National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions

Version 2.2024 — June 19, 2024

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NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024 Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions

NCCN Guidelines Index
Table of Contents
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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024 Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions

NCCN Guidelines Index
Table of Contents
Discussion

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

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.

Updates in Version 2.2024 of the NCCN Guidelines for MLNE from Version 1.2024 include:

MS-1
• The discussion section has been updated to reflect the changes in the algorithm.

Updates in Version 1.2024 of the NCCN Guidelines for MLNE from Version 2.2023 include:

Global Updates
• Mixed lineage disease and mixed lineage blast phase disease have been revised to *mixed phenotype acute leukemias* throughout the Guidelines.
• Rearrangements removed from "gene fusion rearrangements" throughout.
• Removed all instances of elevated serum vitamin B12 and vitamin B12.

MLNE-5
• Column 5, bullet 3, new: Consider BM transplant evaluation.

Footnotes
• s, modified, Avapritinib is approved for *indolent SM (ISM)*, advanced SM ...
• See MLNE-D for response criteria, is new (Also for MLNE-6, MLNE-7, MLNE-8, MLNE-9).

MLNE-7
• Column 3, lower pathway for myeloid, modified: TKI with activity against FGFR1 (eg, ~~pemigatinib~~ ~~or~~ midostaurin or ponatinib) ± AML-type induction chemotherapy, *and* followed by *consideration of* allogeneic HCT (if eligible).
• Added a bullet: Pemigatinib + AML-type induction chemotherapy, *and* followed by *consideration of* allogeneic HCT (if eligible).
• Pathway for lymphoid, modified: TKI with activity against FGFR1 (eg, ~~pemigatinib~~ ~~or~~ midostaurin or ponatinib) ± ALL-type induction chemotherapy, *and* followed by *consideration of* allogeneic HCT (if eligible).
• Added a bullet: Pemigatinib + ALL-type induction chemotherapy, *and* followed by *consideration of* allogeneic HCT (if eligible).
• Lower pathway, modified: mixed ~~lineage~~ *phenotype* (Also for MLNE-8 and MLNE-9).

Footnotes
• See NCCN Guidelines for Acute Myeloid Leukemia or NCCN Guidelines for Acute Lymphoblastic Leukemia.

MLNE-B, 4 of 5
• Modified table header: Table 2. Diagnostic *Assays* ~~Tests~~ for the Detection of .....

MLNE-D
• New page: Response Criteria for MLNE with the following reference: Shomali W, Colucci P, George TI, et al. Comprehensive response critera for myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions: A proposal from the MLN International Working Group. Leukemia 2023;37:981-987.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024 Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions

NCCN Guidelines Index
Table of Contents
Discussion

OVERVIEW[1-5]

Clonal eosinophilia associated with tyrosine kinase (TK) gene fusions (*PDGFRA, PDGFRB, FGFR1, JAK2, ABL1, or FLT3*) can have diverse clinical presentations including Ph-negative myeloproliferative neoplasms (MPN) with eosinophilia, myelodysplastic syndromes (MDS)/MPN with eosinophilia, acute myeloid leukemia (AML), B-cell or T-cell lymphomas, acute lymphoblastic leukemia (ALL), or mixed phenotype acute leukemias/lymphomas.

A diagnosis of myeloid/lymphoid neoplasms with eosinophilia should be suspected in the following clinical situations (MLNE-1):
- Sustained eosinophilia (≥1.5 x 10^9/L) or tissue eosinophilia (any eosinophil count) in a target organ, with the occurrence of characteristic genetic breakpoints, with some not always visible by standard cytogenetics (eg, *FIP1L1::PDGFRA, ETV6::ABL1*)
- Clinical features such as splenomegaly, anemia, thrombocytopenia, leukoerythroblastosis, circulating dysplastic cells, elevated serum tryptase levels, and abnormal mast cell proliferation in the bone marrow (BM)
- Features of systemic mastocytosis (SM) with eosinophilia but with interstitial, not dense aggregates of atypical mast cells (*FIP1L1::PDGFRA* rearrangement)
- Features of chronic myelomonocytic leukemia (CMML) with eosinophilia (*PDGFRB* rearrangement)
- Persistent eosinophilia after intensive treatment of AML, ALL, B-cell lymphoma, or T-cell lymphoma

Myeloid/Lymphoid Neoplasms with Eosinophilia and *FIP1L1::PDGFRA* Rearrangement:

Chronic eosinophilic leukemia (CEL) is the most common clinical presentation. Variant presentations include blast phase MPN, AML with eosinophilia, or rarely T-cell ALL (T-ALL) with *FIP1L1::PDGFRA* or myeloid sarcoma. This entity has a strong male predominance and is commonly associated with elevated serum tryptase and splenomegaly. Peripheral eosinophilia is usually, but not always, observed. BM is hypercellular with increased eosinophil precursors (generally without dysplasia) and proliferation of loosely distributed CD25+ spindle-shaped mast cells. Dense clusters of mast cells typically seen in SM with the *KIT* D816V mutation are usually absent (NCCN Guidelines for Systemic Mastocytosis).

Myeloid/Lymphoid Neoplasms with Eosinophilia and *PDGFRB* Rearrangement:

Clinical presentations associated with this entity are: CMML, atypical chronic myeloid leukemia (CML), MDS/MPN, MPN, juvenile myelomonocytic leukemia (JMML), and blast phase disease involving the BM and/or extramedullary disease (EMD) involving myeloid, lymphoid, or mixed phenotype acute leukemias. This entity also has a strong male predominance. Eosinophilia is not invariably present.

Myeloid/Lymphoid Neoplasms with Eosinophilia and *FGFR1* Rearrangement:

Clinical presentations associated with this entity are: MPN with eosinophilia, AML, B-cell, T-cell lymphoma/ALL, or mixed phenotype acute leukemia, and/or EMD of myeloid/lymphoid, or mixed phenotype acute leukemias. This entity has a moderate male predominance and is generally associated with an aggressive clinical course with rapid progression of chronic phase disease to blast phase/secondary acute leukemia. Eosinophilia is not invariably present.

Continued

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

OVERVIEW[1-5]

Myeloid/Lymphoid Neoplasms with Eosinophilia and *JAK2* Rearrangement:

Chronic myeloid neoplasm with eosinophilia (MPN with eosinophilia or MDS/MPN with eosinophilia) is the characteristic clinical presentation. ALL or de novo AML have also been observed. This entity has a strong male predominance and is generally associated with an aggressive clinical course with rapid progression of chronic phase disease to blast phase/secondary acute leukemia. The presence of eosinophilia is more variable for *BCR::JAK2* and *ETV6::JAK2* variants.

Myeloid/Lymphoid Neoplasms with Eosinophilia and *FLT3* or *ABL1* Rearrangement:

Myeloid and/or lymphoid neoplasm with eosinophilia (MLNE), consistent with the WHO category of CEL, not otherwise specified (CEL, NOS) is the characteristic clinical presentation associated with *FLT3* rearrangement. Peripheral T-cell lymphoma or T-cell lymphoblastic lymphoma (T-LBL) have also been described. De novo ALL is the most common clinical presentation associated with *ABL1* rearrangement; however, various acute leukemia and chronic myeloid/lymphoid phenotypes have also been described. It is generally associated with an aggressive clinical course, disease progression, or relapse. Eosinophilia is not invariably present.

MLNE that Present as Acute Lymphoblastic Leukemia:[6]

For MLNE that initially present as B-cell ALL (B-ALL) or T-ALL, the TK gene fusion should involve the myeloid lineage in addition to lymphoblasts. In such instances, the chronic myeloid neoplasm in MLNE may manifest either prior to or concomitantly or may emerge after therapy for the ALL. Genes fusions typically associated with *BCR::ABL1*–like B-ALL are specifically excluded from this category (eg, *EBF1::PDGFRB* and *ATF7IP::PDGFRB* fusions). *JAK2* fusions with certain partner genes, such as t(5;9)(q14.1; p24.1)/*STRN3::JAK2*, and *PAX5::JAK2* are usually seen in *BCR::ABL1*-like B-ALL, which are, by definition, not MLNE. *ETV6::JAK2* is a genetic variant of *PCM1::JAK2*; however, more than half of the reported cases of *ETV6::JAK2* are de novo B-ALL or de novo T-ALL. Similarly, *FLT3*-rearranged cases also can present as de novo B-ALL and T-ALL without myeloid lineage involvement, and these cases should be classified as *BCR::ABL1*-like B-ALL or *de novo* T-ALL.

References

1 Reiter A, Gotlib J. Myeloid neoplasms with eosinophilia. Blood 2017;129:704-714.
2 Shomali W, Gotlib J. World Health Organization-defined eosinophilic disorders: 2022 update on diagnosis, risk stratification, and management. Am J Hematol 2022;97:129-148.
3 Swerdlow SH, Campo E, Harris NL. et al. World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. Lyon, France: IARC Press; 2017.
4 Jawhar M, Naumann N, Schwaab J, et al. Imatinib in myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRB in chronic or blast phase. Ann Hematol 2017;96:1463-1470.
5 Reiter A, Walz C, Watmore A, et al. The t(8;9)(p22;p24) is a recurrent abnormality in chronic and acute leukemia that fuses PCM1 to JAK2. Cancer Res 2005;65:2662-2667.
6 Wang SA, Orazi A, Gotlib J, et al. The international consensus classification of eosinophilic disorders and systemic mastocytosis. Am J Hematol 2023;98:1286-1306.

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

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions

NCCN Guidelines Index
Table of Contents
Discussion

INITIAL EVALUATION

- Rule out secondary (reactive) eosinophilia[a] (MLNE-A).
- All patients should be evaluated and treated by a multidisciplinary team in specialized centers.
- Assessment for clinical situations that may require urgent intervention is recommended for all patients. Immediate institution of oral or high-dose IV corticosteroids may be necessary.

DIAGNOSTIC TIP-OFFS

- Primary (clonal/neoplastic) eosinophilia[b] may be suggested by one or more of the following:
- Elevated serum tryptase level;
- Abnormal T-cell population;
- Increased blasts, dysplasia, cytogenetic or molecular abnormality, and/or BM fibrosis; or
- Splenomegaly and/or lymphadenopathy.

→

- Exclude the diagnosis of *BCR::ABL1*–positive CML, PV, ET, PMF, CNL, and *BCR::ABL1*–negative atypical CML based on WHO criteria.
- Screen for TK gene fusions or other cytogenetic abnormality (MLNE-3).
- Immunohistochemistry (IHC) for tryptase/CD117/CD25 and molecular testing for *KIT* D816V[c]
- T-cell immunophenotyping flow cytometry (preferred) and/or IHC to establish evidence of abnormal T-cell phenotype or T-cell proliferation; molecular analysis to confirm T-cell clonality when appropriate

→

- ***PDGFRA*, *PDGFRB*, *FGFR1*, *JAK2*, *ABL1*, *FLT3* rearrangements identified[d]** → See Workup (MLNE-2) and Diagnostic Testing Algorithms (MLNE-3)
- **1 major + 1 minor, or ≥3 minor criteria for SM satisfied** → SM (NCCN Guidelines for Systemic Mastocytosis)
- **Other clonal cytogenetic or molecular abnormality or excess blasts (≥5% to <20%)** → CEL, NOS[e]
- **Abnormal T-cell phenotype or T-cell proliferation** → Lymphocyte-variant of hypereosinophilia (HE)/ hypereosinophilic syndrome (HES)
- **Eosinophilia without myeloid/lymphoid neoplasm, genetic/ molecular abnormality, or abnormal T-cell phenotype or T-cell proliferation** → Eosinophilia-related organ damage
  - Yes → Idiopathic HES
  - No → Idiopathic HE

[a] This diagnostic algorithm excludes conditions associated with secondary (reactive) eosinophilia (MLNE-A); it includes eosinophilia associated with non-myeloid malignancies such as T-cell lymphoma, Hodgkin lymphoma, and ALL.
[b] Generally, absolute eosinophil count ≥1.5 x 10^9/L.
[c] Allele-specific oligonucleotide quantitative reverse transcriptase PCR (ASO-qPCR) or alternative high-sensitivity method is recommended for *KIT* D816V mutation testing. See NCCN Guidelines for Systemic Mastocytosis.
[d] The diagnosis requires a combination of histopathologic, clinical, laboratory, and cytogenetic/molecular analyses.
[e] Additional cytogenetic or molecular testing may be required to confirm the differential diagnosis of clonal hematopoiesis of indeterminate potential (CHIP) vs. CEL, NOS.

