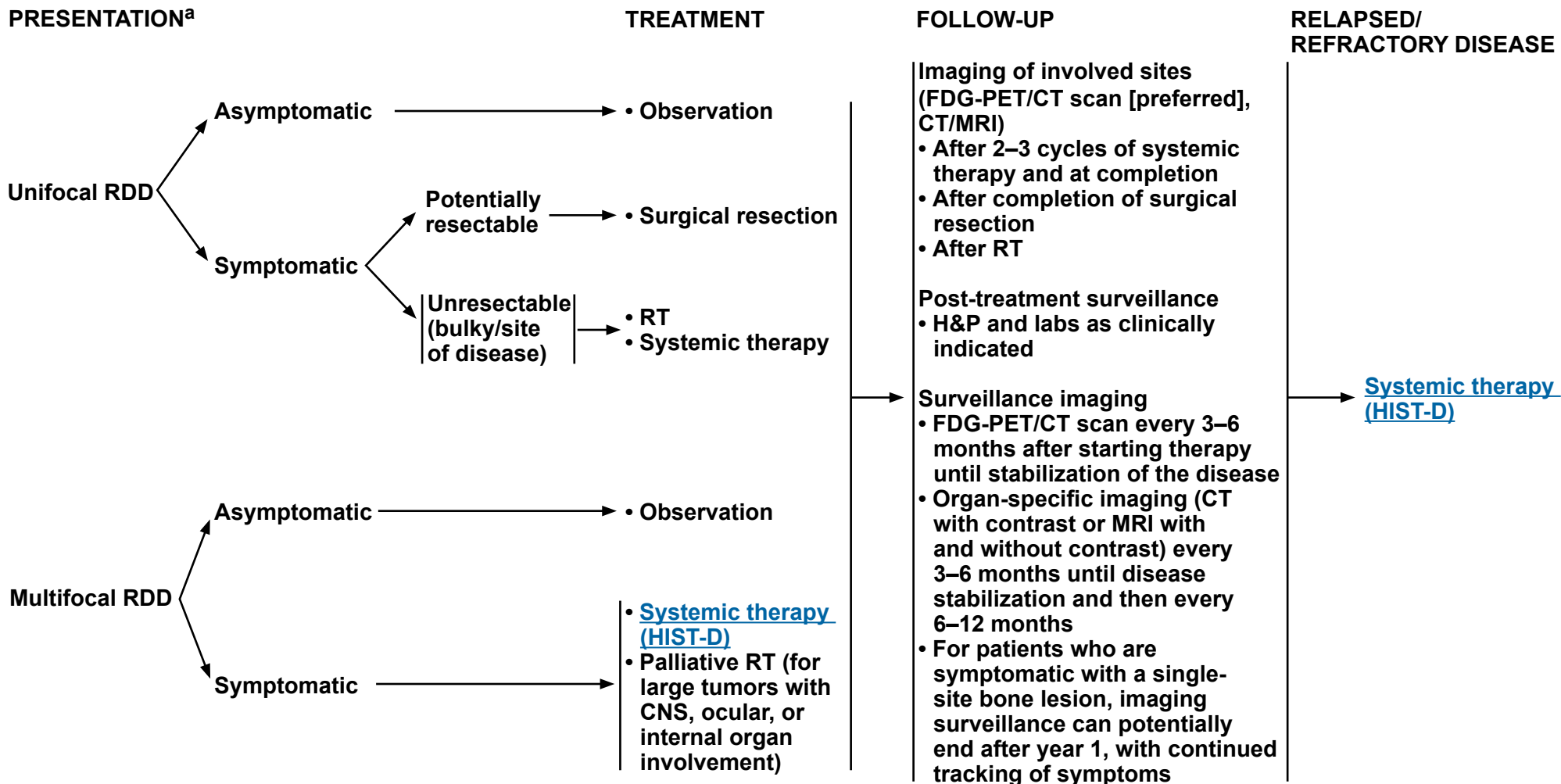
<sup>f</sup> For patients with suspected RDD or histiocytosis and biopsy is not possible because of location or risk factors, liquid biopsy for mutational analysis in the peripheral blood is an option. Janku F, et al. Mol Cancer Ther 2019;18:1149-1157.

<sup>g</sup> A minimal panel would include CD68 or CD163, S100, CD1a, and cyclin D1. Of caution, cyclin D1 could also be positive or detected in concurrent lymphocytic or histiocytic neoplasm. A novel study showed that OCT2 immunohistochemistry might be helpful, if clinically indicated, in select cases to confirm a suspected diagnosis of RDD, together with other common diagnostic markers. Ravindran A, et al. Am J Surg Pathol 2021;45:35-44.

<sup>h</sup> NGS sequencing studies are performed if clinically indicated, which may reveal mutations in the MAPK pathway (eg, *KRAS*, *MAP2K1/2*) with or without additional somatic mutations also seen in myeloid neoplasia.

<sup>i</sup> If a familial RDD is suspected, germline mutations in *SLC29A3* should be considered. A germline gene mutation involving Fas gene *TNFRSF6*- was found in 40% of patients with RDD who had an ALPs type Ia.

**Note: All recommendations are category 2A unless otherwise indicated.**



<sup>a</sup> Adapted with permission from Abla O, et al. Blood 2018;131:2877-2890.

**Note: All recommendations are category 2A unless otherwise indicated.**

**PRINCIPLES OF DIAGNOSTIC EVALUATION****Medical History and Physical Examination:**

- **Constitutional:** fevers, night sweats, fatigue, headache, myalgias, weight loss
- **HEENT (head, eyes, ears, nose, and throat):** double or decreased vision, blurry vision, decreased hearing, mass, lymphadenopathy, retro-orbital pain, xanthelasma, exophthalmos, retro-orbital pain, eyelids/lacrimal swelling, proptosis, nasal obstruction, epistaxis, hyposmia, oral lesions or pain, dysmorphic facies, and enlarged tongue or tonsils
- **Cardiovascular:** dyspnea, orthopnea, hypertension, irregular pulse, bradycardia, cardiomegaly, murmurs
- **Pulmonary:** dyspnea, cough, hemoptysis, chest pain, diminished aeration, rales, crackles, pneumothorax; evaluate smoking history<sup>a</sup>
- **Musculoskeletal:** bone pain, back pain, muscle pain, joint pain, osseous mass
- **Lymphatic:** lymphadenopathy
- **Abdominal/gastrointestinal:** diarrhea, melena, flank mass, hepatosplenomegaly, enlarged inguinal nodes, abdominal pain, constipation, hematochezia
- **Genital:** testicular mass or enlargement
- **Skin:** erythematous rash, subcutaneous nodules, attention to ear canals, periorbital region, perineum, axillae, inguinal region, xanthelasma, pruritus, papules, plaques
- **Thoracic:** diminished lung aeration, rales, axillary nodes, breast mass
- **Renal:** hematuria, flank pain
- **Endocrine:** polydipsia/polyuria, gynecomastia, decreased libido, weight changes, appetite changes, cold intolerance, constipation
- **Neurologic:** headaches, ataxia, dysarthria, seizures, cognitive decline, disconjugate gaze, cranial nerve palsies, ataxic or magnetic gait, sensory or motor impairment, hemiparesis, hyperreflexia, dysphagia, limb or facial weakness, sensory changes, hearing impairment
- **Psychiatric:** depression, anxiety, disinhibition, inappropriate laughing or crying, pseudobulbar affect
- **For RDD:** history of autoimmune disease, autoimmune lymphoproliferative syndrome (ALPS), malignancy, LCH, or another histiocytic disorder
- **For familial RDD:** family history (parents who are consanguineous, autoimmune disease, Turkish/Pakistani or Middle Eastern ancestry)

**Laboratory Evaluation:**

- Complete blood count (CBC) with differential ([LCH-2 or ECD-2 or RDD-2](#))
- Comprehensive metabolic panel including liver and kidney function assessments
- For anemia: Coombs test, haptoglobin, reticulocyte count, and blood smear
- C-reactive protein (CRP)
- Morning urine and serum osmolality
- Morning serum cortisol with adrenocorticotropic hormone (ACTH)
- Follicle-stimulating hormone (FSH)/luteinizing hormone (LH) with testosterone (males) and estradiol (females)
- Thyroid-stimulating hormone (TSH) and free T4

<sup>a</sup> Provide resources for smoking cessation. See [NCCN Guidelines for Smoking Cessation](#).[Continued](#)**Note: All recommendations are category 2A unless otherwise indicated.**



### PRINCIPLES OF DIAGNOSTIC EVALUATION

#### Laboratory Evaluation: (continued)

- Prolactin and insulin-like growth factor 1 (IGF-1)
- Lumbar puncture (for brain lesions inaccessible to biopsy)
- Bone marrow aspirate/biopsy ([LCH-2](#) or [ECD-2](#) or [RDD-2](#))
- For RDD: Serum immunoglobulins
- For RDD: ALPS panel, antinuclear antibody (ANA), antineutrophil cytoplasmic antibodies (ANCA), rheumatoid factor (RF), HLA-B27: if autoimmune disease is suspected and based on clinical findings

#### Subspecialty Consultations as Needed:

- Pulmonary
- Neurology
- Endocrinology
- Dermatology during BRAF or MEK inhibitor therapy<sup>b,c</sup>
- Ophthalmology during MEK inhibitor therapy<sup>b,c</sup>
- Dental/Periodontal
- Smoking cessation<sup>a</sup>
- Palliative medicine<sup>d</sup>

<sup>a</sup> Provide resources for smoking cessation. See [NCCN Guidelines for Smoking Cessation](#).

<sup>b</sup> See [Management of Toxicities Associated with Targeted Therapy \(ME-K\) in the NCCN Guidelines for Melanoma: Cutaneous](#).

<sup>c</sup> [Principles of Supportive Care \(HIST-E\)](#).

<sup>d</sup> See [NCCN Guidelines for Palliative Care](#).

**Note: All recommendations are category 2A unless otherwise indicated.**

**CHARACTERISTIC FEATURES OF HISTIOCYTIC NEOPLASMS<sup>a</sup>**

Feature	ECD	LCH	RDD
Bones	Pathognomonic long-bone osteosclerosis at the metadiaphysis	Osteolytic lesions including skull	Cortex-based osteolytic lesions most common
Nervous system	Brainstem/cerebellum masses; cerebral white matter enhancement; dural and pituitary stalk thickening	MRI with globus pallidus/dentate nucleus T1 hyperintensity; brainstem/cerebellum T2 hyperintensity; dural lesion from intracranial extension of skull lesion; pituitary stalk thickening	Isolated dural or parenchymal lesion
Endocrine	Diabetes insipidus (DI) may present years before diagnosis of ECD	DI may present years before diagnosis of LCH	DI never reported
Respiratory	Mediastinal infiltration; pleural, septal, and maxillary sinus thickening	Mostly seen in smokers; high-resolution computed tomography (HRCT) shows pulmonary nodules in the early stage, cysts in the later stage	Primarily involving large airways and sinuses; rarely interstitial pulmonary or sinus thickening; pleural or pulmonary nodule
Dermatologic	Xanthelasma-like lesions around eyes, face, neck, inguinal folds	Papular rash; rarely subcutaneous nodules or xanthelasma-like lesions	More common subcutaneous nodules, may be seen as macular or papular rash
Cardiac	Right atrial and atrioventricular groove infiltration; pericardial and myocardial infiltration seen on cardiac MRI	Rarely reported	Infiltration of the right atrium, interatrial septum, and left ventricle
Arterial	Periaortic infiltration “coated aorta”; infiltration of the supra-aortic trunk branches, visceral arteries, renal artery stenosis, coronary arteries	Rarely reported	Infiltration of the periaortic and carotid sheath

<sup>a</sup> Adapted with permission from Goyal G, et al. Mayo Clin Proc 2019;94:2054-2071.[Continued](#)**Note: All recommendations are category 2A unless otherwise indicated.**



### CHARACTERISTIC FEATURES OF HISTIOCYTIC NEOPLASMS<sup>a</sup>

Feature	ECD	LCH	RDD
Retroperitoneum, including kidneys	Perinephric infiltration “hairy kidneys” with extension to renal pelvis and ureters causing renal failure; adrenal infiltration	Rarely reported	Commonly hilar masses; subcapsular infiltration; rarely perinephric coating
Lymph nodes	Never reported	Rarely isolated	May present as isolated or generalized lymphadenopathy
Orbits	Orbital masses	Never reported	Orbital masses, sometimes involving the optic nerve

<sup>a</sup> Adapted with permission from Goyal G, et al. Mayo Clin Proc 2019;94:2054-2071.