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

WORKUP

General Diagnostic Studies

- History and physical examination, including skin exam, palpation of spleen, and detailing any family history of eosinophilia and signs/symptoms of immunodeficiency to identify rare primary immunodeficiency disorders and rule out secondary (reactive) eosinophilia (MLNE-A)
- Complete blood count (CBC) with differential
- Examination of blood smear (eg, monocytosis, dysplasia, eosinophilia, circulating blasts)
- Comprehensive metabolic panel with uric acid, lactate dehydrogenase (LDH), and liver function tests (LFTs)
- Serum tryptase, erythrocyte sedimentation rate (ESR), and/or C-reactive protein (CRP)
- Quantitative serum immunoglobulin (Ig) levels (including IgE)
- BM aspirate and biopsy with IHC for CD117, CD25, and tryptase and reticulin/collagen stains for fibrosis
- Peripheral blood (PB) assessment for *PDGFRA* rearrangement by fluorescence in situ hybridization (FISH) and/or nested quantitative reverse transcriptase polymerase chain reaction (RT-qPCR)[f]
- Confirmatory FISH (PB or BM) if chromosome analysis reveals the following breakpoints: 4q12 (*PDGFRA*);[g] 5q31~33 (*PDGFRB*);[h] 8p11~12 (*FGFR1*); 9p24 (*JAK2*); 9q34 (*ABL1*); and 13q12 (*FLT3*)[i]
- T-cell immunophenotyping flow cytometry (preferred) and/or IHC and molecular analysis to confirm T-cell clonality when appropriate
- Myeloid mutation panel (next-generation sequencing [NGS])[i,j]

Evaluation of Target Organ Involvement[k]

Based on clinical presentation requiring engagement of other sub-specialists; organ-directed biopsy generally needed to confirm tissue eosinophilia:

- Chest x-ray
- Electrocardiogram
- Symptom-directed CT/MRI scan of the body
- Cardiac troponin and/or NT-proBNP measurement; if elevated or clinical features of cardiac injury, echocardiogram (ECHO), and/or cardiac MRI
- Lung involvement: pulmonary function tests, bronchoscopy with bronchoalveolar lavage, and lung biopsy
- Gastrointestinal involvement: endoscopy with relevant mucosal biopsy with IHC for CD25, CD117, and tryptase
- Liver involvement: liver biopsy
- Neuropathy: electromyography, nerve biopsy
- Ear, nose, and throat symptoms: evaluation for sinusitis, nasal polyposis, sensorineural hearing loss, etc.
- Cutaneous involvement: skin biopsy
- Eosinophilic fasciitis: deep biopsy that includes fascia, MRI

→

- Diagnostic testing algorithms for tyrosine kinase gene fusions (MLNE-3)
- Diagnosis and staging considerations in myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (MLNE-4)

[f] Testing for imatinib-sensitive TK gene fusions by PB is feasible and appropriate in certain clinical circumstances. See Principles of cytogenetic and molecular testing for myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (MLNE-B).
[g] The overwhelming majority of *PDGFRA* fusions are represented by *FIP1L1::PDGFRA*, which is cytogenetically occult and requires FISH for the detection of *CHIC2* deletion for initial screening.
[h] In rare cases, cryptic *PDGFRB* rearrangements have been found, and FISH may be used to uncover, not only confirm *PDGFRB* rearrangements.
[i] Reverse transcriptase polymerase chain reaction (RT-PCR) may be preferred over NGS for *FLT3.*
[j] Role of NGS in the diagnosis of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (MLNE-C).
[k] Consultation with specialized referral services is recommended for the management of relevant target end-organ damage.

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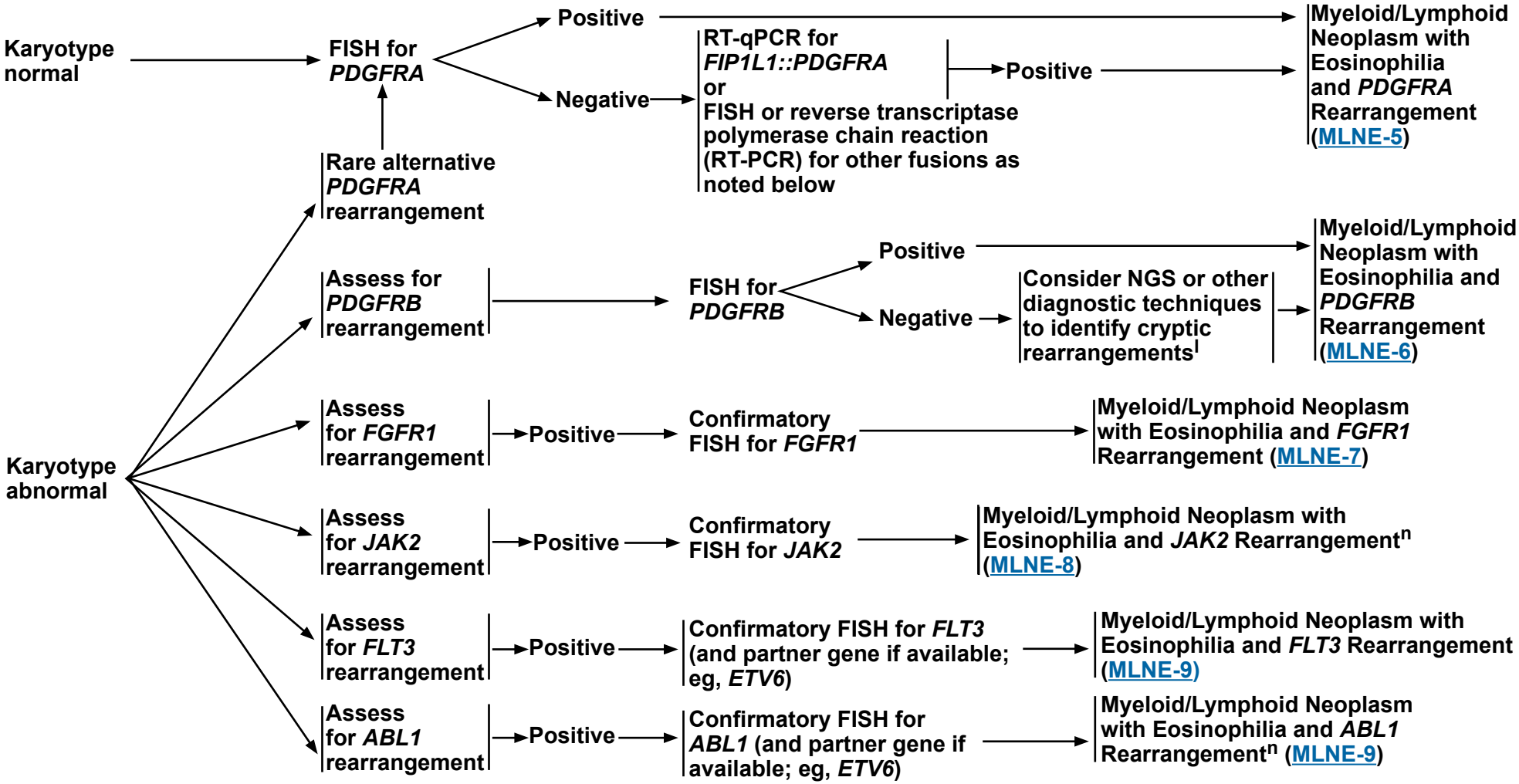
NCCN Guidelines Version 2.2024
Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions

NCCN Guidelines Index
Table of Contents
Discussion

DIAGNOSTIC TESTING ALGORITHMS FOR TYROSINE KINASE GENE FUSIONS[l,m]



[l] Diagnosis and staging considerations in myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (MLNE-4).
[m] Alternative diagnostic testing methods include chromosomal microarray analysis (CMA), chromosome genomic array testing (CGAT), and NGS. See Principles of cytogenetic and molecular testing for myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (MLNE-B).
[n] The differential diagnosis of *JAK2* and *ABL1* fusions with a phenotype of ALL includes Ph-like ALL.

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

DIAGNOSIS AND STAGING CONSIDERATIONS IN MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND TYROSINE KINASE GENE FUSIONS[d,o]

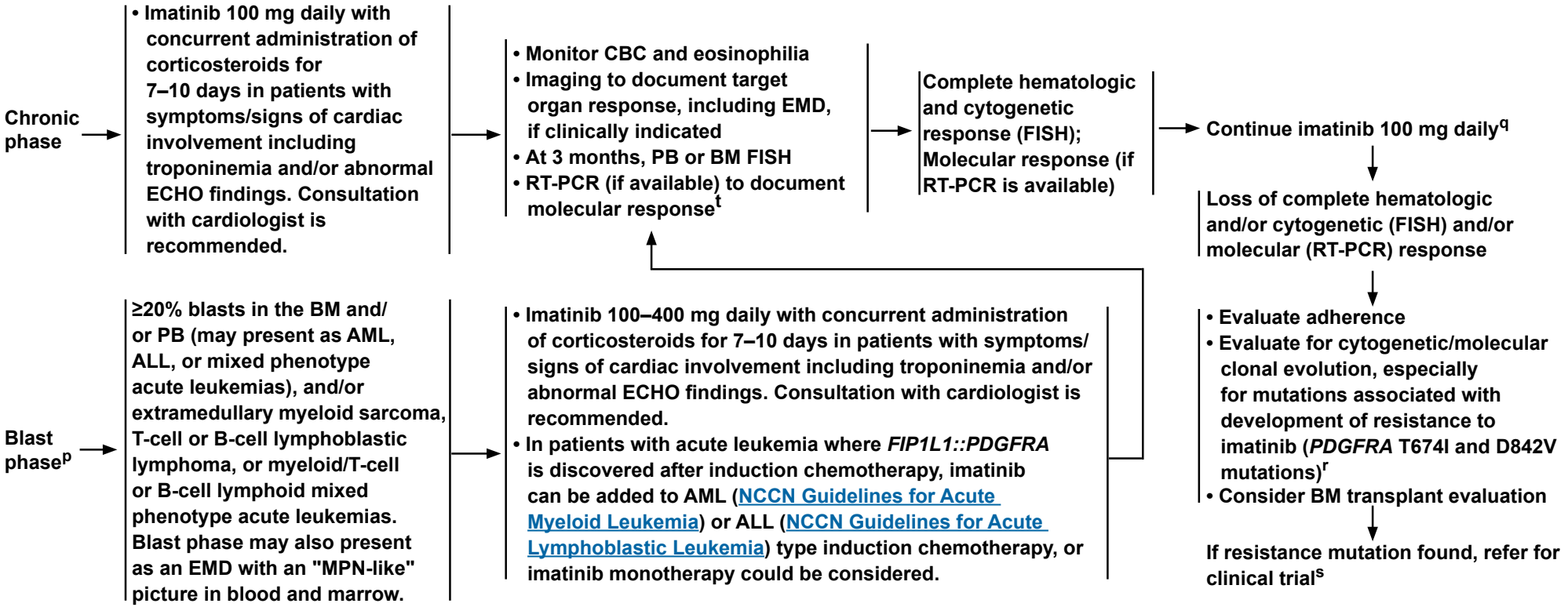
- **Chronic phase may present in the BM or PB as an MPN or MDS/MPN with or without eosinophilia, and the BM may exhibit an atypical mast cell proliferation, often in an interstitial pattern (not typical aggregates found in SM).**
- **Blast phase (≥20% blasts) may present in the BM or PB as AML, ALL,[n] or mixed phenotype acute leukemias. EMD represents a blast phase component. Blast phase may also present as an EMD with an "MPN-like" picture in blood and marrow.**
- **There is no current definition for "accelerated phase" disease; similar to myeloid neoplasms such as CML, 10%–19% blasts in the BM or PB have been used to define "accelerated phase."**
- **EMD may present as extramedullary myeloid sarcoma, T-cell or B-cell lymphoblastic lymphoma, or myeloid/T-cell or B-cell lymphoid mixed phenotype acute leukemias. EMD may present alone, or with chronic or blast phase disease involving the BM or PB. Lineage involvement of the EMD may be different from the lineage involving the BM or PB.**
- **The clinical presentation of these diseases partly reflects the fusion partner gene for the TK. This is best exemplified by the diverse phenotypes in *FGFR1*-rearranged diseases.**

Step 1 →	**DISEASE EXTENT** **Does disease involvement include BM, PB, or EMD, or all?**	→ **If clinically suspected, imaging to identify EMD**
Step 2 →	**DISEASE STAGE** **Is chronic phase or blast phase disease present in the BM or PB? If present, EMD represents a blast phase component.**	→ **Staging of BM or PB to determine if chronic vs. blast phase[n]**
Step 3 →	**DISEASE LINEAGE(S)** **What are the disease lineage(s) of the BM or PB and EMD components?**	→ **Immunophenotyping to determine lineage in BM or PB and/or EMD**

[d] The diagnosis requires a combination of histopathologic, clinical, laboratory, and cytogenetic/molecular analyses.
[n] The differential diagnosis of *JAK2* and *ABL1* fusions with a phenotype of ALL includes Ph-like ALL.
[o] Eosinophilia is not invariably present.

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

MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND THE *FIP1L1::PDGFRA* REARRANGEMENT[l]



[l] Diagnosis and staging considerations in myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (MLNE-4).

[p] The *FIP1L1::PDGFRA* fusion has been identified in patients with AML or ALL with eosinophilia at diagnosis or unmasked after induction chemotherapy; blast phase disease may also develop as progression from chronic phase disease due to cytogenetic/molecular clonal evolution, including mutations associated with development of resistance to imatinib (*PDGFRA* T674I and D842V).

[q] Complete hematologic response (CHR) by 1 month and complete cytogenetic response (CCyR; FISH) by 3 months is achieved in a vast majority of patients. In patients with ongoing CHR and CCyR (FISH), maintenance doses of imatinib as low as 100–200 mg weekly have been used with sustained responses. Continue to monitor hematologic and cytogenetic response (by FISH) every 3–6 months, and if available, molecular response by RT-PCR at these time points. Helbig G, et al. Br J Haematol 2008;141:200-204.