**Note: All recommendations are category 2A unless otherwise indicated.**

**PRINCIPLES OF PATHOLOGY****General Principles**

- Langerhans cell histiocytosis (LCH), Erdheim-Chester disease (ECD), and Rosai-Dorfman disease (RDD) pose a diagnostic challenge given their rarity, their overlap with each other, reactive processes, and co-occurrence with other hematologic or non-hematologic neoplasms.
- Numerous site-specific mimics of histiocytoses exist due to relatively nonspecific appearance and immunophenotype, such as granular cell tumor, giant cell tumors of the bone and soft tissue, xanthogranulomas, multicentric reticulohistiocytosis, and IgG4-related disease. Manifestations may also vary by site.<sup>1,2</sup>
- Comprehensive immunophenotyping should be performed including S100, CD1a, Langerin (CD207), CD68 and/or CD163, cyclin D1, *BRAF* V600E (VE1), factor XIIIa, and, if indicated, *ALK* and fascin. Discriminatory markers for carcinoma, melanoma, lymphoma, sarcoma, and other suspected disorders are useful for differential diagnoses. Cyclin D1 immunohistochemistry can be helpful to distinguish LCH from reactive Langerhans cell collections and has also been reported to be positive in RDD.<sup>3-5</sup>
- *ALK* immunohistochemistry may be considered, as *ALK*+ histiocytosis may carry a targetable *ALK* rearrangement.<sup>6,7</sup>
- It is recommended to perform molecular mutation profiling to aid in confirming a clonal Langerhans or histiocytic process and to identify potential prognostically relevant mutations or therapeutic targets. Correlation with clinical presentation and imaging findings is crucial for accurate diagnosis. Tissue diagnosis should be confirmed by pathologists with expertise in site-specific histiocytic lesions (eg, hematopathology, dermatopathology, pulmonary pathology, neuropathology).<sup>8</sup>
- In patients with unexplained cytopenias, bone marrow biopsy should be considered due to possible concomitant bone marrow processes, such as hemophagocytic lymphohistiocytosis or myeloid neoplasia (ie, myelodysplastic syndrome [MDS], myeloproliferative neoplasms [MPN], chronic myelomonocytic leukemia [CMML]).<sup>9-15</sup>
- For LCH and ECD, molecular testing for somatic mutations and fusions can be performed in a stepwise manner or in parallel, depending on clinical need and institutional protocols. The frequency of suspected molecular lesions should drive the order of testing if a stepwise algorithm is chosen. Allele-specific polymerase chain reaction (PCR) for *BRAF* V600E (VE1) mutations can be the first step if *BRAF* V600E (VE1) immunohistochemistry is not available or is equivocal.<sup>16</sup> Somatic mutation NGS panel testing should cover the common MAPK pathway mutations. RNA-based molecular panel fusion testing should cover *BRAF*, *ALK*, *RET*, and *NTRK1* rearrangements. If there is clinical concern for *ALK* rearrangement, or if fusion panel testing is not available, *ALK* immunohistochemistry and fluorescence in situ hybridization (FISH) studies may be performed. Repeat molecular testing in negative cases, potentially using a different tissue sample.

**Langerhans Cell Histiocytosis**

- LCH is an abnormal proliferation of Langerhans-type cells with frequent driver mutations involving the MAPK pathway (RAS-RAF-MEK-ERK).
- Histopathologic features include cells with oval or twisted, grooved, or lobulated nuclei, finely granular chromatin, inconspicuous nucleoli, and abundant cytoplasm; these cells frequently have admixed eosinophils and histiocytes, including multinucleated forms, but not usually plasma cell rich. Ki-67 is variable.
- Langerhans cells show immunoreactivity for S100, CD1a, and Langerin (CD207).
- Reactive Langerhans cell infiltrates may mimic LCH; by immunohistochemistry, expression of cyclin D1 (BCL1) and *BRAF* V600E (VE1 clone) support LCH.<sup>6</sup> VE1 staining is not 100% sensitive or specific, and concurrent molecular testing is recommended.
- Activating signaling pathway mutations found in LCH include *BRAF* V600E, *BRAF* indels, *MAP2K1/2*, *N/KRAS*, and *ARAF*. Kinase fusions (ie, *BRAF*, *ALK*, *RET*, *NTRK1*) and mutations in the PI3K-AKT-mTOR pathway have been reported in LCH as well.<sup>17-19</sup> Concomitant panel testing for *BRAF* V600E (VE1) and other MAPK pathway mutations is recommended.<sup>20,21</sup>

[References on HIST-C 3 of 5](#)[Continued](#)**Note: All recommendations are category 2A unless otherwise indicated.**



**PRINCIPLES OF PATHOLOGY****Erdheim-Chester Disease**

- **Histopathologic features include foamy (xanthomatous) histiocytes, including Touton cells in a background of spindled cells and fibrosis. Reactive lymphocytes, plasma cells, and neutrophils are also often present. Typical histologic findings vary by site.<sup>8</sup> For example, bone lesions may be masked by significant fibrosis, including, in some cases, storiform fibrosis. In CNS and lung, the lesional histiocytes are non-lipidized, with eosinophilic cytoplasm, and lack the typical inflammatory infiltrate. In skin, the typical xanthomatous histiocytes are common but can be diffuse or interstitial and relatively subtle. In the retroperitoneum, findings are usually xanthomatous but sometimes extensively fibrotic, and can be associated with increased IgG4+ plasma cells meeting criteria for IgG4-related disease. Finally, in cardiac tissues, diffuse infiltrates of xanthomatous histiocytes may be observed.**
- **The neoplastic cells show immunoreactivities for some histiocytic markers (eg, CD68, CD163, fascin, factor XIIIa). They are negative for CD1a and Langerin (CD207) and can be dim S100+.**
- **Activating signaling pathway mutations found in ECD are similar to those found in LCH, though *PIK3CA* activating mutation is more common in ECD. *BRAF V600E* mutation has been detected in about 50% of patients with ECD. Kinase fusions (ie, *BRAF*, *ALK*, *RET*, *NTRK1*) and *CSF1R* mutations have been reported rarely as well.<sup>17,19,22</sup> The revised histiocytic classification recommends classification of all “JXG” with activating MAPK pathway mutations (*BRAF*, *NRAS*, *KRAS*, *MAP2K1/2*) as ECD.<sup>23,24</sup>**

**Rosai-Dorfman Disease**

- **RDD comprises a heterogeneous group of clinical presentations that can be associated with familial, autoimmune, or malignant process. Classical sporadic RDD shows bilateral painless massive cervical lymphadenopathy associated with B symptoms. It is often also found in mediastinal, inguinal, and retroperitoneal lymph nodes. Extranodal RDD presentation is common.**
- **Hallmark histopathologic features of nodal RDD include dilated sinusoidal spaces filled with large histiocytes with a round to oval hypochromatic nucleus, an inconspicuous to distinct nucleolus, and abundant foamy to clear cytoplasm engulfing a variable number of intact inflammatory cells—namely emperipolesis, a phenomenon recognized in either physiologic or pathologic process. Large histiocytes are positive for monocyte-macrophage markers (ie, S100, CD68, CD163) and negative for LCH markers (ie, CD1a, Langerin [CD207]). Cyclin D1/BCL1 immunohistochemistry can be helpful to confirm the diagnosis. There are often increased polyclonal plasma cells, and further study is needed for confirmation of IgG4 disorder.<sup>25</sup> Extranodal RDD shows more fibrosis and less frequent emperipolesis.<sup>26</sup>**
- **A subset of patients with RDD harbor gene mutations involving *NRAS*, *KRAS*, *MAP2K1/2*, and rarely *BRAF*.<sup>22,27,28</sup>**
- **Inherited conditions predisposing to RDD are typically seen in pediatric cases but could be considered in adolescents and young adults:**
  - ▶ **Heterozygous germline gene mutation involving *FAS* gene *TNFRSF6*, which is found in 40% of patients with RDD who had an ALPS type Ia**
  - ▶ ***SLC29A3* germline gene mutation leading to familial or Faisalabad histiocytosis and H syndrome (histiocytosis-lymphadenopathy plus syndrome).**

[References on HIST-C 3 of 5](#)[Continued](#)**Note: All recommendations are category 2A unless otherwise indicated.**

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[Continued](#)**Note: All recommendations are category 2A unless otherwise indicated.**



### SUMMARY OF PATHOLOGIC AND MOLECULAR FEATURES OF HISTIOCYTIC NEOPLASMS<sup>1</sup>

Disease	LCH	ECD	RDD
<b><u>Pathologic features</u></b> <ul style="list-style-type: none"> <li>• Xanthomatous histiocytes</li> <li>• Touton giant cells</li> <li>• Emperipolesis</li> </ul>	No No No	Yes Yes (mainly dermal sites) Rare	No No Abundant
<b><u>Cytologic features</u></b> <ul style="list-style-type: none"> <li>• Nuclei</li> <li>• Nucleoli</li> <li>• Cytoplasm</li> </ul>	<ul style="list-style-type: none"> <li>• Oval; retiform, irregular nuclear contours or grooves</li> <li>• Inconspicuous</li> <li>• Abundant; eosinophilic</li> </ul>	<ul style="list-style-type: none"> <li>• Bland; round-to-oval; small; no grooves</li> <li>• Inconspicuous</li> <li>• Classically abundant, amorphous lipid-laden or granular/xanthomatous but often overlap with JXG/AXG</li> <li>• Inflammatory cells including few small lymphocytes and plasma cells, rare eosinophils, and dense fibrosis</li> </ul>	<ul style="list-style-type: none"> <li>• Large round; hypochromatic</li> <li>• Variable inconspicuous to distinct</li> <li>• Abundant foamy, clear without xanthomatous features; frequent emperipolesis</li> <li>• Increased mature plasma cells, polyclonal, IgG4; occasional neutrophils</li> </ul>
<b>Background cells</b>	<ul style="list-style-type: none"> <li>• Increased eosinophils, eosinophilic microabscesses</li> </ul>		

JXG: juvenile xanthogranuloma; AXG: adult xanthogranuloma.

<sup>1</sup> Adapted with permission from Goyal G, Heaney ML, Collin M, et al. Erdheim-Chester disease: consensus recommendations for evaluation, diagnosis, and treatment in the molecular era. Blood 2020;135:1929-1945.

[Continued](#)

**Note: All recommendations are category 2A unless otherwise indicated.**



### SUMMARY OF PATHOLOGIC AND MOLECULAR FEATURES OF HISTIOCYTIC NEOPLASMS<sup>1</sup>

Disease	LCH	ECD	RDD
<b>Molecular Features</b> <ul style="list-style-type: none"> <li>• <i>BRAF</i> V600E (VE1)</li> <li>• <i>MAP2K1</i></li> <li>• RAS isoforms (<i>KRAS</i>, <i>NRAS</i>)</li> <li>• <i>BRAF</i> deletions</li> <li>• PI3K isoforms (<i>PIK3CA</i>, <i>PIK3CD</i>)</li> <li>• <i>ARAF</i></li> <li>• Other <i>BRAF</i> missense</li> <li>• <i>RAF1</i></li> <li>• <i>MAP2K2</i></li> <li>• <i>MAP3K1</i></li> <li>• <i>CSF1R</i></li> <li>• <i>BRAF</i> fusions</li> <li>• <i>ALK</i> fusions</li> <li>• <i>NTRK1</i> fusions</li> <li>• <i>RET</i> fusions</li> </ul>	55% 15% 2% 6% 1% 1% 3% None None Reported 1% 3% None None 1%	50% 18% 8% 2% 3% 4% None 1% 1% (1 case) (Amplification) 1% 2% 3% 1% 1%	3% 15% 30% None None 3% None None None None 1% None None None 1%
<b>Immunophenotype</b> <ul style="list-style-type: none"> <li>• CD68 (cytoplasmic)</li> <li>• CD163 (surface)</li> <li>• CD14 (surface)</li> <li>• CD1a (surface)</li> <li>• Langerin (CD207) (cytoplasmic)</li> <li>• Cyclin D1</li> <li>• S100 (cytoplasmic/nuclear)</li> <li>• Factor XIIIa (cytoplasmic)</li> <li>• Fascin (cytoplasmic)</li> <li>• <i>BRAF</i> V600E (VE1) (cytoplasmic)<sup>a</sup></li> <li>• <i>ALK</i> (cytoplasmic)<sup>b</sup></li> <li>• <i>NTRK1</i> (cytoplasmic)</li> <li>• OCT2</li> </ul>	+ (paranuclear cytoplasmic dot) - - ++ ++ + + - - +/- +/- + + +/-* - - +/- -	++ ++ ++ - - +/- + +/- + + +/-* +/-* +/- - - +	

Immunophenotype key: ++, strongly positive; +, weakly positive; +/-, positive or negative; -, negative.

\*Moderate to strong positivity should correlate with molecular alteration.

#### Footnotes

<sup>a</sup> Negative or equivocal immunohistochemistry for *BRAF* V600E (VE1) does not exclude mutated *BRAF* V600E. Test with NGS panel to cover the common mutations, including *BRAF*, *MAP2K1/2*, *NRAS*, and *KRAS*.

<sup>b</sup> Testing *BRAF*, *ALK*, *RET*, and *NTRK1* fusions is recommended if clinically histiocytosis is suspected and NGS panel testing does not reveal *BRAF* or other MAPK pathway mutations. Testing for somatic mutations using NGS first or in parallel is recommended.

<sup>1</sup> Adapted with permission from Goyal G, Heaney ML, Collin M, et al. Erdheim-Chester disease: consensus recommendations for evaluation, diagnosis, and treatment in the molecular era. *Blood* 2020;135:1929-1945.

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**PRINCIPLES OF SYSTEMIC THERAPY<sup>b</sup>**

**Langerhans Cell Histiocytosis**

• Regimens may be used in the first- or subsequent-line setting

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
<b>Multisystem or single-system lung LCH</b>	<p><b><u>BRAF V600E mutated disease</u></b></p> <ul style="list-style-type: none"> <li>• Vemurafenib<sup>a,1,2</sup></li> </ul> <p><b><u>MAP kinase pathway mutation, or no other detectable/actionable mutation, or testing not available</u></b></p> <ul style="list-style-type: none"> <li>• Cobimetinib<sup>a,3</sup></li> </ul> <p><b><u>Irrespective of mutation</u></b></p> <ul style="list-style-type: none"> <li>• Cytarabine<sup>4,5</sup></li> <li>• Cladribine<sup>6,7</sup></li> </ul>	<p><b><u>BRAF V600E mutated disease</u></b></p> <ul style="list-style-type: none"> <li>• Dabrafenib<sup>a,2,12</sup></li> </ul> <p><b><u>MAP kinase pathway mutation, or no other detectable/actionable mutation, or testing not available</u></b></p> <ul style="list-style-type: none"> <li>• Trametinib<sup>a,12-16</sup></li> <li>• Binimetinib<sup>a,c,12-16</sup></li> <li>• Selumetinib<sup>a,c,12-16</sup></li> </ul> <p><b><u>Irrespective of mutation</u></b></p> <ul style="list-style-type: none"> <li>• Methotrexate (oral)<sup>9,10</sup></li> <li>• Hydroxyurea<sup>11</sup></li> <li>• Clofarabine<sup>17</sup></li> <li>• Vinblastine/prednisone<sup>4</sup></li> <li>• Methotrexate + cytarabine<sup>18</sup></li> </ul>	<p><b><u>Targeted therapy</u></b></p> <ul style="list-style-type: none"> <li>• Crizotinib for <i>ALK</i> fusion<sup>21</sup></li> <li>• Pexidartinib for <i>CSF1R</i> mutation<sup>21</sup></li> <li>• Larotrectinib for <i>NTRK</i> gene fusion<sup>22,23</sup></li> <li>• Entrectinib for <i>NTRK</i> gene fusion<sup>22,24</sup></li> <li>• Repotrectinib for <i>NTRK</i> gene fusion</li> <li>• Sirolimus or everolimus for <i>PIK3CA</i> mutation<sup>25,26</sup></li> <li>• Selpercatinib for <i>RET</i> fusion<sup>21</sup></li> </ul> <p><b><u>Relapsed/Refractory</u></b></p> <ul style="list-style-type: none"> <li>• Allogeneic hematopoietic cell transplant (for highly select patients)<sup>27,28</sup></li> </ul>
<b>Bone disease only</b>	<ul style="list-style-type: none"> <li>• Bisphosphonate                             <ul style="list-style-type: none"> <li>▶ Zoledronic acid<sup>8</sup></li> <li>▶ Pamidronate<sup>8</sup></li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• None</li> </ul>	<p><b>Multifocal single-system bone disease not responsive to bisphosphonate</b></p> <ul style="list-style-type: none"> <li>• See preferred, other recommended, and useful in certain circumstances options above for multisystem disease</li> </ul>
<ul style="list-style-type: none"> <li>• <b>Single-system multifocal skin disease (including mucosa)</b></li> </ul>	<ul style="list-style-type: none"> <li>• Methotrexate (oral)<sup>9,10</sup></li> <li>• Hydroxyurea<sup>11</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Lenalidomide<sup>19</sup></li> <li>• Thalidomide<sup>20</sup></li> </ul>	<ul style="list-style-type: none"> <li>• None</li> </ul>

<sup>a</sup> See Management of Toxicities Associated with Targeted Therapy (ME-K) in the NCCN Guidelines for Melanoma: Cutaneous.

<sup>b</sup> Consider starting targeted agents at lower dose. See [Principles of Supportive Care \(HIST-E\)](#).

<sup>c</sup> If cobimetinib or trametinib are not tolerated.

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**Note: All recommendations are category 2A unless otherwise indicated.**



### PRINCIPLES OF SYSTEMIC THERAPY<sup>b</sup>

#### Langerhans Cell Histiocytosis

- Regimens may be used in the first- or subsequent-line setting

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
CNS lesions	<p><b><u>BRAF V600E mutated disease</u></b></p> <ul style="list-style-type: none"> <li>• Vemurafenib<sup>a,1,2</sup></li> </ul> <p><b><u>MAP kinase pathway mutation, or no other detectable/actionable mutation, or testing not available</u></b></p> <ul style="list-style-type: none"> <li>• Cobimetinib<sup>a,3</sup></li> </ul> <p><b><u>Irrespective of mutation</u></b></p> <ul style="list-style-type: none"> <li>• Cytarabine<sup>d,4</sup></li> <li>• Cladribine<sup>6,7</sup></li> </ul>	<p><b><u>BRAF V600E mutated disease</u></b></p> <ul style="list-style-type: none"> <li>• Dabrafenib<sup>a,2,12</sup></li> </ul> <p><b><u>MAP kinase pathway mutation, or no other detectable/actionable mutation, or testing not available</u></b></p> <ul style="list-style-type: none"> <li>• Trametinib<sup>a,12-16</sup></li> <li>• Binimetinib<sup>a,c,12-16</sup></li> <li>• Selumetinib<sup>a,c,12-16</sup></li> </ul> <p><b><u>Irrespective of mutation</u></b></p> <ul style="list-style-type: none"> <li>• High-dose methotrexate<sup>29</sup></li> <li>• Methotrexate + cytarabine<sup>18</sup></li> </ul>	<p><b><u>Targeted therapy</u></b></p> <ul style="list-style-type: none"> <li>• Crizotinib for <i>ALK</i> fusion<sup>21</sup></li> <li>• Pexidartinib for <i>CSF1R</i> mutation<sup>21</sup></li> <li>• Larotrectinib for <i>NTRK</i> gene fusion<sup>22,23</sup></li> <li>• Entrectinib for <i>NTRK</i> gene fusion<sup>22,24</sup></li> <li>• Repotrectinib for <i>NTRK</i> gene fusion</li> <li>• Sirolimus or everolimus for <i>PIK3CA</i> mutation<sup>25,26</sup></li> <li>• Selpercatinib for <i>RET</i> fusion<sup>21</sup></li> </ul>

<sup>a</sup> See Management of Toxicities Associated with Targeted Therapy (ME-K) in the NCCN Guidelines for Melanoma: Cutaneous.

<sup>b</sup> Consider starting targeted agents at lower dose. See [Principles of Supportive Care \(HIST-E\)](#).

<sup>c</sup> If cobimetinib or trametinib are not tolerated.

<sup>d</sup> Higher dose (150 mg/m<sup>2</sup>) is indicated for CNS lesions.

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**Note: All recommendations are category 2A unless otherwise indicated.**





### PRINCIPLES OF SYSTEMIC THERAPY<sup>b</sup>

#### Erdheim-Chester Disease

- Regimens may be used in the first- or subsequent-line setting

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
<p><b><u>BRAF V600E mutated disease</u></b></p> <ul style="list-style-type: none"> <li>• Vemurafenib<sup>a,1,30</sup></li> </ul> <p><b><u>MAP kinase pathway mutation, or no other detectable/actionable mutation, or testing not available</u></b></p> <ul style="list-style-type: none"> <li>• Cobimetinib<sup>a,31</sup></li> </ul>	<p><b><u>BRAF V600E mutated disease</u></b></p> <ul style="list-style-type: none"> <li>• Dabrafenib<sup>a,31,32</sup></li> </ul> <p><b><u>MAP kinase pathway mutation, or no other detectable/actionable mutation, or testing not available</u></b></p> <ul style="list-style-type: none"> <li>• Trametinib<sup>a,14,33</sup></li> </ul> <p><b><u>Irrespective of mutation</u></b></p> <ul style="list-style-type: none"> <li>• Cladribine<sup>34</sup></li> <li>• Pegylated interferon alpha-2a and alpha-2b<sup>e,35</sup></li> <li>• Sirolimus + prednisone<sup>36</sup></li> <li>• Methotrexate (oral)<sup>37</sup></li> <li>• Anakinra<sup>a,38,39</sup></li> </ul>	<p><b><u>Targeted therapy</u></b></p> <ul style="list-style-type: none"> <li>• Crizotinib for <i>ALK</i> fusion<sup>21</sup></li> <li>• Alectinib for <i>ALK</i> fusion<sup>40</sup></li> <li>• Brigatinib for <i>ALK</i> fusion<sup>40</sup></li> <li>• Ceritinib for <i>ALK</i> fusion<sup>40</sup></li> <li>• Lorlatinib for <i>ALK</i> fusion<sup>40</sup></li> <li>• Pexidartinib for <i>CSF1R</i> mutation<sup>21,41</sup></li> <li>• Larotrectinib for <i>NTRK</i> gene fusion<sup>22,23</sup></li> <li>• Entrectinib for <i>NTRK</i> gene fusion<sup>22,24</sup></li> <li>• Repotrectinib for <i>NTRK</i> gene fusion</li> <li>• Sirolimus or everolimus for <i>PIK3CA</i> mutation<sup>25,26</sup></li> <li>• Selpercatinib for <i>RET</i> fusion<sup>21</sup></li> </ul>

<sup>a</sup> See Management of Toxicities Associated with Targeted Therapy (ME-K) in the NCCN Guidelines for Melanoma: Cutaneous.

<sup>b</sup> Consider starting targeted agents at lower dose. See [Principles of Supportive Care \(HIST-E\)](#).

<sup>e</sup> Peginterferon alfa-2a is the only peginterferon alfa available for clinical use in the United States and it may be substituted for peginterferon alfa-2b (Schiller M, et al. J Eur Acad Dermatol Venerol 2017;31:1841-1847; Patsatsi A, et al. J Eur Acad Dermatol Venereol 2022;36:e291-e293; Osman S, et al. Dermatologic Therapy 2023;2023:7171937).

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**Note: All recommendations are category 2A unless otherwise indicated.**





### PRINCIPLES OF SYSTEMIC THERAPY<sup>b</sup>

#### Rosai-Dorfman Disease

- Regimens may be used in the first- or subsequent-line setting

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
<p><u>MAP kinase pathway mutation, or no other detectable/actionable mutation, or testing not available</u></p> <ul style="list-style-type: none"> <li>• Cobimetinib<sup>a,42,43</sup></li> </ul> <p><u>Irrespective of mutation</u></p> <ul style="list-style-type: none"> <li>• Cladribine<sup>44</sup></li> <li>• Cytarabine<sup>45</sup></li> <li>• Methotrexate (oral)<sup>46,47</sup></li> <li>• Prednisone or other corticosteroid<sup>44</sup></li> </ul>	<p><u>MAP kinase pathway mutation, or no other detectable/actionable mutation, or testing not available</u></p> <ul style="list-style-type: none"> <li>• Trametinib<sup>a,14</sup></li> </ul> <p><u>Irrespective of mutation</u></p> <ul style="list-style-type: none"> <li>• Vinblastine + prednisone<sup>48</sup></li> <li>• Methotrexate (IV or SC)<sup>49,50</sup></li> <li>• Lenalidomide<sup>51-53</sup></li> </ul>	<p><u>Targeted therapy</u></p> <ul style="list-style-type: none"> <li>• Crizotinib for <i>ALK</i> fusion<sup>21</sup></li> <li>• Pexidartinib for <i>CSF1R</i> mutation<sup>21</sup></li> <li>• Larotrectinib for <i>NTRK</i> gene fusion<sup>22,23</sup></li> <li>• Entrectinib for <i>NTRK</i> gene fusion<sup>22,24</sup></li> <li>• Repotrectinib for <i>NTRK</i> gene fusion</li> <li>• Everolimus for <i>PIK3CA</i> mutation<sup>25,26</sup></li> <li>• Selpercatinib for <i>RET</i> fusion<sup>21</sup></li> <li>• Sirolimus (for those associated with ALPS and/or <i>PIK3CA</i> mutation)<sup>25,26,54</sup></li> </ul> <p><u>Irrespective of mutation</u></p> <ul style="list-style-type: none"> <li>• Rituximab<sup>f</sup> (for IgG4-related, nodal and immune-cytopenia diseases)<sup>55</sup></li> <li>• Thalidomide (for cutaneous involvement only)<sup>56</sup></li> </ul>

<sup>a</sup> See Management of Toxicities Associated with Targeted Therapy (ME-K) in the NCCN Guidelines for Melanoma: Cutaneous.