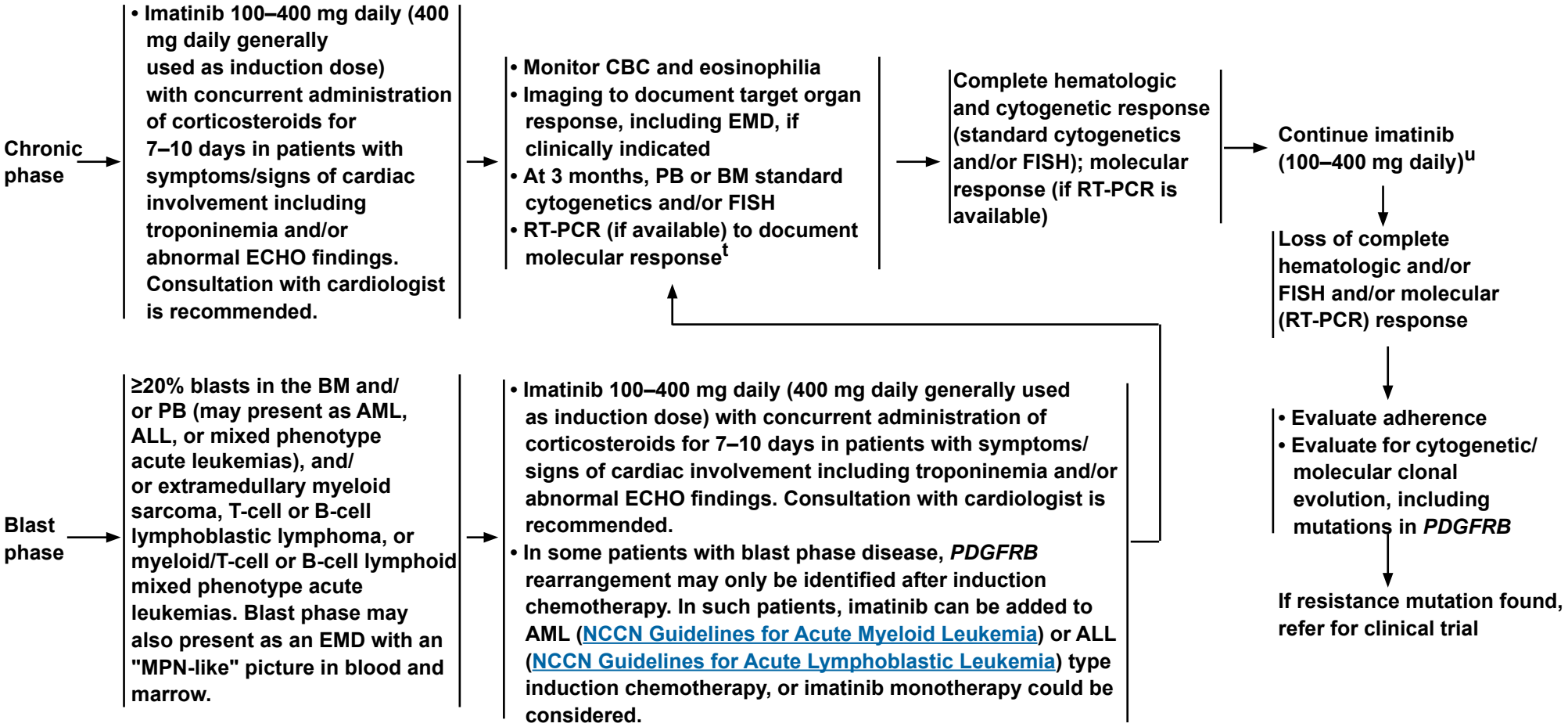
[r] *PDGFRA* T674I and D842V mutations are resistant to imatinib.

[s] Avapritinib is approved for indolent SM (ISM), advanced SM (aggressive SM [ASM], SM with an associated hematologic neoplasm [SM-AHN], and mast cell leukemia [MCL]), and also for unresectable or metastatic gastrointestinal stromal tumors (GISTs) harboring a *PDGFRA* exon 18 mutation, including D842V mutations. This suggests a possible role for avapritinib in patients with *FIP1L1::PDGFRA*–positive myeloid/lymphoid neoplasms with eosinophilia harboring *PDGFRA* D842V mutation resistant to imatinib. If this mutation is identified, a clinical trial of avapritinib is preferred (if available), rather than off-label use.

[t] See MLNE-D for response criteria.

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

MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND *PDGFRB* REARRANGEMENT[l,o]



[l] Diagnosis and staging considerations in myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (MLNE-4).
[o] Eosinophilia is not invariably present.
[t] See MLNE-D for response criteria.
[u] CHR by 1 month and CCyR (standard cytogenetics and/or FISH) by 3 months is achieved in a vast majority of patients. Continue to monitor hematologic and cytogenetic response (by FISH) every 3–6 months, and if available, molecular response by RT-PCR. Reduction of imatinib to 100 mg daily can be considered after achievement of CHR and complete cytogenetic/FISH response.

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

MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND *FGFR1* REARRANGEMENT[l,o]

CLINICAL PRESENTATION

Treatment considerations:
- Treatment options need to take into consideration whether both the BM/PB and EMD components are present and the lineage of each
- Evaluate PB and BM for response,[t] including cytogenetics/FISH, and if available, RT-PCR for *FGFR1* rearrangement
- Clinically relevant imaging to document response in the EMD component, if present
- Allogeneic hematopoietic cell transplant (HCT) is the only potentially curative option and early referral is generally recommended

TREATMENT OPTIONS

Chronic phase

Preferred regimens:
Clinical trial or Pemigatinib[v]

Other recommended regimens:
TK inhibitor (TKI) with activity against *FGFR1* (eg, midostaurin or ponatinib)

→ Consider early referral to allogeneic HCT (if eligible)

Blast phase

- ≥20% blasts in BM and/or PB (may present as AML, ALL, or mixed phenotype acute leukemias), and/or extramedullary myeloid sarcoma, T-cell or B-cell lymphoblastic lymphoma, or myeloid/T-cell or B-cell lymphoid mixed phenotype acute leukemias. Blast phase may also present as an EMD with an "MPN-like" picture in blood and marrow.

Preferred regimens:
Clinical trial or Pemigatinib[v]
and
Consider early referral to allogeneic HCT (if eligible)

Other recommended regimens:

Myeloid →
- TKI with activity against *FGFR1* (eg, midostaurin or ponatinib) ± AML-type induction chemotherapy,[w] and followed by consideration of allogeneic HCT (if eligible) or
- Pemigatinib[v] + AML-type induction chemotherapy,[w] and followed by consideration of allogeneic HCT (if eligible)

Mixed phenotype →
- TKI with activity against *FGFR1* (eg, midostaurin or ponatinib) ± ALL-type induction chemotherapy,[w] and followed by consideration of allogeneic HCT (if eligible) or
- Pemigatinib[v] + ALL-type induction chemotherapy,[w] and followed by consideration of allogeneic HCT (if eligible)

Lymphoid →
- TKI with activity against *FGFR1* (eg, midostaurin or ponatinib) ± ALL-type induction chemotherapy,[w] and followed by consideration of allogeneic HCT (if eligible) or
- Pemigatinib[v] + ALL-type induction chemotherapy,[w] and followed by consideration of allogeneic HCT (if eligible)

[l] Diagnosis and staging considerations in myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (MLNE-4).
[o] Eosinophilia is not invariably present.
[t] See MLNE-D for response criteria.
[v] Pemigatinib (FGFR inhibitor) is FDA-approved for the treatment of adult patients with relapsed or refractory myeloid/lymphoid neoplasms with *FGFR1* rearrangement.
[w] See NCCN Guidelines for Acute Myeloid Leukemia or NCCN Guidelines for Acute Lymphoblastic Leukemia.

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

MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND *JAK2* REARRANGEMENT[l,n,o]

CLINICAL PRESENTATION

Treatment considerations:

- Treatment options need to take into consideration whether both the BM/PB and EMD components are present and the lineage of each
- Evaluate PB and BM for response,[t] including cytogenetics/FISH, and if available, RT-PCR for a *JAK2* rearrangement
- Clinically relevant imaging to document response in the EMD component, if present
- Allogeneic HCT is the only potentially curative option and early referral is generally recommended

TREATMENT OPTIONS

Chronic phase

Preferred regimen:
Clinical trial

Other recommended regimens:[x]
TKI with activity against *JAK2* (ruxolitinib or fedratinib)

→ Consider early referral to allogeneic HCT (if eligible)

Blast phase

- ≥20% blasts in BM and/or PB (may present as AML, ALL, or mixed phenotype acute leukemias), and/or extramedullary myeloid sarcoma, T-cell or B-cell lymphoblastic lymphoma, or myeloid/T-cell or B-cell lymphoid mixed phenotype acute leukemias. Blast phase may also present as an EMD with an "MPN-like" picture in blood and marrow.

Preferred regimen:
Clinical trial and
Consider early referral to allogeneic HCT (if eligible)

Other recommended regimens:[x]

- Myeloid → TKI with activity against *JAK2* (ruxolitinib or fedratinib) ± AML-type induction chemotherapy (NCCN Guidelines for Acute Myeloid Leukemia), and followed by consideration of allogeneic HCT (if eligible)
- Mixed phenotype → TKI with activity against *JAK2* (ruxolitinib or fedratinib) ± AML-type induction chemotherapy (NCCN Guidelines for Acute Myeloid Leukemia), and followed by consideration of allogeneic HCT (if eligible)
- Mixed phenotype → TKI with activity against *JAK2* (ruxolitinib or fedratinib) ± ALL-type induction chemotherapy (NCCN Guidelines for Acute Lymphoblastic Leukemia), and followed by consideration of allogeneic HCT (if eligible)
- Lymphoid → TKI with activity against *JAK2* (ruxolitinib or fedratinib) ± ALL-type induction chemotherapy (NCCN Guidelines for Acute Lymphoblastic Leukemia), and followed by consideration of allogeneic HCT (if eligible)

[l] Diagnosis and staging considerations in myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (MLNE-4).
[n] The differential diagnosis of *JAK2* and *ABL1* fusions with a phenotype of ALL includes Ph-like ALL.
[o] Eosinophilia is not invariably present.
[t] See MLNE-D for response criteria.
[x] Ruxolitinib is most commonly used (Rumi E, et al. J Clin Oncol 2013;31:e269-e271; Rumi E, et al. Ann Hematol 2015;94:1927-1928; Schwaab J, et al. Ann Hematol 2015;94:233-238; Schwaab J, et al. Am J Hematol 2020;95:824-833). Fedratinib may be an appropriate alternative treatment option.

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

MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND *ABL1 OR FLT3* REARRANGEMENT[l,n,o]

CLINICAL PRESENTATION

Treatment considerations:
- Treatment options need to take into consideration whether both the BM/PB and EMD components are present and the lineage of each
- Evaluate PB and BM for response,[t] including cytogenetics/FISH, and if available, RT-PCR for an *ABL1 or FLT3* rearrangement
- Clinically relevant imaging to document response in the EMD component, if present
- Allogeneic HCT is the only potentially curative option and early referral is generally recommended

TREATMENT OPTIONS

Chronic phase

TKI with activity against *ABL1*	TKI with activity against *FLT3*
Preferred regimens: • Clinical trial • Dasatinib[y] • Nilotinib[y]	**Preferred regimen:** • Clinical trial
Other recommended regimens: • Asciminib • Bosutinib • Imatinib • Ponatinib	**Other recommended regimens:** • Gilteritinib • Midostaurin • Sorafenib • Sunitinib

→ Consider early referral to allogeneic HCT (if eligible)

Blast phase

- ≥20% blasts in BM and/or PB (may present as AML, ALL, or mixed phenotype acute leukemias), and/or extramedullary myeloid sarcoma, T-cell or B-cell lymphoblastic lymphoma, or myeloid/T-cell or B-cell lymphoid mixed phenotype acute leukemias. Blast phase may also present as an EMD with an "MPN-like" picture in blood and marrow.

→ **Preferred regimen:**
Clinical trial and
Consider early referral to allogeneic HCT (if eligible)

Other recommended regimens:

- Myeloid → TKI with activity against *ABL1* or *FLT3* ± AML-type induction chemotherapy (NCCN Guidelines for Acute Myeloid Leukemia), and followed by consideration of allogeneic HCT (if eligible)
- Mixed phenotype → TKI with activity against *ABL1* or *FLT3* ± AML-type induction chemotherapy (NCCN Guidelines for Acute Myeloid Leukemia), and followed by consideration of allogeneic HCT (if eligible)
- Mixed phenotype → TKI with activity against *ABL1* or *FLT3* ± ALL-type induction chemotherapy (NCCN Guidelines for Acute Lymphoblastic Leukemia), and followed by consideration of allogeneic HCT (if eligible)
- Lymphoid → TKI with activity against *ABL1* or *FLT3* ± ALL-type induction chemotherapy (NCCN Guidelines for Acute Lymphoblastic Leukemia), and followed by consideration of allogeneic HCT (if eligible)

[l] Diagnosis and staging considerations in myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (MLNE-4).
[n] The differential diagnosis of *JAK2* and *ABL1* fusions with a phenotype of ALL includes Ph-like ALL.
[o] Eosinophilia is not invariably present.
[t] See MLNE-D for response criteria.
[y] Schwaab J, et al. Am J Hematol 2020;95:824-833.