<sup>b</sup> Consider starting targeted agents at lower dose. See [Principles of Supportive Care \(HIST-E\)](#).

<sup>f</sup> An FDA-approved biosimilar is an appropriate substitute for rituximab.

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**Note: All recommendations are category 2A unless otherwise indicated.**

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**Note: All recommendations are category 2A unless otherwise indicated.**

**PRINCIPLES OF SUPPORTIVE CARE<sup>1-4</sup>****Toxicities of BRAF and MEK Inhibitors**

- Most patients are unable to tolerate full doses of BRAF and MEK inhibitors that are approved for melanoma. For patients without CNS involvement, it may be reasonable to start at half the approved dose and modify based on toxicities.
- Routine dermatologic examination is recommended for patients on BRAF and MEK inhibitors to manage cutaneous toxicities and screen for cutaneous squamous cell carcinoma that can occur with BRAF inhibitor use.
- Cutaneous toxicities of MEK inhibitors most commonly manifest as acneiform rash. Topical benzoyl peroxide with or without oral doxycycline/minocycline may be used at the onset of rash.
- Some patients may be able to tolerate chronic low-dose administration of BRAF and MEK inhibitors, especially after attainment of best response. Dose reductions and treatment breaks are highly individualized with close monitoring for relapse.
- See Management of Toxicities Associated with Targeted Therapy (ME-K) in the NCCN Guidelines for Melanoma: Cutaneous.

**Toxicities of Other Targeted Therapies**

- Patients may not be able to tolerate the full doses of tyrosine kinase inhibitors.
- It may be reasonable to start with one or two dose reductions, and then adjust the dose based on response.

**Chronic Pain, Fatigue, Depression, Anxiety, and Poor Quality of Life**

- Patients with histiocytic disorders (especially ECD and LCH) often struggle with chronic generalized pain and fatigue that is out of proportion to the disease involvement.
- Many of these patients fit the criteria for myalgic encephalomyelitis/chronic fatigue syndrome.
- There is a high prevalence of depression and anxiety that compounds these symptoms further.
- In some instances, there is residual pain at the site of a tumor bed despite complete resection, especially in the case of bone lesions from LCH.
- Chronic pain may not respond well to available analgesic drugs.
- These symptoms can worsen the health-related quality of life of these patients significantly.
- It is important for clinicians to acknowledge these symptoms fully and refer the patients to appropriate specialties (eg, palliative medicine, psychiatry, psychology).
- In cases with severe fatigue, oral stimulants like methylphenidate can be used and appear to be safe for long-term use.
- Treatment of depression and anxiety with pharmacotherapy or psychotherapy may help with improvement of these symptoms.
- Continue follow-up with pulmonary/neurology/endocrinology specialist during surveillance.
- See NCCN Guidelines for Supportive Care:
  - ▶ [Adult Cancer Pain](#)
  - ▶ [Cancer-Related Fatigue](#)
  - ▶ [Distress Management](#)

<sup>1</sup> Goyal G, Heaney ML, Collin M, et al. Erdheim-Chester disease: consensus recommendations for evaluation, diagnosis, and treatment in the molecular era. *Blood* 2020;135:1929-1945.

<sup>2</sup> Goyal G, Tazi A, Go RS, et al. International expert consensus recommendations for the diagnosis and treatment of Langerhans cell histiocytosis in adults. *Blood* 2022;139:2601-2621.

<sup>3</sup> Diamond EL, Reiner AS, Buthorn JJ, et al. A scale for patient-reported symptom assessment for patients with Erdheim-Chester disease. *Blood Adv* 2019;3:934-938.

<sup>4</sup> O'Brein K, Dave R, Shekhar S, et al. Survivorship issues in adult patients with histiocytic neoplasms. *J Natl Compr Canc Netw* 2021;19:1312-1318.

**Note: All recommendations are category 2A unless otherwise indicated.**

**ABBREVIATIONS**

<b>ACTH</b>	<b>adrenocorticotrophic hormone</b>	<b>FDG</b>	<b>fluorodeoxyglucose</b>	<b>MDS</b>	<b>myelodysplastic syndrome</b>
<b>ALPS</b>	<b>autoimmune lymphoproliferative syndrome</b>	<b>FISH</b>	<b>fluorescence in situ hybridization</b>	<b>MPN</b>	<b>myeloproliferative neoplasms</b>
<b>ANA</b>	<b>antinuclear antibody</b>	<b>FSH</b>	<b>follicle-stimulating hormone</b>	<b>NGS</b>	<b>next-generation sequencing</b>
<b>ANCA</b>	<b>antineutrophil cytoplasmic antibodies</b>	<b>H&amp;P</b>	<b>history and physical</b>	<b>PCR</b>	<b>polymerase chain reaction</b>
<b>AXG</b>	<b>adult xanthogranuloma</b>	<b>HEENT</b>	<b>head, ears, eyes, nose, throat</b>	<b>PFT</b>	<b>pulmonary function test</b>
<b>CBC</b>	<b>complete blood count</b>	<b>HRCT</b>	<b>high-resolution computed tomography</b>	<b>RDD</b>	<b>Rosai-Dorfman disease</b>
<b>CMML</b>	<b>chronic myelomonocytic leukemia</b>	<b>IGF-1</b>	<b>insulin-like growth factor 1</b>	<b>RF</b>	<b>rheumatoid factor</b>
<b>CNS</b>	<b>central nervous system</b>	<b>IgG4</b>	<b>immunoglobulin G4</b>	<b>TSH</b>	<b>thyroid-stimulating hormone</b>
<b>DI</b>	<b>diabetes insipidus</b>	<b>JXG</b>	<b>juvenile xanthogranuloma</b>	<b>TTE</b>	<b>transthoracic echocardiogram</b>
<b>ECD</b>	<b>Erdheim-Chester disease</b>	<b>LCH</b>	<b>Langerhans cell histiocytosis</b>	<b>UVA</b>	<b>ultraviolet A</b>
<b>ERCP</b>	<b>endoscopic retrograde cholangiopancreatography</b>	<b>LFT</b>	<b>liver function test</b>	<b>UVB</b>	<b>ultraviolet B</b>
		<b>LH</b>	<b>luteinizing hormone</b>		

**NCCN Categories of Evidence and Consensus**

<b>Category 1</b>	Based upon high-level evidence ( $\geq 1$ randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus ( $\geq 85\%$ support of the Panel) that the intervention is appropriate.
<b>Category 2A</b>	Based upon lower-level evidence, there is uniform NCCN consensus ( $\geq 85\%$ support of the Panel) that the intervention is appropriate.
<b>Category 2B</b>	Based upon lower-level evidence, there is NCCN consensus ( $\geq 50\%$ , but $< 85\%$ support of the Panel) that the intervention is appropriate.
<b>Category 3</b>	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

**NCCN Categories of Preference**

<b>Preferred intervention</b>	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
<b>Other recommended intervention</b>	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
<b>Useful in certain circumstances</b>	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.





# NCCN Guidelines Version 2.2024 Histiocytic Neoplasms

## Discussion

This discussion corresponds to the NCCN Guidelines for Histiocytic Neoplasms. Last updated: September 8, 2021.

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Discussion  
update in  
progress





## Overview

Histiocytic neoplasms represent hematologic disorders characterized by the accumulation of myeloid-dendritic cell-derived neoplastic cells with an accompanying inflammatory infiltrate.<sup>1,2</sup> They are rare, accounting for less than 1% of cancers of the soft tissue and lymph nodes.<sup>2</sup> Histiocytic neoplasms are heterogeneous, and presentation varies from localized and mild to disseminated and lethal.<sup>1</sup> Initial presentation is often nonspecific, which can lead to a significant delay in the diagnosis and treatment of histiocytic disorders,<sup>3</sup> and these patients should ideally be evaluated and treated at centers of expertise.

There are over 100 subtypes of histiocytoses.<sup>1</sup> The original classification of histiocytic neoplasms by the Working Group of the Histiocyte Society, which was published in 1987, categorized these disorders as follows: Langerhans cell, non-Langerhans cell, and malignant histiocytoses.<sup>4</sup> However, the categorization of histiocytic neoplasms as Langerhans/non-Langerhans may not be appropriate, as neoplasms classified as Langerhans cell histiocytosis (LCH) were discovered to share many of the same molecular features as those classified as Erdheim-Chester disease (ECD), following emerging deep sequencing diagnostic methods.<sup>1,2</sup> For example, clonal mutations of genes in the MAPK pathway have been found in the majority of Langerhans and non-Langerhans histiocytoses.<sup>5-8</sup> In 2016, the Histiocyte Society published a revised classification based on clinical, radiographic, histologic, phenotypic, and other molecular features, further dividing them into five groups of diseases: 1) Langerhans-related; 2) cutaneous and mucocutaneous; 3) malignant histiocytoses; 4) Rosai-Dorfman disease (RDD); and 5) hemophagocytic lymphohistiocytosis and macrophage activation syndrome.<sup>1</sup>

The NCCN Guidelines for Histiocytic Neoplasms include recommendations for diagnosis and treatment of adults with LCH, ECD,

and RDD (though the WHO does not yet officially recognize RDD as a neoplasm). The evidence supporting the management of histiocytic neoplasms in adults is largely based on small retrospective studies, case series, and case reports, due to the paucity of prospective studies in adults. In addition, some of the diagnostic and treatment recommendations for adults with histiocytic neoplasms are, of necessity, extrapolated from prospective studies in children and young adults, except when stated otherwise.

## Pathologic Analysis of Histiocytic Neoplasms

Immunohistochemical (IHC) analysis plays an important role in the diagnosis and should be carried out when a histiocytic neoplasm is suspected. The basic IHC panel should include CD163/CD68, S100, CD1a, langerin/CD207, cyclin D1, and factor XIIIa as indicated.<sup>3</sup> *BRAF* V600E (VE1) IHC is recommended for LCH and ECD. Anaplastic lymphoma kinase (ALK) may also be included as clinically indicated to identify *ALK*-rearranged histiocytoses.<sup>9</sup> IHC analysis can be helpful in the broad differential diagnosis of histiocytosis, including varied entities such as composite IgG4-related disease and B-cell lymphoma, as well as infection, fat necrosis, and idiopathic retroperitoneal fibrosis.<sup>3</sup>

Next-generation sequencing (NGS) of tumor tissue for identification of mutations in the RAS/RAF/MAPK/ERK and PI3K/AKT pathway genes can be instrumental in the diagnosis of histiocytic neoplasms and can also inform systemic therapy decision-making.<sup>3</sup> Additionally, fusion testing should include *BRAF*, *ALK*, and *NTRK1* rearrangements. A complete list of fusions and rearrangements to include in the evaluation can be found in the *Summary of Pathologic and Molecular Features of Histiocytic Neoplasms* in the NCCN Guidelines for Histiocytic Neoplasms (available at [www.NCCN.org](http://www.NCCN.org)). If fusion panel testing is unavailable, then IHC or fluorescence in situ hybridization (FISH) may be used to evaluate for *ALK* rearrangements. Molecular testing can be



done either in a stepwise fashion or in parallel, depending on clinical indication and institutional protocols. If a specific histiocytic disorder is suspected, then stepwise testing should be tailored based on the mutations known to be associated with that disorder. FDG-PET/CT may be useful for determining the extent of the disease and for guiding biopsies. Details regarding recommendations for pathologic analysis related to LCH, ECD, and RDD are detailed below and in the NCCN Guidelines for Histiocytic Neoplasms (available at [www.NCCN.org](http://www.NCCN.org)).

### Langerhans Cell Histiocytosis

LCH is the most common histiocytic disorder. It is more common in children than adults, with 5 to 9 cases per 1 million in children (>15 years) and 1 case per 1 million in adults (>15 years).<sup>10,11</sup> Though many cases are mild and asymptomatic, rapidly progressing and/or disseminated life-threatening disease that is resistant to treatment may also occur. Common sites of involvement of LCH include bone, skin, pituitary gland, liver, spleen, bone marrow, lungs, and lymph nodes.<sup>12</sup> A pulmonary form of LCH can occur in adults and is associated with smoking.<sup>13-15</sup> Multifocal bone lesions without the involvement of other organs may also be observed in some cases, and bone mineral density may be lower than the expected range in adults with LCH.<sup>16</sup> Permanent endocrinopathy is common in LCH, such as diabetes insipidus (DI), which more commonly occurs with multisystem disease.<sup>14,17,18</sup> Though there are cases of solitary CNS-involved LCH, CNS involvement is most often accompanied with multi-system disease.<sup>12</sup> There is a high prevalence of concomitant and subsequent malignancies, especially solid tumors or myeloid malignancies, in adults with LCH.<sup>19,20</sup>

CNS-involved LCH can present as space-occupying granulomatous tumors, frequently in the hypothalamic-pituitary region but also involving the choroid plexus, meninges, grey or white matter, or as neurodegenerative LCH (ND-LCH) lesions in the cerebellum and brain

stem.<sup>21</sup> The bone lesions in the mastoid, sphenoid, orbit, temporal bone, and clivus represent CNS-risk lesions, indicating increased risk of developing CNS LCH.<sup>21</sup> ND-LCH is frequent in patients with pituitary, skin, and base-of-skull bone involvement. A study of children and young adults with LCH (N = 1,897) showed that a *BRAF* mutation was present in 93.7% of patients with ND-LCH, compared to 54.1% in patients without ND-LCH.<sup>22</sup> The 10-year risk of developing neurodegenerative disease is 33.1% in patients with a *BRAF* mutation, compared to 2.9% in patients without a *BRAF* mutation ( $P = .002$ ).

The Histiocyte Society's initial 1987 classification categorized LCH as an immunologic inflammatory disease but not as a neoplasm.<sup>4</sup> However, presence of clonal histiocytes supports the neoplastic origin of LCH.<sup>14,23</sup> Recurrent activating mutations in the MAPK pathway are found in the vast majority of cases.<sup>8,24</sup> These discoveries support the WHO's classification of histiocytic disorders, particularly LCH as a neoplastic process.<sup>25</sup> In the Histiocyte Society's revised classification, four categories of LCH are identified: single system, pulmonary-involved, multisystem with risk organ involvement, and multisystem without risk organ involvement.<sup>1</sup>

### Diagnosis of LCH

Diagnosis of LCH is based on clinical and radiologic findings, though biopsy of tumor tissue is also recommended (see *Histopathologic Characterization of LCH* in this Discussion).<sup>14</sup> Initial diagnostic testing is dependent on clinical presentation. A detailed review of symptoms and comprehensive physical examination of the skin; head, eyes, ears, nose, and throat (HEENT); and cardiovascular, pulmonary, musculoskeletal, lymphatic, gastrointestinal, endocrine, and neurologic systems should be performed.<sup>14</sup> Comprehensive neurocognitive and psychological assessments are also recommended in select patients.<sup>14</sup>



PET/CT is recommended for the staging of LCH. FDG-PET/CT is superior to other cross-sectional imaging techniques for detection of sites of active LCH, with the exception of pulmonary lesions.<sup>26-28</sup> Bone involvement, which may appear as aggressive cortically based lytic lesions, is best detected using full-body (vertex-to-toes) FDG-PET/CT.<sup>3</sup> It is controversial whether whole-body imaging is required for every patient with LCH, such as those presenting only with skin involvement, or those with symptoms limited to the lungs. However, whether a patient's LCH is single or multisystem is unknown in the absence of staging. Therefore, whole-body PET/CT should be considered for patients with suspected multisystem disease.

Abnormal brain MRI is often observed in LCH, even in the absence of neurologic symptoms.<sup>12</sup> Findings on brain MRI can mimic primary CNS tumors, brain metastases, or inflammatory granulomatous diseases.<sup>12</sup> In ND-LCH, signal changes in white and deep gray matter with cortical atrophy may be observed with MRI.<sup>21</sup> In cases that manifest with DI, the earliest change seen on MRI may be an enlargement of the pituitary stalk, and later the space-occupying tumors extending to the pituitary gland and hypothalamus. There is typically a “loss of bright spot” (ie, the lack of the physiologic hyperintense signal in the posterior pituitary on T1-weighted images), which is secondary to the loss of antidiuretic hormone-containing granules. Not all patients with DI will have an abnormal MRI.

Ultrasound of the abdomen and neck can discover hepatic and thyroid involvement, respectively.<sup>14</sup> However, ultrasound is probably not needed if a PET has been performed. Other imaging techniques (eg, endoscopic retrograde cholangiopancreatography; CT of chest, abdomen, and pelvis; and panorex x-ray) may be carried out as clinically indicated.

High-resolution chest CT may detect nodules 2 mm or less in the early stages of pulmonary LCH, and irregular cysts in the lungs may be observed in advanced disease.<sup>3,14</sup> Pulmonary function testing should be considered to evaluate obstructive airway disease, air trapping, and carbon monoxide diffusing capacity.<sup>13,14</sup> Echocardiogram is also recommended to screen for pulmonary hypertension.<sup>3</sup>

Laboratory tests should include complete blood count (CBC), blood chemistry, coagulation studies, thyroid-stimulating hormone (TSH), free T4, urine analysis, C-reactive protein, and morning serum cortisol with ACTH.<sup>14</sup> Prolactin and insulin-like growth factor-1 (IGF-1) level should be considered in select patients, as well as follicle-stimulating hormone/luteinizing hormone (FSH/LH) with testosterone and estradiol as clinically indicated. Bone marrow evaluation should be performed in all patients with abnormal CBC to rule out marrow involvement of LCH and a concomitant myeloid neoplasm. Biopsy of tumor tissue is recommended in all cases. *BRAF* V600E (VE1) IHC is recommended on all tissue biopsy samples, and NGS of tumor tissue for somatic variants in the MAPK pathway genes, as well gene fusion assay, is recommended in patients with *BRAF* V600E wild-type or equivocal disease. NGS of the peripheral blood is an alternative if biopsy is not feasible due to tumor location or other reasons (see *Pathologic Analysis of Histiocytic Disorders and Histopathologic Characterization of LCH* in this Discussion).

Because LCH frequently presents with lytic bone lesions, differential diagnosis may include multiple myeloma and metastatic bone involvement from other cancers. Skin involvement may be mistaken for seborrheic dermatitis, eczema, psoriasis, *Candida* infection, intertrigo, and lichen planus.<sup>14</sup> Langerhans cell hyperplasia can be associated with mycosis fungoides, which could be misinterpreted as a composite LCH.<sup>29</sup> Differential diagnosis for single-system pulmonary LCH includes





hypersensitivity pneumonitis, interstitial pneumonia, pulmonary lymphangioleiomyomatosis, and sarcoidosis.

The complete recommendations for evaluation of LCH are provided in the algorithm and are adapted from recommendations in the consensus statement by the Mayo Clinic Histiocytosis Working Group<sup>3</sup> (see *Langerhans Cell Histiocytosis: Workup/Evaluation* in the NCCN Guidelines for Histiocytic Neoplasms, available at [www.NCCN.org](http://www.NCCN.org)).

Subspecialty consultations (eg, pulmonary and smoking cessation, neurology, endocrinology) should be carried out as clinically indicated. Dermatology consultation is recommended for patients treated with certain targeted therapies (ie, BRAF and MEK inhibitors) for diagnosis and treatment of skin-related toxicities.<sup>30</sup> Retinal evaluation may be considered due to the high incidence of serous retinopathy with MEK inhibitors.<sup>31,32</sup>

### **Histopathologic Characterization of LCH**

LCH tumors often demonstrate neoplastic histiocytes admixed with marked inflammatory cell infiltration. On H&E stain, neoplastic LCH cells are mononucleated, typically with a coffee bean-shaped nucleus.<sup>1,24,33</sup> Abundant eosinophils and multinucleated giant cells are frequently observed.<sup>1-3</sup> Fibrosis may be present, particularly in bone lesions.<sup>3</sup> IHC analysis of the LCH tumors shows abundant CD1a- and CD207- (langerin) positive neoplastic histiocytes and can also be positive for S100.<sup>3,24,33</sup> Pathology of lesions from LCH-associated abnormal CNS imaging (LACI) and LCH-associated abnormal CNS symptoms (LACS) show infiltrating CD8+ lymphocytes, and, unlike other LCH tumors, lack CD1a-positive histiocytes.<sup>34</sup> Cyclin D1 can be helpful for differentiating neoplastic Langerhans cells from reactive Langerhans cell proliferation.<sup>35,36</sup> Birbeck granules can be identified by electron microscope, which is, however, now not commonly performed.

Activation of RAS-RAF-MAPK pathway is universal in all patients with LCH.<sup>5,37</sup> *BRAF* V600E activating mutation is present in 38% to 64% of LCH cases,<sup>5,6,38-42</sup> and this mutation is more frequent in mixed LCH/ECD, when compared to isolated LCH or ECD.<sup>43</sup> Mutations in *MAP2K1* are also prevalent in LCH (~20%).<sup>8,38,42,44</sup> *BRAF* V600E and *MAP2K1* mutations are mutually exclusive in LCH.<sup>44</sup> *KRAS*, *NRAS*, *ARAF*, and *CSF1R* mutations are less frequently observed in LCH.<sup>45,46</sup>

*BRAF* V600E (VE1) should be evaluated using IHC. However, studies evaluating IHC versus PCR testing of *BRAF* V600E mutations in pediatric patients with LCH (using stringent scoring criteria<sup>47</sup>) showed sensitivity values ranging from 35.6% to 80%; specificity values ranged from 75.5% to 100%.<sup>48,49</sup> *BRAF* V600E allele-specific PCR is recommended if IHC is unavailable or when *BRAF* V600E (VE1) IHC results are equivocal or negative. A comprehensive NGS panel including other genes in the MAPK pathway (ie, *ARAF*, *NRAS*, *KRAS*, *MAP21K*, *PIK3CA*) should be performed in patients with *BRAF* wild-type disease.

For complete recommendations regarding pathologic analysis of LCH cases, see the *Principles of Pathology* in the NCCN Guidelines for Histiocytic Neoplasms (available at [www.NCCN.org](http://www.NCCN.org)).

### **Treatment of LCH**

Much of the evidence for treatment of LCH is extrapolated from prospective studies of children and adolescents. Studies of adults with LCH are limited to case series and retrospective studies. Treatment decisions of LCH should be made based on sites and extent of disease.<sup>14</sup>



### ***Unifocal and Single System Disease with No Critical Organ Involvement***

For patients with single system disease and no involvement of critical organs (ie, CNS, liver spleen, heart), treatment is limited to local therapy and observation (watch and wait).<sup>14</sup>

Limited curettage is recommended for patients with isolated bone lesions,<sup>50</sup> but complete resection of bone lesions is not recommended, as this may result in an increase in the size of the bony defect and permanent skeletal defects.<sup>14</sup> Steroid injection may facilitate healing after limited curettage.<sup>14</sup> Radiation therapy for treatment of bone-involved LCH is associated with excellent local disease control.<sup>51,52</sup> For patients with single system bone disease, radiation therapy may be used for some patients with limited sites of disease, specifically in cases with impending neurologic dysfunction and if surgical risk is high.<sup>14</sup> “Limited” sites of disease is generally defined as 1 to 2 lesions in this context, though radiation therapy may be considered for up to three bone lesions as clinically indicated. The recommended radiation dose for treatment of bone-involved LCH in adults is 10 to 20 Gy.<sup>14,51</sup> Watch and wait is also reasonable for asymptomatic and isolated bone lesions.

For patients with single system isolated skin disease, topical therapies may be used.<sup>50</sup> Case reports describing treatment of older adults with cutaneous LCH support the use of psoralen with ultraviolet A and narrow band ultraviolet B.<sup>53,54</sup> Other topical therapies such as nitrogen mustard (eg, mechlorethamine) and steroids are alternative options that have been shown to be effective in children with cutaneous LCH,<sup>55,56</sup> though there are no published data in adults with LCH. Surgery should only be done for solitary skin lesions, and only for those in which surgery will not result in disfigurement. Systemic therapy may be used for symptomatic disease including pain, secondary infection, or if there are complications from skin lesions.<sup>50</sup> Isolated skin-involved LCH has

been reported to resolve spontaneously,<sup>57</sup> so watch and wait is also an option for these patients.