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

CAUSES OF SECONDARY (REACTIVE) EOSINOPHILIA[1,2]

Category	Examples
Infections	Parasitic (strongyloidiasis, *Toxocara canis*, *Trichinella spiralis*, schistosomiasis, *Echinococcus, Entamoeba*, *Cystoisospora, Ascaris*, *Ancylostoma duodenale* [hookworm], *Toxoplasma gondii, Fasciola hepatica, Paragonimus, Clonorchis,* filariasis) Viral (human immunodeficiency virus [HIV], herpes simplex virus [HSV], human T-cell leukemia virus type 2 [HTLV-2]) Fungal (coccidioides, histoplasma, cryptococcus, pneumocystis) Bacterial/Mycobacterial Consultation with infectious disease specialist is recommended for the management of complications related to specific infections.
Allergic/hypersensitivity diseases	Asthma, rhinitis, allergic rhinitis, bronchopulmonary aspergillosis, allergic gastroenteritis
Pulmonary diseases	Bronchiectasis, cystic fibrosis, chronic eosinophilic pneumonia, Löffler's syndrome
Cardiac diseases	Tropical endocardial fibrosis, eosinophilic endomyocardial fibrosis or myocarditis
Skin diseases	Atopic dermatitis, urticaria, eczema, bullous pemphigoid, dermatitis herpetiformis, episodic angioedema with eosinophilia (Gleich syndrome)
Connective tissue/autoimmune diseases	Inflammatory bowel disease, celiac disease, eosinophilic granulomatosis with polyangiitis, rheumatoid arthritis, systemic lupus erythematosus, polyarteritis nodosa, sarcoidosis, systemic sclerosis, Sjogren's syndrome, bullous pemphigoid, IgG4-related disease, eosinophilic fasciitis
Medications	Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), antimicrobials, drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome
Malignancies	Solid tumors (eg, renal, lung, breast, vascular neoplasms, female genital tract cancers), Hodgkin and non-Hodgkin lymphoma, ALL, Langerhans cell histiocytosis, angiolymphoid hyperplasia with eosinophilia (Kimura disease)
Metabolic	Adrenal insufficiency
Immune system diseases	Hyper IgE syndrome, Omenn syndrome, Wiskott-Aldrich syndrome, IgA deficiency
Other	Acute/chronic graft-versus-host disease, solid organ rejection, cholesterol emboli, L-tryptophan ingestion, IL-2 therapy, toxic oil syndrome

[1] Gotlib J, Cools J, Malone JM 3rd, et al. The FIP1L1-PDGFR alpha fusion tyrosine kinase in hypereosinophilic syndrome and chronic eosinophilic leukemia: implications for diagnosis, classification, and management. Blood 2004;103:2879-2891.
[2] Shomali W, Gotlib J. World Health Organization-defined eosinophilic disorders: 2022 update on diagnosis, risk stratification, and management. Am J Hematol 2022;97:129-148.

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

PRINCIPLES OF CYTOGENETIC AND MOLECULAR TESTING FOR MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND TYROSINE KINASE GENE FUSIONS

See Table 1. TK Gene Fusions in Myeloid/Lymphoid Neoplasms with Eosinophilia (MLNE-B, 3 of 5) and Table 2. Diagnostic Assays for the Detection of TK Gene Fusions in Myeloid/Lymphoid Neoplasms (MLNE-B, 4 of 5)

***PDGFRA*-Rearranged Eosinophilia:**
The *FIP1L1::PDGFRA* rearrangement is found in approximately 10% of patients with idiopathic eosinophilia.[1-4] Elevated serum tryptase level and/or mast cell proliferation in the BM are surrogate markers for *FIP1L1::PDGFRA* rearrangement (these patients are *KIT* D816V-negative and do not satisfy WHO criteria for SM). PB or BM FISH have similar sensitivities and the diagnosis can be made from either source. Decalcified BM should not be used as this results in a yellow autofluorescence in cells that precludes FISH interpretation.

FIP1L1::PDGFRA rearrangement results from an approximately 800-kb submicroscopic deletion in chromosome 4q12 leading to the fusion of *FIP1L1* and *PDGFRA* genes. Metaphase karyotype is unrevealing and the diagnosis is made by FISH and/or RT-PCR. The FISH probe used to identify these rearrangements detects loss of the intervening material, such as the gene *CHIC2*.[5,6] An alternative approach is a nested RT-PCR or RT-qPCR assay. Although the breakpoints in *PDGFRA* occur exclusively in exon 12, the breakpoints in *FIP1L1* are more variable but still amenable to detection by RT-qPCR. The sensitivity of this assay in most labs is 0.01%–0.001%, but as the fusion can be difficult to detect in some patients a combination strategy of FISH and RT-PCR is the most sensitive method for the detection of this rearrangement, particularly in patients where clinical suspicion is high (eg, male, elevation of serum tryptase) and for detecting minimal residual disease (MRD). Although not widely available, chromosome genomic array testing (CGAT; also known as CMA), single nucleotide polymorphism array (SNP-A), or array comparative genomic hybridization (aCGH) can readily detect submicroscopic deletions at diagnosis when a clone size is at least 20%.

Other rarer partner gene fusions for *PDGFRA* have been described (eg, *BCR, ETV6, KIF5B, CDK5RAP2, STRN, TNKS2, FOXP1*).[2,7] Detection of these alternate *PDGFRA* rearrangements is critical due to the excellent prognosis these patients have when they are treated with imatinib. Conventional cytogenetics will detect these rearrangements, but these other rearrangements can be best detected by FISH with the break-apart *PDGFRA* FISH probe. The break-apart FISH can detect a rearrangement with any gene partner and is more sensitive than karyotype analysis. RT-PCR for specific gene rearrangements is also informative, if available.[8]

A multiplexed approach using NGS to detect gene fusions is now being increasingly adopted by clinical diagnostic laboratories and may be used for both diagnosis of and monitoring for MRD.

Lastly, focused sequencing of exons 9–19 can detect mutations. Activating point mutations in *PDGFRA* have been identified in patients with *FIP1L1::PDGFRA*–negative HES and some are implicated in disease pathogenesis and may be imatinib responsive.[9]

***PDGFRB*-Rearranged Eosinophilia:**
The *ETV6::PDGFRB* [t(5;12)(q31~33;p13.2)] is the most common abnormality with a hematologic presentation similar to CMML.[4,6,7,10] The breakpoints in *PDGFRB* are located in the chromosomal region 5q31~q33. In addition to *ETV6*, more than 30 different partner gene fusions for *PDGFRB* rearrangements have been described. Rare cases with normal karyotype have been demonstrated to harbor *PDGFRB* rearrangements (eg, *TNIP1-PDGFRB* in MPN with eosinophilia).

Continued

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

PRINCIPLES OF CYTOGENETIC AND MOLECULAR TESTING IN MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND TYROSINE KINASE GENE FUSIONS

***PDGFRB*-Rearranged Eosinophilia: (continued)**

Not all patients with t(5;12)(q32;p13) have a *PDGFRB* rearrangement; other genes in this region include *IL-3, ACSL6*, and others. Eosinophilia without *PDGFRB* rearrangement is resistant to imatinib therapy.

Conventional cytogenetic analysis is the most cost-effective approach to confirm the diagnosis due to the large number of partner genes; however, it may miss subtle or cryptic translocations. Confirmation of *PDGFRB* rearrangement by FISH is indicated in all patients with 5q31~33 breakpoint. FISH break-apart probes will demonstrate all *PDGFRB* gene rearrangements with higher sensitivity and can be important in confirming the diagnosis and in treatment monitoring, but they will not identify the specific translocation partner. A dual-fusion probe can be used to confirm the partner if a specific one is suspected.[3,6]

Sensitive RT-PCR has the benefit of small clone detection, in addition to the ability to detect complex and/or cryptic cases not evident by conventional cytogenetics. However, outside of *ETV6::PDGFRB*, the feasibility of RT-PCR is limited by the large number of partner genes.

A multiplexed approach using NGS to detect gene fusions is now being increasingly adopted by clinical diagnostic laboratories and may be used for both diagnosis of and monitoring for MRD.

***FGFR1*-Rearranged Eosinophilia:**

To date, 16 partner genes with *FGFR1* have been described.[4,6,7] The most common rearrangement is t(8;13) (p11;q12), which results in the fusion of *ZMYM2* with *FGFR1* in about 50% of cases. This entity is associated with a high incidence of T-cell lymphoblastic lymphoma/leukemia. Two other common rearrangements include t(8;9)(p11;q33) (~15%) and t(6;8)(q27;p11) (~10%), which result in the fusions of *CNTRL* and *FGFR1OP* with *FGFR1*, respectively.

Conventional cytogenetics will identify *FGFR1*-associated translocations, which can be confirmed by FISH using *FGFR1* break-apart probes.

***JAK2*-Rearranged Eosinophilia:**

To date, translocations involving *PCM1::JAK2* t(8;9)(p22;p24), *ETV6::JAK2* [t(9;12)(p24;p13)], and *BCR::JAK2* [t(9;22)(p24;q11)] have been described. Conventional cytogenetics can identify these translocations, but they should be confirmed by *JAK2* break-apart probes.[4,6,7]

***FLT3*- or *ABL1*-Rearranged Eosinophilia:**

ETV6::FLT3 [t(12;13)(p13;q12)] is the gene fusion involved in the majority of cases with *FLT3* rearrangement.[7] Other variants with *SPTBN1::FLT3, GOLGB1::FLT3,* and *TRIP11::FLT3* gene fusions have also been reported.[7] Conventional cytogenetics to identify t(12;13) followed by confirmatory FISH with break-apart probes or nested RT-PCR can be used to confirm the presence of an *ETV6::FLT3* gene fusion.[7]

ETV6::ABL1 [t(9;12)(q34;p13)] is the gene fusion involved in the majority of cases with *ABL1* rearrangement.[7] Other complex rearrangements have also been reported. Routine karyotyping can be inconclusive and FISH can miss small insertions. A multiplexed approach using NGS to detect gene fusions is now being increasingly adopted by clinical diagnostic laboratories and may be used for both diagnosis of and monitoring for MRD. FISH with *ETV6* and *ABL1* probes, RT-PCR, or RNA sequencing are more reliable for the identification of *ETV6::ABL1* rearrangement.[7,11]

Continued

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

PRINCIPLES OF CYTOGENETIC AND MOLECULAR TESTING IN MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND TYROSINE KINASE GENE FUSIONS

Table 1. TK Gene Fusions in Myeloid/Lymphoid Neoplasms with Eosinophilia

Tyrosine Kinase Gene	Most Frequent Partner Gene Fusion	Other Partner Genes	
PDGFRA (4q12)	*FIP1L1* (4q12)	*BCR* (22q11.23) *ETV6* (12p13) *KIF5B* (10p11) *CDK5RAP2* (9q33)	*STRN* (2p24) *TNKS2* (10q23) *FOXP1* (3p14)
PDGFRB (5q31-33)	*ETV6* (12p13)	*SPTBN1* (2p16) *TPM3* (1q21) *PDE4DIP* (1q22) *SPDR* (2q32) *WDR48* (3p22) *GOLGA4* (3p22) *GOLGB1* (3q12) *PRKG2* (4q21) *DIAPH1* (5q31) *TNIP1* (5q33) *KANK1* (9p24) *SART3* (12q23) *CEP85L* (6q22) *CCDC6* (10q21) *GIT2* (12q24) *NDEL1* (17p13)	*HIP1* (7q11) *GPIAP1* (11p13) *NIN* (14q24) *SPECC1* (17p11) *ERC1* (12p13) *TRIP11* (14q32) *DTD1* (20p11) *RABEP1* (17p13) *MYO18A* (17q11) *MPRIP* (17p11) *NDE1* (16p13) *TP53BP1* (15q22) *CPSF6* (12q15) *BIN2* (12q13) *CCDC88C* (14q32)
FGFR1 (8p11)	*ZMYM2* (13q12)	*FGFR1OP* (6q27) *CNTRL* (9q33) *LRRFIP1* (2q37) *RANBP2* (2q13) *SQSTM1* (5q35) *CUX1* (7q22) *TRIM24* (7q34)	*TPR1* (1q25) *HERV-K* (19q13) *FGFR1OP2* (12p11) *BCR* (22q11) *MYO18A* (17q11) *PCM1* (8p21) *CPSF6* (12q15) *TFG* (3q12)
JAK2 (9p24)	*PCM1* (8p21)	*ETV6* (12p13) *BCR* (22q11)	
FLT3 (13q12)	*ETV6* (12p13)	*SPTBN1* (2p16) *GOLGB1* (3q12) *TRIP11* (14q32)	*NTRK3* (15q25) *LYN* (8q12) *SYK* (9q22)
ABL1 (9q34)	*ETV6 (12p13)*		

Reiter A, Gotlib J. Myeloid neoplasms with eosinophilia. Blood 2017;129:704-714.

Continued

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

PRINCIPLES OF CYTOGENETIC AND MOLECULAR TESTING IN MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND TYROSINE KINASE GENE FUSIONS

Table 2. Diagnostic Assays for the Detection of TK Gene Fusions in Myeloid/Lymphoid Neoplasms

Tyrosine Kinase Gene	Prototypic Genetic Rearrangement	Chromosome Location of Tyrosine Kinase Gene	Rearrangement Detected by Standard Cytogenetics	Diagnostic Assays
PDGFRA	*FIP1L1-PDGFRA*	4q12	No	FISH,[a] RT-PCR
PDGFRB	*ETV6-PDGFRB*	5q31~33	Yes	Cytogenetics, FISH, RT-PCR
FGFR1	*ZMYM2-FGFR1*	8p11~12	Yes	Cytogenetics, FISH, RT-PCR
JAK2	*PCM1-JAK2*	9p24	Yes	Cytogenetics, FISH, RT-PCR
FLT3	*ETV6-FLT3*	13q12	Yes	Cytogenetics, FISH, RT-PCR
ABL1	*ETV6-ABL1*	9q34	Yes[b]	Cytogenetics,[b] FISH,[b] RT-PCR, RNA-sequencing

[a] *FISH* for the *CHIC2* deletion is used to diagnose the *FIP1L1::PDGFRA* fusion.
[b] *ETV6::ABL1* can result from complex rearrangements, including cryptic insertions; routine karyotyping can be inconclusive and *FISH* can miss small insertions.

Reiter A, Gotlib J. Myeloid neoplasms with eosinophilia. Blood 2017;129:704-714.

Continued

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

PRINCIPLES OF CYTOGENETIC AND MOLECULAR TESTING IN MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND TYROSINE KINASE GENE FUSIONS

REFERENCES

[1] Pardanani A, Ketterling RP, Li CY, et al. FIP1L1-PDGFRA in eosinophilic disorders: prevalence in routine clinical practice, long-term experience with imatinib therapy, and a critical review of the literature. Leuk Res 2006;30:965-970.
[2] Gotlib J, Cools J. Five years since the discovery of FIP1L1-PDGFRA: what we have learned about the fusion and other molecularly defined eosinophilias Leukemia 2008;22:1999-2010.
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[4] Shomali W, Gotlib J. World Health Organization-defined eosinophilic disorders: 2022 update on diagnosis, risk stratification, and management. Am J Hematol 2022;97:129-148.
[5] Pardanani A, Ketterling RP, Brockman SR, et al. CHIC2 deletion, a surrogate for FIP1L1-PDGFRA fusion, occurs in systemic mastocytosis associated with eosinophilia and predicts response to imatinib mesylate therapy. Blood 2003;102:3093-3096.
[6] Vega F, Medeiros LJ, Bueso-Ramos CE, et al. Hematolymphoid neoplasms associated with rearrangements of PDGFRA, PDGFRB, and FGFR1. Am J Clin Pathol 2015;144:377-392.
[7] Reiter A, Gotlib J. Myeloid neoplasms with eosinophilia. Blood 2017;129:704-714.
[8] Erben P, Gosenca D, Muller MC, et al. Screening for diverse PDGFRA or PDGFRB fusion genes is facilitated by generic quantitative reverse transcriptase polymerase chain reaction analysis. Haematologica 2010;95:738-744.
[9] Elling C, Erben P, Walz C, et al. Novel imatinib-sensitive PDGFRA-activating point mutations in hypereosinophilic syndrome induce growth factor independence and leukemia-like disease. Blood 2011;117:2935-2943.
[10] Bidet A, Chollet C, Gardembas M, et al. Molecular monitoring of patients with ETV6-PDGFRB rearrangement: Implications for therapeutic adaptation. Br J Haematol 2018;182:148-152.
[11] Zaliova M, Moorman AV, Cazzaniga G, et al. Characterization of leukemias with ETV6-ABL1 fusion. Haematologica 2016;101:1082-1093.

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

ROLE OF NGS IN THE DIAGNOSIS OF MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND TYROSINE KINASE GENE FUSIONS

- **NGS studies have identified driver mutations involving a broad spectrum of genes most frequently involved in DNA methylation/chromatin modification.[1-3] The rate of mutation detection is variable (11%, 28%, and 53% in 3 different studies) and the number of genes screened in these studies was also variable (23, 45, and 88, respectively).[1,4,5]**

- **Mutations detected by NGS may also provide a means to identify primary (clonal/neoplastic) eosinophilia from secondary (reactive) eosinophilia, including in patients where no rearrangements of *PDGFRA, PDGFRB, FGFR1, PCM1::JAK2, ETV6::JAK2,* or *BCR::JAK2* are detected. Mutations described include *TET2*, *ASXL1*, *EZH2,* or *SETBP1* and, recently, activating *STAT5* N642H mutations.[6]**

- **A recent survey of 61 patients with WHO-defined myeloid/lymphoid neoplasms associated with eosinophilia and harboring *PDGFRA, PDGFRB, FGFR1, or PCM1::JAK2* identified that 14 patients (23%) had at least one mutation.[7] The mutations detected were *ASXL1, BCOR, DNMT3A, TET2, RUNX1, ETV6, NRAS, STAT5B, and ZRSR2*. Multiple mutations were identified in 3 patients, and *RUNX1* was found to be recurrently mutated (6 of 19 mutations detected) and was detected in 5 of 6 patients with *FGFR1* rearrangements (83%). For the other groups, the mutation rates were 14% for *PDGFRA*, 23% for *PDGFRB*, and 14% for *PCM1::JAK2*.**

- **NGS can be used to identify novel gene fusion or cryptic rearrangements when clinical suspicion is high and FISH for *PDGFRA*, *PDGFRB*, *FGFR1*, *JAK2*, *ABL1*, or *FLT3* are negative. As these diagnostics are not broadly available, it is recommended that these cases be discussed with a hematopathologist. Currently the impact on outcomes of additional mutations detected by NGS is unclear. Further studies are needed to determine the impact of mutations on disease course.**

- **For NGS studies, the pathogenicity of the variant(s) and relevance to eosinophilia need to be determined, including whether specific variants could be clonal hematopoiesis of indeterminate potential (CHIP) mutations.**

References

[1] Pardanani A, Lasho T, Barraco D, et al. Next generation sequencing of myeloid neoplasms with eosinophilia harboring the *FIP1L1-PDGFRA* mutation. Am J Hematol 2016;91:E10-E11.

[2] Pardanani A, Lasho T, Wassie E, et al. Predictors of survival in WHO-defined hypereosinophilic syndrome and idiopathic hypereosinophilia and the role of next-generation sequencing. Leukemia 2016;30:1924-1926.

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[6] Cross NCP, Hoade Y, Tapper WJ, et al. Recurrent activating STAT5B N642H mutation in myeloid neoplasms with eosinophilia. Leukemia 2019;33:415-425.

[7] Baer C, Muehlbacher V, Kern W, et al. Molecular genetic characterization of myeloid/lymphoid neoplasms associated with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB, FGFR1 or PCM1-JAK2*. Haematologica 2018;103:e348-e350.

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

RESPONSE CRITERIA

Response Criteria for MLNE:
Shomali W, Colucci P, George TI, et al. Comprehensive response critera for myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions: A proposal from the MLN International Working Group. Leukemia 2023;37:981-987.

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

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NCCN Guidelines Version 2.2024 Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions

NCCN Guidelines Index
Table of Contents
Discussion

ABBREVIATIONS

aCGH	array comparative genomic hybridization
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
ASM	aggressive systemic mastocytosis
B-ALL	B-cell acute lymphoblastic leukemia
BM	bone marrow
CBC	complete blood count
CCyR	complete cytogenetic response
CEL	chronic eosinophilic leukemia
CEL, NOS	chronic eosinophilic leukemia, not otherwise specified
CGAT	chromosome genomic array testing
CHIP	clonal hematopoiesis of indeterminate potential
CHR	complete hematologic response
CMA	chromosome microarray analysis
CML	chronic myeloid leukemia
CMML	chronic myelomonocytic leukemia
CNL	chronic neutrophilic leukemia
DRESS	drug reaction with eosinophilia and systemic symptoms
ECHO	echocardiogram
EMD	extramedullary disease
ESR	erythrocyte sedimentation rate
ET	essential thrombocythemia
FISH	fluorescence in situ hybridization
GIST	gastrointestinal stromal tumor
HCT	hematopoietic cell transplant
HE	hypereosinophilia
HES	hypereosinophilic syndrome
HIV	human immunodeficiency virus
HSV	herpes simplex virus
HTLV-2	human T-cell leukemia virus type 2
Ig	immunoglobulin
IHC	immunohistochemistry
ISM	indolent systemic mastocytosis
JMML	juvenile myelomonocytic leukemia
LDH	lactate dehydrogenase
LFT	liver function test
MCL	mast cell leukemia
MDS	myelodysplastic syndromes
MLNE	myeloid and/or lymphoid neoplasm with eosinophilia
MPN	myeloproliferative neoplasms
MRD	minimal residual disease
NGS	next-generation sequencing
NSAID	nonsteroidal anti-inflammatory drug
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
PB	peripheral blood
Ph	Philadelphia chromosome
PMF	primary myelofibrosis
PV	polycythemia vera
RT-PCR	reverse transcriptase polymerase chain reaction
RT-qPCR	quantitative reverse transcriptase polymerase chain reaction
SM	systemic mastocytosis
SM-AHN	systemic mastocytosis with an associated hematologic neoplasm
SNP-A	single nucleotide polymorphism array
T-ALL	T-cell acute lymphoblastic leukemia
TKI	tyrosine kinase inhibitor
T-LBL	T-cell lymphoblastic lymphoma

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	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	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

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NCCN Guidelines Version 2.2024 Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions

Discussion

This discussion corresponds to the NCCN Guidelines for Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions. Last updated: June 19, 2024.

Table of Contents

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Overview

Eosinophilic disorders and related syndromes represent a heterogeneous group of neoplastic and non-neoplastic conditions, characterized by an increased number of eosinophils in the peripheral blood, and may involve eosinophil-induced organ damage.[1-3]

Hypereosinophilia (HE) is defined as persistent elevated eosinophil count >1.5 x 10^9/L in blood and/or tissue and is divided into four variant types per an international consensus proposal: hereditary (familial), HE_{FA}; primary (clonal/neoplastic), HE_N; secondary (reactive), HE_R; and HE of undetermined significance, HE_{US}.[4] Hypereosinophilic syndrome (HES) is the term applied for any of these HE variants with evidence of eosinophil-induced tissue/organ damage and the term idiopathic HES should be applied when HE with associated organ damage is detected with no apparent underlying disease or syndrome.[4] The international consensus criteria, definition and classification of HE, HES, and other conditions accompanied by HE are outlined in Table 1 and Table 2.

HE_N is characterized by neoplastic proliferation of eosinophils and can be associated with any of the World Health Organization (WHO)-defined myeloid and/or lymphoid neoplasms.[4] A number of dysregulated tyrosine kinase (TK) gene fusions have been implicated in the pathogenesis of myeloid/lymphoid neoplasms with eosinophilia (MLNE).[5-7]

In 2008, the WHO classification of eosinophilic disorders was revised to include clonal/neoplastic eosinophilia resulting from TK gene fusions as a new category termed, “myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA, PDGFRB,* or *FGFR1*.”[8] In the 2017 WHO classification, myeloid/lymphoid neoplasms with *PCM1::JAK2* rearrangement was added as a provisional entity.[9-11] In addition to these aforementioned TK gene fusions, rearrangements involving *FLT3* and *ABL1* genes were described in MLNE, but were not formally added to the WHO classification.[6] In both the 2022 International Consensus Classification (ICC)[12] and 2022 5th edition of the WHO Classification,[13] the major category name for these diseases is changed to “myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions.” It now includes gene rearrangements including *PDGFRA*, *PDGFRB*, *FGFR1*, *JAK2*, *FLT3*, and *ETV6::ABL1*. The WHO 5th edition additionally includes other defined fusions including *ETV6::FGFR2*; *ETV6::LYN*; *ETV6::NTRK3*; *RANBP2::ALK*; *BCR::RET*; and *FGFR1OP::RET*.

Myeloproliferative neoplasms (MPNs) with peripheral blood eosinophilia (eosinophil count >1.5 x 10^9/L) that lack all of the aforementioned TK gene fusions as well as *BCR::ABL1*, and exhibit increased blasts (5% to <20%) and/or non-specific cytogenetic and/or molecular abnormalities, are classified as chronic eosinophilic leukemia (CEL) in the absence of another WHO-defined myeloid neoplasm.[11] The 2022 ICC and WHO classifications highlight the frequent dysplastic morphology observed in cases of CEL, although it is still included in the MPN (and not myelodysplastic syndromes [MDS]/MPN) category.[12,13]

The identification of specific TK gene fusions and the emergence of tyrosine kinase inhibitors (TKIs) has significantly improved the diagnosis and treatment of some patients with MLNE.[14] The treatment of patients with MLNE requires a multidisciplinary team approach, preferably in specialized medical centers.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions include recommendations for the diagnosis, staging, and treatment of any one of the MLNE associated with a TK gene fusion included in the 2022 ICC and WHO 5th edition classification.

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Literature Search Criteria

Prior to the development of this version of the NCCN Guidelines® for Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions, an electronic search of the PubMed database was performed to obtain key literature published on myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions since the previous Guidelines update using the following search terms: eosinophilic disorders, tyrosine kinase fusion gene rearrangements, and tyrosine kinase inhibitors. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[15]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines as discussed by the panel during the Guidelines update have been included in this version of the discussion section. Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[16] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms *men, women, female,* and *male* when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Diagnostic Criteria

The diagnosis requires the presence of a TK gene fusion confirmed by cytogenetic and/or molecular testing (See *Cytogenetic and Molecular Testing* in this discussion on MS-9).[11]

Eosinophilia is frequently observed, but it is not a prerequisite for the diagnosis of these neoplasms. While prominent eosinophilia is present in most patients with *FIP1L1::PDGFRA*, it is variably present in patients with a *PDGFRB, FGFR1, JAK2, FLT3,* or *ETV6::ABL1* rearrangement.[5] Patients also present with other blood count abnormalities, and organ damage may develop irrespective of the underlying TK gene fusion. See *Clinical Presentation* in this discussion on MS-5.

The clinical phenotype of MLNE is driven by the TK (eg, *PDGFRA*, *PDGFRB*, *FGFR1*, *JAK2*, *FLT3*, *ABL1*) as well as the partner gene. Many variant fusion partner genes (>70) have been characterized to date.[5-7] See

Table 1. TK Gene Fusions in Myeloid/Lymphoid Neoplasms with Eosinophilia in the algorithm.

Myeloid/Lymphoid Neoplasms with Eosinophilia and *FIP1L1::PDGFRA* Rearrangement

The diagnosis requires the presence of *FIP1L::PDGFRA* gene fusion (resulting from an interstitial deletion of *CHIC2* gene on chromosome 4q12) or a *PDGFRA* rearrangement with a variant gene fusion or an activating *PDGFRA* mutation.[11,17-19] If appropriate molecular analysis is not available, this diagnosis should be suspected in the presence of a Ph-negative MPN with the hematologic features of CEL associated with splenomegaly, elevation of serum tryptase, and an increased number of mast cells and/or fibrosis in the bone marrow.[5,7,20] MLNE with *FIP1L1::PDGFRA* rearrangement has a very strong male predominance.