### ***Multifocal or Multisystem Disease or Unifocal Disease with Critical Organ Involvement***

Systemic therapy is often required for the treatment of multisystem LCH, multifocal single system, or unifocal but involving a critical organ such as CNS, liver, spleen, or heart (see *Systemic Therapy*, described below). However, if asymptomatic or if there is no impending organ dysfunction, watch and wait may be considered. Imaging changes precede clinical progression in ND-LCH, warranting consideration of early treatment.

Since pulmonary LCH is associated with smoking, treatment should include smoking cessation (see the NCCN Guidelines for Smoking Cessation, available at [www.NCCN.org](http://www.NCCN.org)). Pulmonary LCH could resolve with smoking cessation alone.<sup>50</sup> Therefore, watch and wait is an option, particularly in patients with asymptomatic disease or who have minor symptoms. Systemic therapy can be considered in patients with symptomatic and/or progressive pulmonary LCH, as well as in patients with persistent disease despite smoking cessation (see *Systemic Therapy*, described below). High-dose prednisone (1 mg/kg/day for 1 month, followed by a slow taper) can also be effective in treatment of pulmonary LCH.<sup>14</sup> Steroid treatment is often associated with radiographic improvements in pulmonary LCH but may not improve the respiratory function.<sup>58</sup> Lung transplant should be considered only in select patients with highly refractory and severe disease.<sup>50</sup>

Bisphosphonates (eg, zoledronic acid or pamidronate) for treatment of multifocal bone disease is supported by small retrospective studies and case series.<sup>59,60</sup> In the absence of disease response following treatment with a bisphosphonate, other systemic therapy regimens may be considered (see *Systemic Therapy*, described below). Radiation therapy



can also be considered in patients with persistent disease with limited disease sites following systemic treatment.<sup>14</sup> Systemic treatment with indomethacin was reported as a successful alternative therapeutic approach for some patients with primary and recurrent bone LCH.<sup>61</sup>

### Systemic Therapy

Systemic therapy is the standard treatment for multisystem and/or multifocal LCH, but responses to commonly used regimens in adults with LCH tend to be less robust compared to children.<sup>14</sup> Evidence supporting use of chemotherapy in adults with LCH is based on small nonrandomized studies. Vinblastine and prednisone is the preferred chemotherapy-based treatment for LCH in the pediatric setting.<sup>24</sup> In a retrospective study conducted at a single center including 58 adults with bone-involved LCH, use of vinblastine and prednisone was associated with worse outcomes. In this study, 84% of patients who received vinblastine and prednisone developed progressive disease within the first year, compared to 21% of patients who received cytarabine (OR, 20.3; 95% CI, 4.20–98.20;  $P < .001$ ).<sup>62</sup> For patients who received cladribine, 59% did not respond to treatment or relapsed in the first year. Cytarabine was the least toxic of the three regimens, with grade 3 to 4 adverse events being reported in 20% of patients who received cytarabine, compared to 37% and 75% who received cladribine and vinblastine/prednisone, respectively. Low-dose cytarabine is better tolerated in adults, but higher doses should be used for patients with CNS lesions.

Cladribine is another chemotherapy option that has been shown to be active in adults with LCH (overall response rate [ORR], 75%), based on results from a small phase II trial.<sup>63</sup> A more recent retrospective study conducted at an NCCN Member Institution also showed a high ORR (79%) in adults with multifocal LCH (N = 38; 82% multisystem) who were treated with cladribine, with complete response (CR) and partial

response (PR) observed in 26% and 53% of patients, respectively.<sup>64</sup> Five-year overall survival (OS), progression-free survival (PFS), and duration of response (DOR) for the sample was 75%, 58%, and 70%, respectively. There is also evidence supporting clofarabine for relapsed/refractory LCH in the pediatric setting, with disease improvement observed in 73% of 11 patients.<sup>65</sup> Neutropenia occurred in all patients.

A prospective single-center phase II trial from China examined combination of cytarabine (100 mg/m<sup>2</sup>) and methotrexate (1 g/m<sup>2</sup>) as treatment for adults with multisystem or single system multifocal LCH (N = 83). ORR, 3-year OS, and 3-year event-free survival (EFS) were 87.9%, 97.7%, and 68.0%, respectively.<sup>66</sup> A retrospective study conducted at a hospital in China examined cytarabine and methotrexate combination in adults with multisystem pulmonary-involved LCH (N = 29). Pulmonary function was stable in 72.4% (n = 24), improved in 13.8% (n = 4), and deteriorated in 13.8% (n = 4) of patients.<sup>67</sup> Since both cytarabine and methotrexate cross the blood-brain barrier, this combination regimen may be ideal for treatment of CNS-involved LCH.<sup>66</sup> High-dose methotrexate is also an option for CNS-involved LCH, based on a case report of a patient with CNS-involved ECD.<sup>68</sup> In addition, cytarabine in combination with intravenous immunoglobulin (IVIG) or vincristine demonstrated therapeutic potential in children and young adults with CNS-LCH and ND-LCH.<sup>69,70</sup>

Multifocal skin disease may respond to systemic therapy treatment for multisystem LCH in general.<sup>14</sup> However, small retrospective studies and case reports also support use of specific chemotherapy options for multifocal skin-involved LCH. A single-center retrospective study evaluated hydroxyurea monotherapy and in combination with oral methotrexate in 15 patients with relapsed/refractory LCH (mostly skin-involved) with a median age of 41.2 years (range 2–73 years).<sup>71</sup> An





ORR of 80.0% was observed, and symptom progression or relapse after initial response was observed in 40%, with median time to progression of 5.7 months. Grade 3 to 4 adverse events were reported in only two patients. Retrospective data also support use of oral methotrexate combined with prednisone in children with low-risk LCH (ie, no bone marrow involvement or organ dysfunction) that was mostly bone- and/or skin-involved.<sup>72</sup>

Immunomodulating agents may also be used to treat multifocal skin disease. Thalidomide was evaluated in a phase II study including 12 children and four adults with LCH.<sup>73</sup> Among 10 patients with low-risk disease (involvement of skin, lungs, and lymph nodes), an ORR of 70% was observed (4 CRs, 3 PRs). All of the patients but one who had low-risk disease had skin involvement. Administration of this drug was associated with significant toxicity and should be avoided in patients with critical organ involvement, for whom this drug was not effective. A case report also describes a CR from lenalidomide in an adult with relapsed/refractory multisystem LCH (involvement of skin, lungs, and lymph nodes).<sup>74</sup>

### Targeted Therapies

Prior to 2012, there were relatively few effective treatment options for histiocytic neoplasms. The discovery of *BRAF* V600E and other gene mutations resulting in overactive MAPK pathway in histiocytic neoplasms led to a promising avenue of targeted therapies for patients with these rare cancers. The phase II VE-BASKET study evaluated the efficacy of BRAF inhibitor vemurafenib.<sup>75</sup> The final efficacy and safety analysis included 26 adults with *BRAF* V600E-mutated LCH or ECD (85% ECD) and showed an ORR of 61.5% (95% CI, 40.6%–79.8%).<sup>76</sup> Two-year PFS and OS rates were 86% (95% CI, 72%–100%) and 96% (95% CI, 87%–100%), respectively. Median PFS and OS were not reached. A metabolic response as measured with FDG-PET/CT was

achieved in all of the patients who were evaluated (n = 15; 80% CR, 20% PR). The most common grade 3 to 4 adverse events were hypertension (27%), maculopapular rash (23%), increased lipase (15%), arthralgia (12%), hyperkeratosis (8%), and actinic keratosis (8%). All patients required dose reduction due to toxicities. Encouraging results from a case series also support the use of dabrafenib, a second-generation BRAF inhibitor, in adults with LCH. Dabrafenib may be better tolerated than vemurafenib based on this case series, although there was no prospective head-to-head comparison.<sup>77</sup> Use of dabrafenib in patients with ND-LCH led to rapid symptomatic and radiographic improvement.

There is also evidence supporting the use of MEK inhibitors for treatment of histiocytic neoplasms. The MEK inhibitor cobimetinib was evaluated in a phase II trial including 18 adult patients diagnosed with a histiocytic neoplasm (67% ECD, 11% LCH, 11% RDD, and 11% mixed histiocytosis).<sup>31</sup> The ORR was 89% (one-sided 90% CI, 73%–100%), with a CR having been observed in 72% of patients. Median DOR and PFS were not reached after a median follow-up of 11.9 months. The most common adverse events that led to a dose reduction were ejection fraction decrease (27.8%), rash (11.1%), and diarrhea (11.1%). Though a mutation in the MAPK pathway was detected in 83% of patients, the efficacy of cobimetinib was not limited to these patients, indicating that cobimetinib can be used in any patient with a histiocytic disorder for whom systemic therapy is indicated.

Use of the MEK inhibitor trametinib for treatment of LCH is supported by case series and case reports.<sup>78-80</sup> In one case report, a combination of dabrafenib and trametinib demonstrated a sustained response in an adult woman with *BRAF* V600E-mutated LCH.<sup>81</sup>

Adverse events in patients with histiocytic disorders treated with BRAF and MEK inhibitors are consistent with those observed in previously





published studies (eg, rash, pyrexia),<sup>24</sup> but the VE-BASKET trial showed that rates of hypertension and skin-related adverse events were higher in histiocytic neoplasms than previously observed in patients with metastatic melanoma.<sup>76</sup>

Activating mutations in *CSF-1R* and rearrangements involving *RET* and *ALK* in rare cases of LCH highlight the potential clinical benefit of other kinase inhibitors and should be considered in select cases with such alterations.<sup>46</sup> Since *NTRK* fusions can occur in histiocytic disorders,<sup>82</sup> the TRK inhibitors larotrectinib<sup>83</sup> and entrectinib<sup>84</sup> may also be used as indicated. Sirolimus and everolimus can be effective for *PIK3CA*-mutated LCH, based on extrapolation of data from ECD patients (see *Treatment of ECD* in this Discussion, below).<sup>7,85</sup>

### Follow-up

Imaging (PET/CT [preferred], CT, or MRI) of involved sites to evaluate treatment response should be done after 2 to 3 cycles of systemic therapy and after completion of treatment. LCH may relapse or reactivate following systemic therapy, which most commonly occurs in the first 2 years following treatment.<sup>50</sup> Development of diabetes insipidus after treatment may be a sign of disease reactivation.<sup>50</sup> Follow-up assessment depends on extent of disease and organ involvement, and a complete list of recommendations for surveillance following treatment of LCH can be found in the algorithm (see *Langerhans Cell Histiocytosis: Follow-up* in the NCCN Guidelines for Histiocytic Neoplasms, available at [www.NCCN.org](http://www.NCCN.org)).