The bone marrow is hypercellular with increased eosinophil precursors (generally without dysplasia) and proliferation of loosely distributed, interstitial CD25+ spindle-shaped mast cells may be seen, whereas *KIT* D816V mutation and dense clusters of mast cells typically seen in systemic mastocytosis (SM) are usually absent except in rare cases.[20]

CEL is the most common clinical presentation. Blast phase MPN, acute myeloid leukemia (AML) with eosinophilia, and rarely T-cell acute lymphoblastic lymphoma (T-ALL) or myeloid sarcoma have also been described.[5,21,22] Pediatric cases have also been reported.[23-26]

Myeloid/Lymphoid Neoplasms with Eosinophilia and *PDGFRB* Rearrangement

The diagnosis requires the presence of t(5;12)q31~q33;p13) or a variant translocation resulting in an *ETV6::PDGFRB* gene fusion or a *PDGFRB* rearrangement with a variant gene fusion.[11,27]

Chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia (CML), MDS/MPN-unclassifiable, MPN, juvenile myelomonocytic leukemia (JMML), and blast-phase disease involving the bone marrow and/or extramedullary disease (EMD) involving myeloid, lymphoid, or mixed phenotype acute leukemias are the clinical presentations associated with MLNE and *PDGFRB* rearrangement.[5,28] This entity also has a strong male predominance.

Myeloid/Lymphoid Neoplasms with Eosinophilia and *FGFR1* Rearrangement

The diagnosis requires the presence of t(8;13)(p11;q12) or a variant translocation leading to *FGFR1* rearrangement demonstrated in myeloid cells, lymphoblasts, or both.[11,29,30]

MLNE with *FGFR1* rearrangement has a moderate male preponderance, and it is generally associated with an aggressive clinical course with rapid progression of chronic phase disease to blast phase/secondary acute leukemia.[5,31,32]

MPN with eosinophilia are the most common myeloid neoplasms associated with *FGFR1*-rearranged eosinophilia. *FGFR1::ZMYM2* gene fusion and t(8;13) are associated with high incidence of T-ALL.[6] AML, B-cell, T-cell lymphoma/ALL, or mixed phenotype acute leukemia (usually associated with peripheral blood or bone marrow eosinophilia), and/or EMD of myeloid, lymphoid, or mixed phenotype acute leukemias have also been described in some patients.[5,33]

Myeloid/Lymphoid Neoplasms with Eosinophilia and *JAK2* Rearrangement

MLNE with *PCM1::JAK2* rearrangement was included as a provisional entity in the 2017 WHO classification, and the diagnosis requires the presence of t(8;9)(p22;p24.1) or a variant translocation leading to *JAK2* rearrangement.[9-11]

MLNE with *JAK2* rearrangement has a strong male preponderance and is generally associated with an aggressive clinical course with rapid progression of chronic phase disease to blast phase/secondary acute leukemia.[9,10]

MPN or MDS/MPN with eosinophilia is the characteristic clinical presentation and ALL or de-novo AML has been described in some patients.[9,10] The differential diagnosis of *JAK2* and *ABL1* fusions with a phenotype of ALL includes Ph-like ALL.

Myeloid/Lymphoid Neoplasms with Eosinophilia and *FLT3* or *ABL1* Rearrangement

MLNE with *FLT3* rearrangement and MLNE with *ETV6::ABL1* fusion were added as part of the WHO classification for MLNE and TK gene fusions.[13] The diagnosis requires the presence of t(12;13)(p13;q12) leading to *FLT3* rearrangement (*ETV6* is the most common partner gene in both cases) or t(9;12)(q34;p13) leading to *ABL1* rearrangement.[34] Rarely, other gene fusion partners of *FLT3* have been described.[6]

MLNE with *FLT3* or *ABL1* rearrangement is generally associated with an aggressive clinical course, disease progression, or relapse. CEL, not otherwise specified (NOS) is the characteristic clinical presentation in MLNE with *FLT3* rearrangement. Peripheral T-cell lymphoma or T-ALL have also been described.[6] De novo ALL is the most common clinical presentation associated with *ABL1* rearrangement in children; various acute leukemia and chronic myeloid/lymphoid phenotypes have been described in adults.[35] The differential diagnosis of *JAK2* and *ABL1* fusions with a phenotype of ALL includes Ph-like ALL.[34]

Myeloid/Lymphoid Neoplasms with Eosinophilia that Present as Acute Lymphoblastic Leukemia

For MLNE that initially present as B-cell acute lymphoblastic leukemia (B-ALL) or T-ALL, the TK gene fusion should involve the myeloid lineage as well as lymphoblasts.[36] In such instances, the chronic myeloid neoplasm in MLNE may manifest either prior to or concurrently or may emerge following therapy for ALL. Gene fusions (eg, *EBF1::PDGFRB*, *ATF7IP::PDGFRB*) that are typically associated with *BCR::ABL1*-like B-ALL are specifically excluded from this category. *JAK2* fusions with certain partner genes, such as t(5;9)(q14.1; p24.1)/*STRN3::JAK2* and *PAX5::JAK2* are usually observed in *BCR::ABL1*-like B-ALL, which are, by definition, not MLNE. *ETV6::JAK2* is a genetic variant of *PCM1::JAK2*. However, more than half of the reported cases of *ETV6::JAK2* are de novo B-ALL or de novo T-ALL. Similarly, *FLT3*-rearranged cases can also present as de novo B-ALL or T-ALL without myeloid lineage involvement, and these cases should be classified as *BCR::ABL1*-like B-ALL or de novo T-ALL.

Clinical Presentation

Chronic phase disease may present in the bone marrow or peripheral blood, with or without eosinophilia. Bone marrow may exhibit an atypical mast cell proliferation, often in an interstitial pattern but not the typical aggregates found in SM.[20]

There is no current definition for accelerated phase disease; however, the presence of 10% to 19% blasts in the bone marrow or peripheral blood has been used to define accelerated phase similar to myeloid neoplasms such as CML. Blast phase (≥20% blasts in the bone marrow and/or peripheral blood) may present as AML or ALL, or acute leukemias with mixed phenotype acute leukemias and/or extramedullary myeloid sarcoma, T-ALL, or B-ALL. Blast phase may also present as an EMD with MPN-like features in the bone marrow or peripheral blood. TK gene fusions have been identified in a number of patients where eosinophilia is concurrently diagnosed with T-cell lymphomas or blast phase acute leukemias of myeloid, lymphoid, or mixed phenotype acute leukemias (de novo or secondary).[6]

EMD may present as extramedullary myeloid sarcoma, T-ALL or B-ALL, or myeloid/T- or B-cell lymphoid mixed phenotype blast phase disease. EMD may present alone or with chronic or blast phase disease involving the bone marrow or peripheral blood, and lineage may be different from the lineage involving the bone marrow/peripheral blood.

MLNE with TK gene fusions are associated with a variety of symptoms related to the overproduction of cytokines, growth factors, and eosinophil-derived mediators.[2] The most common presenting signs and symptoms include weakness and fatigue, cough, dyspnea, myalgias or angioedema, rash or fever, and rhinitis.[7] In addition, patients also present with various blood count abnormalities depending on the underlying neoplasm (eg, neutrophilia, basophilia, thrombocytosis, monocytosis, myeloid immaturity, and both mature and immature eosinophils with varying degrees of dysplasia and anemia and/or thrombocytopenia with or without increased blast cells or dysplasia).[2,7]

Organ damage may occur in HES irrespective of the underlying subtype of HE due to the increased production and/or persistent accumulation of eosinophils in tissue.[2] The skin, lungs, gastrointestinal (GI) tract, heart, and nervous system are the most commonly involved organ systems, although all organ systems may be susceptible to eosinophilia.[2,7] Endomyocardial thrombosis and fibrosis are often documented in primary (neoplastic) HES variants (HES_N), particularly in association with the *FIP1L1::PDGFRA* gene fusion.[2,7] Imaging studies and organ-directed biopsy are useful for the documentation of target organ involvement.[2] See *Evaluation for Target Organ Involvement* in this discussion on MS-9.

Diagnosis

Accurate diagnosis of the underlying cause of HE, taking into account the histopathologic, clinical, laboratory, cytogenetic, and molecular criteria, is essential to establish the appropriate treatment plan. It is important to rule out HE_R caused by the reactive expansion of eosinophils that can be associated with a wide range of non-neoplastic (ie, allergies, infections, autoimmune or inflammatory disorders) or neoplastic (hematologic or solid malignancies) conditions.[1,3] Differential diagnoses of the non-neoplastic conditions, immunodeficiency syndromes, solid tumors, and hematologic malignancies should be considered in patients presenting with HE. See *Causes of Secondary (Reactive) Eosinophilia* in the algorithm.

Allergic disorders (eg, allergic asthma, food allergy, atopic dermatitis, drug reactions) are the most common cause of HE_R occurring in about 80% of patients, and parasitic infections represent the second most common cause.[1,3] Strongyloidiasis due to Strongyloides stercoralis exposure is generally the most common parasitic infection, although infections due to several other organisms have also been reported. If exposure to an infectious agent is suspected, initiation of appropriate treatment is necessary to prevent superinfection and consultation with an infectious agent specialist is recommended.

HE may also be present in individuals with certain immunodeficiency syndromes associated with abnormal immunoglobulin (Ig) levels (eg, hyperimmunoglobulin E syndrome [formerly known as Job syndrome], Omenn syndrome, Wiskott-Aldrich syndrome) and pulmonary eosinophilic diseases (eg, allergic bronchopulmonary aspergillosis [ABPA], eosinophilic granulomatosis with polyangiitis [EGPA] [also known as Churg-Strauss syndrome]).[1,3] HES may also be associated with a wide spectrum of dermatologic conditions (eg, atopic dermatitis, urticaria, eczema).[3]

HE_R is frequently observed in patients with solid tumors and lymphoid malignancies (eg, Hodgkin lymphoma, B-cell and T-cell lymphomas) due to the increased production of growth factors and eosinophilopoietic cytokines.[3] In solid tumors, the incidence of HE is generally limited to advanced stage disease, and among the lymphoid malignancies, the incidence of HE is more frequent in T-cell lymphomas.[3] In myeloid

malignancies (eg, CML, AML, advanced SM), HE may similarly develop. In some patients, the eosinophilia may be part of the abnormal clone; however, in some circumstances, it may be secondary, related to the elaboration of eosinophilopoietic cytokines from neoplastic cells. The term "myeloproliferative variant of HE" has been used to describe patients with MPN features such as splenomegaly or an increased serum tryptase. While many of these patients have *FIP1L1::PDGFRA*–positive disease, the term has not been formally recognized by the WHO classification.[7]

Lymphocyte-variant HES (L-HES) is characterized by clonal T-cells with an aberrant immunophenotype and is associated with an increased number of eosinophils, elevated serum thymus and activation-related chemokine (TARC), and IgE levels (although these findings are neither sensitive nor specific).[3,7,20] It is considered a mixture of a clonal disease with immunophenotypically aberrant T-cells (eg, double-negative immature T-cells [CD3+,CD4-,CD8-] or absence of CD3 [CD3-,CD4+] or CD3+, CD4+, $CD7^-$) and secondary (reactive) HE due to the elaboration of T helper 2 cytokines, such as IL-4, IL-5, and IL-13 from the abnormal T-cell population. Approximately 10% to 20% of patients have disease that can evolve to various types of T-cell lymphoma or Sézary syndrome. Flow cytometry with T-cell immunophenotyping and molecular analysis to confirm T-cell clonality may provide additional support to confirm the diagnosis of L-HES.[20] While there are no consensus diagnostic criteria for L-HES, it is felt that a clonal T-cell receptor (*TCR*) gene rearrangement alone is not sufficient to make the diagnosis of L-HES, as this finding can be non-specific and can also be identified in patients with HES of undetermined significance or even patients with a *PDGFRA* rearrangement.[37,38]

A diagnosis of a HE_N should be suspected in patients with elevated serum tryptase level, abnormal T-cell population, increased blasts, cytogenetic or molecular abnormality, and/or bone marrow fibrosis, splenomegaly, and/or lymphadenopathy, after ruling out all possible causes of HE_R. Screening for TK gene fusions (*PDGFRA, PDGFRB, FGFR1, JAK2, FLT3, or ABL1*) or other cytogenetic abnormality is recommended for patients with a suspected HE_N.

The diagnosis of CEL, NOS should be considered in the absence of TK gene fusions, when there are other cytogenetic or molecular abnormalities or increased blasts (≥5% to <20%) and/or morphologic evidence of an eosinophilic myeloid neoplasm. CEL, NOS may be distinguished from idiopathic HES by the presence of a non-specific cytogenetic abnormality (trisomy 8 or isochromosome 17) or increased blast cells (>2% in the peripheral blood or >5% in the bone marrow, but <20% blasts in both compartments).[11] Bone marrow morphology is incorporated into the diagnostic criteria for CEL.[12] Bone marrow morphologic abnormalities often include hypercellularity, dysplastic megakaryocytes with variable dysplasia in other cell lineages, and bone marrow fibrosis accompanying an eosinophil infiltrate. These features are important to help distinguish CEL, NOS from idiopathic HES.[39] In the WHO 5th edition, the qualifier "NOS" is removed from the name, but is retained in the ICC.[12,13]

Next-generation sequencing (NGS) studies have revealed that somatic mutations associated with a hematologic malignancy can be detected in people with normal blood counts in the absence of diagnostic criteria for a hematologic malignancy, and the term clonal hematopoiesis of indeterminate potential (CHIP) has been proposed to describe such situations.[40] In patients with eosinophilia in whom causes for HE_R have been excluded, additional cytogenetic or molecular testing and morphologic evaluation of the bone marrow and peripheral blood may be useful to confirm the differential diagnosis of CHIP versus CEL, NOS, since the composite picture of morphology and cytogenetic/molecular testing may allow for a more definitive determination of the presence of an eosinophilia-associated hematolymphoid neoplasm. However, the

prevalence of CHIP and technical issues related to using NGS to define clonality can be challenging when trying to ascribe certain mutations as pathogenetically relevant to CEL.