### Relapsed/Refractory Disease

In relapsed and refractory LCH, an alternate systemic therapy regimen other than the one used in the first line may be considered. However, if DOR to the first-line regimen was greater than 1 year, repeating the same treatment may also be considered.<sup>14</sup>

### Erdheim-Chester Disease

ECD is a rare histiocytic neoplasm, with approximately 800 cases having been reported as of May 2020.<sup>45</sup> An increase in detection of cases has been observed more recently, potentially due to improved recognition of this disease through imaging and pathology.<sup>12,45,86</sup> ECD predominantly affects adults, with a median age of approximately 45 years in the United States, and is more common in men than women.<sup>12,45,86</sup> ECD is rarely observed in children. Mixed ECD/LCH is fairly common, with LCH lesions reported in 20% of patients with ECD.<sup>43</sup>

Similar to LCH, ECD presentation can range from single system and asymptomatic disease to severe multisystem and life-threatening disease. Prognosis is predominantly influenced by specific organ involvement.<sup>86</sup> Bone involvement affects almost all patients with ECD, with lower extremity bone pain being an especially common initial presenting symptom. Cardiovascular involvement, including pericardial disease, is reported to occur in about half of all patients<sup>87-89</sup> and is associated with poor prognosis.<sup>90</sup> Other affected organs/systems include the lungs, endocrine system, skin, and kidneys.<sup>12,91</sup> Periarterial fibrosis of the thoracic and/or abdominal aorta, referred to as “coated aorta,” is also commonly observed.<sup>86,88,90,92-95</sup> Retroperitoneal involvement tends to be asymptomatic, but extension to the renal sinus or middle to distal ureters may result in hydronephrosis.<sup>96-98</sup> CNS involvement occurs in 15% to 55% of cases<sup>12,86,99</sup> and is associated with worse prognosis.<sup>100</sup> Some ECD-related CNS lesions cause intracranial vascular infiltration, putting these patients at risk of ischemic stroke. Diabetes insipidus is the most common endocrine disorder in ECD, affecting about 25% to 50% of patients.<sup>3,86,101</sup> Other commonly observed endocrine manifestations of ECD include hyperprolactinemia, hypogonadism, adrenal insufficiency, and hypothyroidism.<sup>3,101</sup> Exophthalmos is also fairly common in ECD, and xanthelasma of the eyelids and periorbital spaces is a common cutaneous manifestation of



ECD.<sup>1,86</sup> Involvement of the facial bones and maxillary sinuses has also been observed.<sup>92</sup>

Two retrospective studies demonstrated that a concomitant myeloid neoplasm can occur in 3% to 10% of ECD;<sup>102,103</sup> the higher rate (10%) in one study is likely due to inclusion of patients with mixed LCH/ECD.<sup>102</sup> In one case series, median age of patients with ECD and a concomitant myeloid neoplasm was 65.4 years and tended to affect more men than women (male:female ratio = 2:1).<sup>104</sup>

### Diagnosis of ECD

The diagnosis of ECD is largely made based on characteristic clinical and radiographic abnormalities. Evaluation of tumor tissue for molecular alterations should be performed, where available, as this would aid both in the diagnosis of ECD and treatment decision-making.<sup>45</sup>

Comprehensive physical examination of the skin; HEENT; and cardiovascular, pulmonary, musculoskeletal, lymphatic, gastrointestinal, endocrine, neurologic systems should be performed. Neurocognitive and psychological assessments are also recommended in select patients. FDG-PET scan or bone scan should be used to evaluate bone involvement. Full-body (vertex-to-toes) FDG-PET is preferred to bone scan, as it allows for evaluation of metadiaphyseal osteosclerosis of the knees as well as other organ involvement.<sup>3,45</sup> Bilateral, symmetric diaphyseal, and metaphyseal osteosclerosis of the long bones of lower extremities is a characteristic finding of ECD.<sup>2,12,45</sup> CNS involvement may be detected using brain MRI with gadolinium contrast, and common findings include cerebellar and brain stem hyperintensities, cerebral white matter enhancement, and thickening of the pituitary stalk.<sup>3,12</sup> “Coated aorta” may be detected with CT, and arterial lesions characterized by circumferential thickening may be observed.<sup>3,12,86,97</sup> “Hairy kidney” detected on abdominal CT is characteristic of ECD (rarely seen in RDD and not seen in LCH) due to diffuse bilateral

infiltration leading to stellate pattern of perinephric soft tissue thickening.<sup>3,97</sup> Adrenal hypertrophy may be observed if the perirenal infiltration extends to the adrenal gland.<sup>97</sup> In ECD with pulmonary involvement, chest CT may demonstrate mediastinal infiltration, pleural thickening, pleural effusion, and other pulmonary parenchymal abnormalities.<sup>3</sup> Cardiac involvement should be evaluated with echocardiography and/or cardiac MRI. Findings and radiographic abnormalities include pericardial thickening, pericardial effusion, and myocardial infiltration, which, if present, most often involve the right atrioventricular groove and right atrial wall.<sup>3</sup>

Similar to LCH, laboratory evaluation for ECD should include CBC, blood chemistry, coagulation studies, TSH, free T4, morning urine and serum osmolality, morning serum cortisol with ACTH, prolactin, IGF-1, FSH/LH with testosterone, and estradiol. C-reactive protein should be evaluated, as it is often elevated in patients with ECD.<sup>12</sup> *BRAF* V600E (VE1) IHC is recommended on the tissue biopsy, and NGS of tumor tissue for mutations in the MAPK pathway in cases that are *BRAF* V600E wild-type or equivocal, as well as gene fusion assay, is also recommended (see *Pathologic Analysis of Histiocytic Disorders* and *Histopathologic Characterization of ECD* in this Discussion). A biopsy of tumor tissue is recommended, but analysis of the peripheral blood for NGS may be done if biopsy is not feasible, and bone marrow evaluation should be performed in patients with abnormal CBC. Differential diagnosis should include evaluation for IgG4-related disease, which has a clinical presentation similar to that for ECD.<sup>12</sup>

The complete recommendations for evaluation of ECD are provided in the algorithm and are adapted from recommendations from an expert consensus group<sup>45</sup> (see *Erdheim-Chester Disease: Workup/Evaluation* in the NCCN Guidelines for Histiocytic Neoplasms, available at [www.NCCN.org](http://www.NCCN.org)). Subspecialty consultations (eg, neurology,



endocrinology, nephrology, urology) should be carried out as clinically indicated. As with LCH, dermatology and ophthalmology evaluations may be considered for management of toxicities associated with BRAF and MEK inhibitors.<sup>30-32</sup>

### **Histopathologic Characterization of ECD**

On hematoxylin and eosin (H&E) stain, ECD tumor tissue often demonstrates foamy mononucleated histiocytes with a small nucleus, surrounding fibrosis, xanthogranulomatosis, and Touton giant cells.<sup>2,3,12</sup>

On IHC, neoplastic histiocytes are typically CD68-positive, CD163-positive, CD14-positive, factor XIIIa-positive, CD1a-negative, and CD207 (langerin)-negative.<sup>2,12,86</sup> Typical features of stroma and histiocytic and reactive infiltrate have been found to vary depending on disease location (ie, bone, central nervous system [CNS], lung, skin, orbit, retroperitoneum, cardiac tissue).<sup>105</sup> CD1a-positive, S100-positive, and langerin-positive findings can help distinguish LCH from ECD.<sup>1,86</sup> The possible presence of S100-positive cells with emperipolesis may lead to challenges in distinguishing ECD from RDD.<sup>1</sup>

Somatic mutations contributing to ECD partially overlap with that of LCH.<sup>2</sup> *BRAF V600E* activating mutations are present in 38% to 68% of ECD cases.<sup>6,7,86,92,105,106</sup> Other prevalent gene mutations in ECD include *MAP2K1*, *ARAF*, *NRAS*, *KRAS*, and *PIK3CA*.<sup>7,8,105,106</sup> *CSF1R* mutations and *BRAF*, *ALK*, and *NTRK1* fusions are found in a small number of ECD cases.<sup>8,46,106</sup> ECD co-occurring with RDD is most commonly driven by mutations in *MAP2K1*.<sup>105,107</sup> Extracutaneous or disseminated juvenile xanthogranuloma with mutations in the *MAPK* pathway has similar histopathology and phenotype to ECD and thus may be considered ECD.<sup>1</sup> *BRAF V600E* (VE1) should be evaluated using IHC, but allele-specific PCR for *BRAF V600E* may be considered; see *Histopathologic Characterization of LCH* above. As with LCH, panel testing should include other mutations in the *MAPK* pathway.

For complete recommendations regarding pathologic analysis of ECD cases, see the *Principles of Pathology* in the NCCN Guidelines for Histiocytic Neoplasms (available at [www.NCCN.org](http://www.NCCN.org)).

### **Treatment of ECD**

Treatment of ECD mainly consists of systemic therapy, though watch and wait may be considered for patients with asymptomatic disease not involving critical organs such as the heart, brain, and CNS.

As discussed in the LCH section (see *Systemic Therapy: Targeted Therapies*), the phase II VE-BASKET study showed that vemurafenib is highly effective in patients with *BRAF V600E*-mutated ECD that is associated with near universal responses.<sup>76</sup> Results from the VE-BASKET study led to the FDA approval of vemurafenib for treatment of ECD. However, the FDA-approved dose (960 mg twice daily) is associated with significant toxicity that very often results in discontinuation, dose interruption, or dose modification.<sup>76</sup> A retrospective study carried out at an NCCN Member Institution including 23 patients with *BRAF V600E*-mutated ECD showed that progressive disease did not occur in patients (n = 14) who received vemurafenib administered at half the FDA-approved dose (ie, 480 mg twice daily), though half of these patients still required further dose reduction, with 29% discontinuing vemurafenib treatment due to adverse events.<sup>108</sup>

The efficacy of dabrafenib for *BRAF V600E*-mutated ECD is supported by a retrospective single-center French study<sup>109</sup> and a multicenter case series.<sup>110</sup> As with LCH, dabrafenib appears to be less toxic than vemurafenib.<sup>110</sup> As described above for LCH (see *Systemic Therapy: Targeted Therapies*), in a phase II trial in which 67% of patients were diagnosed with ECD, a 72% CR rate was demonstrated for cobimetinib.<sup>31</sup> These promising results were not limited to patients with a mutation in the *MAPK* pathway. A small study supports use of the





MEK inhibitor trametinib for treatment of non-LCH histiocytic neoplasms, regardless of molecular profile.<sup>111</sup>

Prior to the availability of targeted therapy for ECD, the largest body of evidence supported the use of interferon alpha-2a and pegylated interferon alpha for the treatment of ECD.<sup>86</sup> In a multicenter, prospective, nonrandomized study conducted in Europe (N = 53), interferon alpha or pegylated interferon alpha treatment was associated with improved survival (HR, 0.32; 95% CI, 0.14–0.70; *P* = .006).<sup>100</sup> A single-center report from France (N = 8) showed that interferon alpha was most effective for relieving exophthalmos, bilateral hydronephrosis, and xanthelasma related to ECD, and was associated with a decrease in C-reactive protein.<sup>112</sup> This report cautioned against the use of interferon alpha in patients with ECD involving the CNS and/or cardiovascular system. However, a more recent single-center study from France reported outcomes of a larger cohort (N = 24) that high-dose interferon alpha was associated with a clinical and/or radiologic improvement in 46% of patients, including those with severe ECD with CNS or cardiovascular involvement.<sup>113</sup> Interferon alpha as a treatment option for ECD is also supported by several case reports.<sup>114,115</sup> Interferon alpha has been discontinued in the United States and is therefore not recommended in the NCCN Guidelines. Pegylated interferon alpha, which has a favorable toxicity profile compared to interferon alpha, is recommended as a substitute based on evidence discussed above.

Evidence supporting other systemic therapy options for treatment of ECD is primarily based on retrospective single-center studies and case series. A retrospective study conducted at an NCCN Member Institution evaluated the efficacy of cladribine as first- or subsequent-line treatment of ECD (n = 21).<sup>116</sup> The clinical ORR was 52%, with CR and PR observed in 4% and 46% of patients, respectively. Progressive disease

was observed in 30% of patients. The response was durable, with the median DOR of 9 months in the responders. Toxicities associated with cladribine were relatively minimal. In a single-center study from Italy including 10 patients with ECD, sirolimus combined with prednisone was associated with an ORR of 60% (all PRs).<sup>117</sup> Oral methotrexate as first- or subsequent-line treatment of ECD was evaluated in a retrospective study conducted at an NCCN Member Institution (N = 13).<sup>118</sup> Oral methotrexate was administered either alone or in combination with prednisone or infliximab and was associated with a clinical ORR of 23% (all PRs). Progressive disease occurred in 70%. Despite the low ORR, methotrexate-based treatment was well-tolerated, and response was durable in some of those who responded to the treatment, especially those with ocular ECD. Finally, two small single-center studies showed good efficacy with the IL-1 receptor antagonist anakinra as a treatment option for ECD.<sup>119,120</sup>

As with LCH, a targeted therapy can be selected based on the respective molecular alteration. Crizotinib and selpercatinib for ECD with rearrangements in *ALK* and *RET*, respectively, as well as pexidartinib for ECD with activating mutations in *CSF-1R*, and larotrectinib and entrectinib for ECD with *NTRK* fusions, are all reasonable systemic therapy options when clinically indicated.<sup>46,82-84</sup> Since mutations in *PIK3CA* are fairly common in ECD,<sup>7</sup> mTOR inhibitors such as sirolimus and everolimus should also be considered when clinically indicated.<sup>85</sup>

### Follow-up

As with LCH, follow-up assessment for patients with ECD depends on extent of disease and organ involvement. FDG-PET/CT should be used to monitor disease response once treatment is initiated. Organ-specific cross-sectional imaging (CT or MRI) may also be utilized as needed. Regular skin examination and ECG is recommended for patients treated



with *BRAF* inhibitors, as well as ongoing evaluation for pituitary hormone abnormalities.