A diagnosis of idiopathic HE (organ damage absent) is equivalent to the respective term, HE_{US} per international consensus criteria and HES (organ damage present) with no apparent underlying disease or syndrome is referred to as idiopathic HES.[4] These are diagnoses of exclusion that are assigned after ruling out HE_N and all possible causes of HE_R. NGS via myeloid mutation panels may also be useful to establish the clonality in selected circumstances where no TK gene fusions are detected. Mutations detected by NGS may also provide a means to identify HE_N from HE_R. See *Role of NGS* below on MS-11.

Workup

Initial evaluation should include a history (especially assessment of travel, new medications, recurrent history of infections, and/or family history of eosinophilia) and physical examination, including skin evaluation, palpation of the liver and spleen, and signs/symptoms of an immunodeficiency syndrome.

Diagnostic Studies

An elevated IgE level is a non-specific finding in many of the underlying conditions (allergies, infections, and L-HES) related to secondary or reactive eosinophilia.[5,20] As previously noted, an elevated serum tryptase is commonly observed in myeloproliferative variants of HE, particularly in myeloid neoplasms with a *PDGFRA* gene fusion.[5,7,20] Serum tryptase is elevated in the vast majority of patients with all subtypes of SM, and eosinophilia is more prevalent in patients with advanced SM.[41-43] Aspergillus-specific immunoglobulins and increased serum IgE are characteristic findings of ABPA.[3]

Laboratory testing should include complete blood count (CBC) with differential, comprehensive metabolic panel with uric acid, lactate dehydrogenase, and liver function tests, and serum tryptase levels. Peripheral blood smear should be reviewed for the evidence of other blood count abnormalities (eg, eosinophilia, dysplasia, monocytosis, circulating blasts).[20]

Additional laboratory testing may be considered based on the patient's history, symptoms, and findings on physical examination.[7] This includes serology testing for Strongyloides and other parasitic infections; testing for antineutrophil cytoplasmic antibodies (ANCA) and antinuclear antibodies (ANA); stool ova and parasites (O&P) test and GI polymerase chain reaction (PCR); quantitative serum Ig levels (including IgE), erythrocyte sedimentation rate (ESR), and/or C-reactive protein (CRP); and aspergillus IgE to evaluate for ABPA.

Bone marrow aspirate and biopsy with immunohistochemistry (IHC) for CD117, CD25, tryptase, and reticulin/collagen stains for fibrosis; conventional cytogenetics; fluorescence in situ hybridization (FISH) and/or nested reverse transcriptase polymerase chain reaction (RT-PCR) to detect the TK gene fusion; and confirmatory FISH testing to identify breakpoints associated with TK gene fusion is recommended for all patients to confirm the diagnosis of myeloid/lymphoid neoplasms.[11,20]

The diagnostic testing algorithms for TK gene fusions are outlined in MLNE-3. See also the section below on *Cytogenetic and Molecular Testing* (MS-9). Evaluation of bone marrow and peripheral blood including immunophenotyping, will help determine lineage and disease phase (chronic phase vs. accelerated or blast phase). Diagnosis and staging considerations to determine the disease extent, disease phase, and lineage are outlined in MLNE-4.

Flow cytometry (preferred) and/or IHC to identify an immunophenotypically aberrant T-cell population and molecular analysis to confirm T-cell clonality may be useful in selected circumstances if a diagnosis of L-HES is suspected. The typical immunophenotype of L-HES is CD3-, CD4+, CD7-, and CD5++. Other abnormal immunophenotypes include CD3+, CD4+, and CD7- or CD3+, CD4-, and CD8-.[20] When flow cytometry results are equivocal, molecular analysis to detect clonal *TCR* gene rearrangements may be additionally helpful to support the diagnosis of L-HES.[20] *STAT3* mutation has also been identified in the CD3-, CD4+ T-cells in a patient with L-HES.[44]

Evaluation of Target Organ Involvement

Electrocardiogram, cardiac troponin, and/or N-terminal prohormone of brain natriuretic peptide (NT-proBNP) measurement and echocardiogram (ECHO) and/or cardiac MRI (in the presence of elevated cardiac troponin or clinical features of cardiac injury) are helpful to establish cardiac involvement and/or organ damage.[38,45,46]

Pulmonary function tests, chest x-ray, and bronchoscopy with bronchoalveolar lavage are useful to confirm lung involvement in patients with respiratory symptoms.[2] Electromyography and nerve biopsy are needed to confirm eosinophil-induced peripheral neuropathy. Evaluation for sinusitis, nasal polyposis, and sensorineural hearing loss is recommended for patients presenting with ear, nose, and throat symptoms.[2]

Organ-directed biopsy (skin, lung, or liver biopsy) with appropriate IHC is needed to confirm tissue eosinophilia and eosinophil-induced organ damage.[2] Endoscopy with relevant mucosal biopsy with IHC (CD25, CD117, and tryptase) is recommended for patients with GI involvement. Deep skin biopsy that includes fascia and MRI are useful to confirm cutaneous involvement with eosinophilic fasciitis.

Cytogenetic and Molecular Testing

MLNE with PDGFRA Rearrangement

FIP1L1::PDGFRA is the most common gene fusion in MLNE and results from an interstitial deletion of *CHIC2* gene on chromosome 4q12.[17-19] *CHIC2* deletion on chromosome 4q12 is undetectable by standard cytogenetics and can only be detected by FISH with specific probes (FISH for the *CHIC2* deletion) used for the identification of the *FIP1L1::PDGFRA* rearrangement.[18,47] Nested RT-PCR and quantitative RT-PCR (RT-qPCR) are more sensitive for the detection of *FIP1L1::PDGFRA* gene fusion in peripheral blood.[5,19,47-49]

PDGFRA fusions with other partner genes (*BCR, ETV6, KIF5B, CDK5RAP2, STRN, TNKS2*, and *FOXP1*) that are detectable by standard cytogenetics have been described. These fusions can be best detected by FISH with break-apart probes or RT-PCR for specific TK gene fusions.[5,6,19] In addition to these rearrangements, several novel imatinib-sensitive point mutations in *PDGFRA* have also been identified in patients with *FIP1L1::PDGFRA*–negative HES.[50] These alternate *PDGFRA* rearrangements, like *FIP1L1::PDGFRA*, are associated with an excellent prognosis when treated with imatinib.

Peripheral blood or bone marrow FISH have similar sensitivities, and the diagnosis can be made from either source. However, peripheral blood FISH may not robustly detect the deletion due to low clone size, and false-negative results have also been reported with bone marrow FISH.[51,52] Decalcified bone marrow should not be used as this results in a yellow autofluorescence in cells that precludes FISH interpretation. Nested RT-PCR or RT-qPCR are the methods of choice to monitor response to treatment during follow-up. However, RT-qPCR is not appropriate for screening at diagnosis and the use of RT-PCR is complicated due to the considerable diversity of break points within the *FIP1L1* gene.[53] Therefore,

a combination of RT-PCR and FISH is the most sensitive method for the detection of *FIP1L1::PDGFRA* rearrangement.

Chromosome genomic array testing (comparative genomic hybridization or single-nucleotide polymorphism arrays) can readily detect submicroscopic deletions at diagnosis when a clone size is at least 20%; however, these are not widely available.[5]

MLNE with PDGFRB Rearrangement

ETV6::PDGFRB resulting from t(5;12)(q31-33;p13) is the most common gene fusion.[27] However, not all patients with t(5;12)(q31-33;p13) have a *PDGFRB* rearrangement, and gene fusions involving non-TK genes in the 5q31~q33 region (eg, *IL-3* or *ACSL6)* have also been reported in patients with t(5;12)(q31-33;p13).[54] Identification of the gene fusions involved in t(5;12) is crucial to direct an effective treatment plan.

PDGFRB fusions with more than 30 different partner genes, in addition to *ETV6*, have been described and subtle or cryptic translocations have also been increasingly recognized.[5,55-57] While the presence of *PDGFRB* gene fusions can be detected using FISH with break-apart probes, this approach will not identify the specific translocation partner gene or the cryptic translocations. A dual color break-apart probe can be used to confirm the partner gene if a specific one is suspected.

Conventional cytogenetic analysis for t(5;12) followed by confirmatory FISH testing with break-apart probes to assess the involvement of *PDGFRB* is the most effective approach to identify the gene fusion.[58] Confirmation of *PDGFRB* rearrangement by FISH is indicated in all patients with a 5q31~33 breakpoint.

RT-PCR and RT-qPCR are more sensitive for the detection of complex and/or cryptic cases not evident by conventional cytogenetics and are well suited to monitor response to treatment.[49,59] However, the use of RT-PCR is limited by the large number of partner genes. RNA sequencing may also be considered in patients with complex/cryptic fusions.[60]

MLNE with FGFR1 Rearrangement

FGFR1::ZMYM2 resulting from t(8;13)(p11;q12) is the most common gene fusion occurring in approximately 50% of patients.[6,29,30] Several other partner genes have been described. *CNTRL::FGFR1* [t(8;9)(p11;q33)], *FGFR1OP::FGFR1* [t(6;8)(q27;p11)], and *BCR::FGFR1* [t(8;22)(p11.2; q11.2)] are the other common gene fusions occurring in about 10% to 29% of patients.[5,6,30,61,62] *RUNX1* mutations have also been reported in patients with acute leukemia and an *FGFR1* rearrangement confirmed by FISH.[30]

Conventional cytogenetic analysis for t(8;13) followed by confirmatory FISH testing using dual-color break-apart probes for *FGFR1* is the effective diagnostic approach for the detection of *FGFR1::ZMYM2* gene fusion and can be applied to other *FGFR1* rearrangements.[5,30]

MLNE with JAK2 Rearrangement

PCM1::JAK2 resulting from t(8;9)(p22;p24) is the most common gene fusion.[6,10,63-65] *ETV6::JAK2* [t(9;12)(p24;p13)] and *BCR::JAK2* [t(9;22)(p24;q11)] are the other gene fusions reported only in few patients.[6,10,66-68]

As with other gene fusions resulting from a translocation, conventional cytogenetics to identify t(8;9) followed by confirmatory FISH with *JAK2* break-apart probes is recommended to confirm the diagnosis.[6,10]

MLNE with FLT3 or ABL1 Rearrangement

ETV6::FLT3 resulting from t(12;13)(p13;q12) and *ETV6::ABL1* resulting from t(9;12)(q34;p13) are the common gene fusions involved in the majority of patients.[6,34,35,69] *FLT3* fusion with other partner genes (*SPTBN1, GOLGB1, TRIP11, and ZMYM2*) and complex rearrangements

resulting from fusion of *ABL1* with partner genes (other than *ETV6*) have also been reported.[6,55,70-72]

Conventional cytogenetics for t(12;13) followed by confirmatory FISH with break-apart probes or nested RT-PCR (to identify reciprocal *ETV6::FLT3* and *FLT3::ETV6* transcripts) can be used to confirm the presence of *ETV6::FLT3* gene fusion.[34] However, conventional cytogenetics may be inconclusive for the detection of *ETV6::ABL1*, mainly because the creation of the *ETV6::ABL1* gene fusion requires at least three chromosomal breaks. In addition, the gene fusion is not uniform across patients and typically involves cryptic insertions that can be missed with routine cytogenetics.[35] A multiplexed approach using NGS to detect gene fusions is now being increasingly adopted by clinical diagnostic laboratories and may be used for both diagnosis and monitoring for minimal residual disease (MRD). FISH with a combination of *ETV6* and *ABL1* probes, RT-PCR, or RNA sequencing are more reliable tests for the identification of an *ETV6::ABL1* fusion.[6,35]

Role of NGS

NGS studies have also identified driver mutations involving a broad spectrum of genes most frequently involved in DNA methylation/chromatin modifications in patients with idiopathic HES, although the number of genes screened and the rate of mutation detection in these studies have been variable.[73-76] In one study, myeloid neoplasm-related somatic mutations involving a single gene or ≥2 genes have been identified in 28% of patients (14 of 51) with idiopathic HES, with *ASXL1* (43%), *TET2* (36%), *EZH2* (29%), *SETBP1* (22%), *CBL* (14%), and *NOTCH1* (14%) being the most frequently mutated genes.[74] In another study, 53% of patients (16 of 30) had at least one candidate mutation with *NOTCH1* (27%), *SCRIB* and *STAG2* (17%), and *SH2B3* (13%) being the most frequently mutated genes; clonal *TCR* rearrangement was present in 13% of patients.[75] Somatic *STAT5B* N642H mutations were reported in 1.6% (27/1715) of patients with eosinophilia.[76] The presence of *STAT5B* N642H mutation as a sole abnormality was associated with a shorter overall survival compared to published series in patients with HES, suggesting that these cases should be reclassified as CEL-NOS.[76] Thus, targeted NGS studies will be helpful to establish clonality in a subset of patients with idiopathic HES leading to re-classification of some cases as CEL-NOS.

NGS studies are also useful for the detection of additional molecular abnormalities in patients with MLNE and rearrangement of *PDGFRA, PDGFRB, FGFR1*, or *PCM1::JAK2*.[77-79] In an analysis of 61 patients with MLNE and rearrangement of *PDGFRA, PDGFRB, FGFR1*, or *PCM1::JAK2*, at least one additional mutation in several other genes (*ASXL1, BCOR, DNMT3A, TET2, RUNX1, ETV6, NRAS, STAT5B*, and *ZRSR2*) was detected in 14 patients (23%).[77] Patients with *FGFR1* rearrangement had a significantly higher frequency of additional mutations (83%; 5 of 6 patients; all had *RUNX1* mutation) in comparison to those with *PDGFRA* (14%; 5 of 35 patients), *PDGFRB* (23%; 3 of 13 patients), or *PCM1::JAK2* (14%;1 of 7 patients) rearrangements. NGS-based gene fusion detection techniques have identified genetic variants of *CSF3R* and *KIT* mutations (*CSF3R* M696T and *KIT* P155S) in patients with myeloid neoplasms with eosinophilia and *FIP1L1::PDGFRA* rearrangement.[78]

NGS studies are not broadly available and currently the prognostic impact and pathogenicity of additional mutations detected by NGS have not been established. Further studies are needed to determine the impact of these novel mutations on disease course.