### Rosai-Dorfman Disease

RDD is another rare histiocytic disorder that mainly affects children but is also diagnosed in adults. In RDD, accumulation of abnormal histiocytes in lymph node sinuses, lymphatic vessels of internal organs, and other extranodal sites is observed. This disease is more common in men than in women and often affects individuals of African ancestry.<sup>12,121</sup> Cause is unknown but may be associated with familial, autoimmune, and/or malignant processes. It is a heterogeneous condition with a presentation that may be classified as single or regional lymph node-involved or localized to the skin and other organs. Prognosis is generally very good but becomes worse as the number of involved nodal groups increases.<sup>121</sup> Recurrent disease is reported to occur in about one in three patients with RDD.<sup>122</sup>

Extranodal involvement occurs often in RDD, with common sites of involvement including the skin, soft tissue, upper respiratory tract, multifocal bone (mostly osteolytic lesions), retroperitoneum, and eye/retro-orbital tissue with lymphadenopathy.<sup>3,121,122</sup> Bilateral massive cervical lymphadenopathy also commonly occurs and is often painless, though involvement of the mediastinal, inguinal, and axillary lymph nodes may also occur.<sup>121</sup> Skin involved-RDD often presents as subcutaneous masses and, less often, as cutaneous lesions.<sup>122</sup> Involvement of the nasal cavity, paranasal sinuses, and parotid gland have also been reported.<sup>12,121,123</sup> CNS involvement may also occur but is generally rare.<sup>121,122,124,125</sup> CNS-involved RDD may mimic meningioma.<sup>121</sup>

RDD may co-occur with Hodgkin and non-Hodgkin lymphoma, other histiocytic disorders, cutaneous clear-cell sarcoma, and following

myelodysplastic syndrome and allogeneic stem transplant for precursor B-cell acute lymphoblastic leukemia.<sup>12,121,122</sup> Germline mutations in *SLC29A3*, which is associated with Faisalabad histiocytosis, H syndrome, and pigmented hypertrichotic dermatosis with insulin-dependent diabetes, have been found in cases of familial RDD.<sup>121</sup> About 20% of patients with H syndrome also have RDD.<sup>126</sup> Germline mutation in the *FAS* gene *TNFRSF*, which is associated with autoimmune lymphoproliferative syndrome (ALPS) type I, has also been found in RDD cases.<sup>121</sup> Immunologic diseases associated with RDD include systemic lupus erythematosus, idiopathic juvenile arthritis, and autoimmune hemolytic anemia.<sup>121</sup>

### Diagnosis of RDD

Diagnosis of RDD should include a clinical and radiologic examination, as well as histopathologic analysis. Comprehensive physical examination should include evaluation of the HEENT, endocrine system, and intrathoracic/pulmonary, cardiovascular, gastrointestinal, musculoskeletal genital, renal, and cutaneous symptoms. Neurologic and psychological assessment are also recommended. History of inherited conditions predisposing to RDD (eg, ALPS), malignancies and other neoplasia associated with RDD (eg, Hodgkin and non-Hodgkin lymphoma, other histiocytic disorders), and other autoimmune disorders (eg, systemic lupus erythematosus, idiopathic juvenile arthritis) should be evaluated based on clinical symptoms and family history.

Full-body FDG-PET/CT is recommended as part of the baseline evaluation of RDD. A single-center retrospective study including 109 FDG-PET/CT scans in 27 patients with RDD showed that PET/CT detected lesions not recognized by anatomic cross-sectional imaging in 30% of patients with available prior CT or MRI (n = 20).<sup>127</sup> Results of PET/CT scans also led to changes in treatment in 41% of patients. Cross-sectional imaging can reveal dermatologic involvement in the



form of lobular soft tissue lesions in the subcutaneous space.<sup>3</sup> Pulmonary involvement in RDD tends to manifest as mediastinal lymphadenopathy, airway disease, pleural effusion, and cystic and interstitial lung disease.<sup>128</sup> Extranodal retroperitoneal involvement, if present, would appear in radiologic findings as wispy infiltration and/or renal hilar masses.<sup>3</sup> MRI of the head tends to be superior for evaluation of the sinuses and orbits, compared to PET/CT.<sup>3</sup> MRI of the brain and spine is useful for identification of asymptomatic neurologic involvement.<sup>121</sup>

Laboratory evaluation should include CBC, comprehensive metabolic panel, coagulation studies, and an evaluation of C-reactive protein, uric acid, LDH, and serum immunoglobulins.<sup>121</sup> If autoimmune disease is suspected based on clinical examination, then laboratory evaluation should include antinuclear antigen, antineutrophil cytoplasmic antibodies, rheumatoid factor, and HLA-B27. The ALPS panel is clinically indicated in patients with autoimmunity and lymphadenopathy. Laboratory evaluation in patients with anemia should include a Coombs test, haptoglobin, reticulocyte count, and blood smear. Lumbar puncture should be carried out if there are brain lesions that cannot be biopsied due to location. Bone marrow aspirate and biopsy are recommended for patients with unexplained cytopenias or abnormal CBC.<sup>121</sup> As with LCH and ECD, biopsy of tumor tissue is recommended for diagnosis and NGS testing. If biopsy is not feasible, then peripheral blood analysis is reasonable. NGS of tumor tissue should include mutations in the MAPK pathway, as well as gene fusion assay (see *Pathologic Analysis of Histiocytic Disorders* and *Histopathologic Characterization of RDD* in this Discussion).

The complete recommendations for evaluation of RDD are provided in the algorithm and are adapted from recommendations from an expert consensus group<sup>121</sup> (see *Rosai-Dorfman Disease: Workup/Evaluation* in

the NCCN Guidelines for Histiocytic Neoplasms, available at [www.NCCN.org](http://www.NCCN.org)). Like LCH and ECD, dermatology and ophthalmology evaluations may be considered due to toxicities associated with BRAF and MEK inhibitors.<sup>30-32</sup>

### **Histopathologic Characterization of RDD**

Compared to LCH and ECD, histopathologic analysis of RDD can be challenging, as RDD tissue tends to contain relatively few lesional cells.<sup>122</sup> Large histiocytic cells with hypochromatic nuclei and an abundant amount of pale cytoplasm are required for diagnosis of RDD.<sup>1</sup> Emperipolesis, specifically intracytoplasmic leukocytes, is a frequently observed feature of RDD.<sup>1-3,12,121,122</sup> However, emperipolesis may be observed less often in extranodal lesion tissue.<sup>121</sup> Abundant plasma cells in the medullary cords and around the venules is a hallmark of nodal RDD.<sup>121</sup> Other pathologic hallmarks include the accumulation of CD68-positive, CD163-positive, CD14-positive, and S100-positive histiocytic cells.<sup>1-3,121,122</sup> RDD histiocytes tend to be CD1a- and CD207-negative, which helps to distinguish from LCH.<sup>121</sup> Cyclin D1 expression by the abnormal histiocytes, and increased IgG4-positive plasma cells in the background inflammatory infiltrate, may also be found.<sup>129,130</sup>

Unlike LCH and ECD, *BRAF V600E* activating mutations are not commonly observed in patients with RDD.<sup>3,12,121</sup> *KRAS*, *MAP21K*, *ARAF*, and *NRAS* mutations have been found in patients with RDD.<sup>8,121,131</sup> Though the WHO does not classify RDD as a neoplasm, the presence of mutations in the MAPK/ERK pathway in about 1 in 3 patients and supports the categorization of RDD as a neoplasm.<sup>122,131</sup> As with LCH and ECD, NGS panel testing should include mutations in the MAPK pathway. Even though some of these mutations (eg, *BRAF V600E*) are less common in RDD, a comprehensive panel test is helpful for distinguishing RDD from other histiocytic neoplasms. Germline





testing for *SLC29A3*, if familial RDD is suspected, and *TNFRSF* may be considered if clinically indicated.

For complete recommendations regarding pathologic analysis of RDD cases, see the *Principles of Pathology* in the NCCN Guidelines for Histiocytic Neoplasms (available at [www.NCCN.org](http://www.NCCN.org)).

### Treatment of RDD

Observation (“watch and wait”) is a reasonable treatment strategy for patients with asymptomatic and mild disease, as spontaneous remission has been reported to occur 40% of these patients.<sup>121,122</sup>

Surgery is also a reasonable curative option for those with isolated disease or for debulking of symptomatic disease of the CNS, sinuses, or airways.<sup>121,122</sup> Patients with extranodal disease impacting critical organs and those with serious RDD-related complications require treatment. RT should only be used for palliative purposes in patients with multifocal symptomatic disease.<sup>121</sup> Case reports have shown some efficacy for RT when used to treat refractory disease in the eyelid and soft tissue of the cheek,<sup>132</sup> as well as RDD lesions causing airway obstruction.<sup>133</sup> RT dosing for RDD is not well-established, but 30 to 50 Gy may be used.<sup>121,133</sup>

### Systemic Therapy

Systemic therapy is recommended for first-line treatment of symptomatic unresectable or multifocal disease and for treatment of relapsed/refractory disease. There is a dearth of research in this area, and some systemic therapy options that may be used for treating RDD are extrapolated from ECD.<sup>122</sup> The strongest evidence supporting systemic therapy options for adults with RDD comes from two single-center retrospective studies, both conducted at NCCN Member Institutions. The first study, conducted at Mayo Clinic (N = 57), showed that corticosteroid treatment (most often prednisone) was associated

with a 56% ORR in the first-line setting, with relapse occurring in 53% of patients, and a 67% ORR in the subsequent-line setting.<sup>122</sup> This study also showed that cladribine was the most commonly used systemic therapy for treatment of recurrent disease and was associated with a 67% ORR.<sup>122</sup> In the second study, which was conducted at the University of Pennsylvania and included patients with massive lymphadenopathy (N = 15), rituximab treatment was associated with a 64% PFS at 24 months (n = 7) and a 40% ORR (PRs only), with complete resolution of symptoms when administered in the first-line setting (n = 5).<sup>134</sup> This drug was generally well-tolerated.

Case reports support use of cytarabine and oral methotrexate for treatment of RDD, as well as thalidomide for cutaneous RDD.<sup>135-138</sup> A case report describing treatment of a pediatric patient with RDD supports use of methotrexate delivered intravenously,<sup>139</sup> although oral administration is generally used. Use of sirolimus, which has demonstrated efficacy in patients with ALPS,<sup>140</sup> is supported for treatment of RDD by a case report describing treatment of a pediatric patient with RDD and severe autoimmunity.<sup>141</sup>

Steroids may be used to treat patients with symptomatic nodal or cutaneous disease, for unresectable or multifocal extranodal disease, and/or for relief of symptoms from CNS- or orbit-involved disease.<sup>121,122</sup> As described above, the Mayo Clinic study supports use of prednisone for treatment of RDD, both in the first- and subsequent-line settings.<sup>122</sup> This study showed that prednisone combined with 6-mercaptopurine and either methotrexate or azathioprine was also associated with disease response in the subsequent-line setting in patients with subcutaneous and lymph node involvement, and a PR was achieved in one patient who was treated with cyclophosphamide, vincristine, and prednisone. Prednisone combined with vinblastine is also supported by a case report describing treatment of a pediatric patient with RDD,<sup>142</sup>





but this regimen is associated with increased risk of neuropathy in adults.<sup>62</sup> Optimal duration of steroid treatment is unknown at this time; treating to optimal response, followed by a slow taper, is a reasonable strategy.<sup>121</sup> Adverse effects from steroids should be carefully monitored, though these are generally well-tolerated.<sup>122</sup>

Evidence supporting use of targeted agents for RDD is evolving, particularly for MEK inhibitors, and some options may be used based on extrapolation of evidence for use in ECD and LCH. In a retrospective multicenter French study of lung-involved RDD, cobimetinib was associated with decreased lung infiltration and SUV<sub>max</sub> values.<sup>143</sup>

Cobimetinib is also supported by a case report describing treatment of a patient with RDD and a *KRAS* activating mutation.<sup>144</sup> The MEK inhibitor trametinib is also an option, regardless of molecular profile.<sup>111</sup> Just as with LCH and ECD, targeted systemic therapy options (ie, crizotinib for *ALK* rearrangements, selpercatinib for *RET* rearrangements, pexidartinib for activating mutations in *CSF-1R*, larotrectinib and entrectinib for *NTRK* fusions) may be recommended as clinically indicated.<sup>46,82-84</sup>

#### **Follow-up**

As with LCH and ECD, follow-up assessment for patients with RDD depends on extent of disease and organ involvement. A complete list of recommendations for surveillance following treatment of RDD can be found in the algorithm (see *Rosai-Dorfman Disease: Follow-up* in the NCCN Guidelines for Histiocytic Neoplasms; available at [www.NCCN.org](http://www.NCCN.org)).

Discussion  
Update in  
progress



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Discussion  
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