Treatment Considerations

All patients should be evaluated and treated by a multidisciplinary team (including engagement of other subspecialists based on clinical presentation and organ involvement) in specialized centers.

Assessment for clinical situations that may require urgent intervention is recommended for all patients. Immediate institution of oral or high-dose intravenous corticosteroids may be necessary as clinically indicated, especially in patients in whom eosinophil-mediated cardiac damage/heart failure is present or suspected.

As noted earlier, consultation with an infectious disease specialist is recommended as clinically indicated for the management of infectious disease-related complications.

Myeloid/Lymphoid Neoplasms with Eosinophilia and *PDGFRA* or *PDGFRB* Rearrangement

Imatinib has resulted in high rates of durable hematologic and molecular responses in the vast majority of patients with MLNE and *PDGFRA* or *PDGFRB* rearrangement.[22,28,38,80-93] Concurrent administration of corticosteroids for 7 to 10 days and consultation with a cardiologist is recommended for patients with symptoms/signs of cardiac involvement including troponinemia, elevated NT-proBNP, and/or abnormal ECHO findings.[83]

Imatinib 100 mg daily is the recommended dose for induction therapy for chronic phase disease in patients with *FIP1L1::PDGFRA* rearrangement. Imatinib 100 to 400 mg daily is the recommended dose for chronic phase disease in patients with *PDGFRB* rearrangement, although 400 mg daily is generally used as the induction dose. Reduction to 100 mg daily can be considered after achievement of complete hematologic response (CHR) and complete cytogenetic response (CCyR).

Blast phase disease may present either as de novo or as disease progression from chronic phase due to cytogenetic/molecular clonal evolution, including *PDGFRA* mutations associated with development of resistance to imatinib including T674I or D842V.[81]

Imatinib monotherapy (100–400 mg daily) is recommended for blast phase disease (400 mg daily is generally used as the induction dose in patients with *PDGFRB* rearrangement). Durable remissions are only rarely achieved with induction chemotherapy or allogeneic hematopoietic cell transplant (HCT). In instances when *FIP1L1::PDGFRA* or a *PDGFRB* rearrangement is identified only after the initiation of induction chemotherapy, imatinib should be added to induction chemotherapy (ALL-type chemotherapy for lymphoid blast phase and AML-type chemotherapy for myeloid blast phase), or a return to imatinib monotherapy may also be considered.[28,86]

Monitoring Response and Additional Treatment

CHR (defined as the normalization of peripheral blood counts and eosinophilia) by 1 month and CCyR by 3 months is achieved in a vast majority of patients.[94]

Monitoring blood counts (CBC and eosinophilia), imaging to document target organ response (as clinically indicated), and peripheral blood or bone marrow evaluation (FISH for *FIP1L1::PDGFRA* since standard karyotyping cannot detect the fusion; standard cytogenetics and/or FISH for *PDGFRB*) are recommended at 3 months after initiation of imatinib. RT-PCR (if available) can be considered to document molecular response.

Continuation of imatinib at the initial dose is recommended for patients achieving a complete response (CHR, CCyR, or complete molecular response [CMR]). While low doses of 100 to 200 mg daily have been sufficient to maintain molecular remission in the majority of patients with *FIP1L1::PDGFRA* rearrangement, and in some patients this dose range has been used only once weekly,[82] higher doses (maximum of 400 mg daily) may be required for some patients.[83,84]

Monitoring hematologic response, cytogenetic response (FISH), and molecular response (if RT-qPCR is available) every 3 and 6 months is

recommended for patients achieving a durable complete response to initial treatment. Clinical trial and/or early referral to allogeneic HCT should be considered for patients with loss of response. Evaluation of patient compliance or drug interactions is recommended prior to initiation of additional treatment for patients with loss of response.

Acquired resistance to imatinib mediated by *PDGFRA* T674I and D842V mutations has been reported in few patients with primarily blast phase disease.[81,95] Nilotinib, ponatinib, and sorafenib have shown limited activity in patients with *PDGFRA* T674I and D842V mutations.[95-98] *PDGFRB* T681I has been shown to confer resistance to imatinib in vitro, but has not yet been identified in patients treated with imatinib; acquired resistance to imatinib mediated by other *PDGFRB* mutations has been described only in two case reports.[99-101] Evaluation for cytogenetic/molecular clonal evolution can identify *PDGFRA* (T674I and D842V) or *PDGFRB* mutations conferring resistance to imatinib in patients with loss of response. If a resistance mutation is found, referral to a specialized treatment center and enrollment in a clinical trial (if available) is recommended. A bone marrow transplant evaluation should be considered for patients with one of these resistance mutations in the *FIP1L1::PDGFRA* rearrangement.[102]

Avapritinib is approved for indolent SM, advanced SM (aggressive SM, SM with an associated hematologic neoplasm, and mast cell leukemia) and also for unresectable or metastatic gastrointestinal stromal tumors (GIST) harboring a *PDGFRA* exon 18 mutation, including D842V mutations.[103-106] This suggests a possible role for avapritinib in patients with MLNE and *PDGFRA* rearrangement harboring *PDGFRA* D842V mutation resistant to imatinib. If this mutation is identified, a clinical trial of avapritinib is preferred (if available), rather than off-label use.

The feasibility of discontinuation of imatinib in patients with MLNE and *PDGFRA* rearrangement who have achieved CMR has been studied mostly in retrospective studies in a limited number of patients.[38,80,107,108] There is substantial variability in the relapse-free survival rates (57%–91% at 12 months; 42%–65% at 24 months), although molecular remissions have been re-established after restarting imatinib in most patients experiencing relapse after discontinuation of imatinib.[108] The feasibility of discontinuation of imatinib in patients with MLNE and a *PDGFRB* rearrangement has not been evaluated. At the present time, there are no definite criteria to identify patients suitable for discontinuation of imatinib and it is therefore not recommended outside the context of clinical trials.

Myeloid/Lymphoid Neoplasms with Eosinophilia and *FGFR1 or JAK2 or ABL1 or FLT3* Rearrangement

General Approach

MLNE with the above-mentioned TK gene fusions are generally associated with an aggressive clinical course, relapse, or disease progression to blast phase and allogeneic HCT is the only potentially curative option.[9,10,31,35,109]

Clinical trial is the preferred treatment option for patients with chronic phase disease. Pemigatinib is also a preferred treatment option for patients with chronic phase disease and *FGFR1* rearrangement. In the absence of a clinical trial, patients with chronic phase disease can be treated with TKI monotherapy. However, early referral to allogeneic HCT should be considered for eligible patients, since TKI therapy alone typically does not result in durable remissions.

Clinical trial and early consideration of allogeneic HCT for eligible patients is the preferred treatment approach for patients with blast phase disease. Pemigatinib and early consideration of allogeneic HCT for eligible patients is also a preferred treatment option for patients with blast phase disease and *FGFR1* rearrangement. In the absence of a suitable clinical trial, TKI ± induction chemotherapy followed by consideration of allogeneic HCT (if eligible) is the appropriate treatment approach.

MLNE with FGFR1 Rearrangement

Enrollment in a clinical trial and pemigatinib are both preferred options for patients with an *FGFR1* rearrangement. Pemigatinib is FDA-approved for the treatment of adult patients with relapsed or refractory myeloid/lymphoid neoplasms with *FGFR1* rearrangement. In the phase 2 FIGHT-203 study, which included 35 patients with prior treatment and 5 patients with no prior treatment, treatment with pemigatinib resulted in 73.7% (N = 38) and 70% (N = 40) of patients achieving a complete response and a complete cytogenetic response, respectively.[110] These response rates were more pronounced in patients with chronic phase disease compared to blast phase (complete response: 90.5% vs. 52.9%; complete cytogenetic response: 85.7% vs. 47.1%). Stomatitis (17%) and anemia (15%) were the most common grade 3 and above treatment-emergent adverse events.

The selection of chemotherapy for blast phase disease should be based on the cell lineage (ALL-type chemotherapy for lymphoid blast phase and AML-type chemotherapy for myeloid blast phase; either of these induction chemotherapy regimens can be considered for mixed phenotype blast phase disease and needs to be evaluated on a case-by-case basis based on immunophenotype of the leukemia and other disease or patient factors).

TKIs with activity against *FGFR1*, *JAK2*, *FLT3,* or *ABL1*, are listed in the table below. Given the rare nature of this disease, available evidence is mainly from case reports and/or their potential clinical activity is extrapolated from other diseases with the same target. Although TKI ± induction chemotherapy typically does not result in long-term disease control, it may be of potential benefit when used as a bridge to allogeneic HCT for disease cytoreduction prior to transplantation.[30,109,111-113]

Other TKIs besides FDA-approved Pemigatinib[a,110] with Activity Against *FGFR1*	TKI with Activity Against *JAK2*	TKI with Activity Against *FLT3*	TKI with Activity Against *ABL1*[b]
Midostaurin[114] Ponatinib[30,98,112,115,116]	Ruxolitinib[113,117-119] Fedratinib[c]	Gilteritinib[c] Midostaurin[c] Sorafenib[111,120] Sunitinib[120]	Dasatinib[113] Nilotinib[113] Asciminib[c] Bosutinib[c] Imatinib[113] Ponatinib[c]

a. Pemigatinib (FGFR inhibitor) is FDA-approved for the treatment of adult patients with relapsed or refractory MLN with *FGFR1* rearrangement.
b. Dasatinib or nilotinib are more effective than imatinib to induce durable complete remissions in patients with *ETV6::ABL1* gene fusion.[113] Among the TKIs with activity against *ABL1*, dasatinib and nilotinib are preferred options.
c. The inclusion of these TKIs is based on the extrapolation of data from MPN (fedratinib for MF) and other myeloid neoplasms (gilteritinib and midostaurin for AML; bosutinib, asciminib, and ponatinib for CML). See NCCN Guidelines for Acute Myeloid Leukemia and Chronic Myeloid Leukemia.

Clinically relevant imaging studies to document response in the EMD component and evaluation of peripheral blood or bone marrow (FISH or cytogenetics) and RT-PCR (if available) for specific TK fusion gene fusion to document response (hematologic, cytogenetic, or molecular response) should be considered for all patients after initiation of treatment. New comprehensive response criteria for MLNE have now been published.[121]

Monitoring MRD after allogeneic HCT and maintenance therapy with TKI (eg, ponatinib) or hypomethylating agent (eg, 5-azacytidine) has been shown to be effective for MLNE with *FGFR1* rearrangement in single case reports.[116,122] The role for TKI as maintenance therapy following allogeneic HCT has not been systematically evaluated but may be considered in patients felt to be at high risk for relapse. Additional studies are needed to confirm the efficacy of this treatment approach.

Table 1. Classification and Definition of Hypereosinophilia[4]

Proposed Terminology	Proposed Abbreviation	Definition and Criteria
Blood eosinophilia	—	>0.5 eosinophils × 10^9/L blood
Hypereosinophilia	**HE**	>1.5 x 10^9/L eosinophils in the blood on 2 examinations (interval ≥1 month[a]) and/or tissue HE defined by the following[b] 1. Percentage of eosinophils in bone marrow exceeds 20% of all nucleated cells; and/or 2. Pathologist is of the opinion that tissue infiltration by eosinophils is extensive; and/or 3. Marked deposition of eosinophil granule proteins is found (in the absence or presence of major tissue infiltration by eosinophils).
• Hereditary (familial) HE	HE_{FA}	Pathogenesis unknown; familial clustering, no signs or symptoms of hereditary immunodeficiency, and no evidence of a reactive or neoplastic condition/disorder underlying HE
• HE of undetermined significance	HE_{US}	No underlying cause of HE, no family history, no evidence of a reactive or neoplastic condition/disorder underlying HE, and no end-organ damage attributable to HE
• Primary (clonal/neoplastic) HE[c]	HE_N	Underlying stem cell, myeloid, or eosinophilic neoplasm, as classified by WHO criteria; eosinophils considered neoplastic cells[d]
• Secondary (reactive) HE[c]	HE_R	Underlying condition/disease in which eosinophils are considered nonclonal cells[d]; HE considered cytokine-driven in most cases[e]
Eosinophil-associated single-organ diseases		Criteria of HE fulfilled and single-organ disease

a. In the case of evolving life-threatening end-organ damage, the diagnosis can be made immediately to avoid delay in therapy.

b. Validated quantitative criteria for tissue HE do not exist for most tissues at the present time. Consequently, tissue HES is defined by a combination of qualitative and semiquantitative findings that will require revision as new information becomes available.

c. HE_N and HE_R are prediagnostic checkpoints that should guide further diagnostic evaluations but cannot serve as final diagnoses.

d. Clonality of eosinophils is often difficult to demonstrate or is not examined. However, if a myeloid or stem cell neoplasm known to present typically with clonal HE is present or a typical molecular defect is demonstrable (eg, *PDGFR* or *FGFR* mutations or *BCR/ABL1*), eosinophilia should be considered clonal.

e. In a group of patients, HE_R might be caused/triggered by other as yet unknown processes because no increase in eosinophilopoietic cytokine levels can be documented.

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Table 2. Classification and Definition of Hypereosinophilic Syndrome and Conditions Accompanied by HE[4]

Proposed Terminology	Proposed Abbreviation	Definition and Criteria
Hypereosinophilic syndrome	**HES**	Defined as blood HE with (plus) end-organ damage attributable to tissue HE: 1. Criteria for peripheral blood HE fulfilled[a]; and 2. Organ damage and/or dysfunction attributable to tissue HE[b]; and 3. Exclusion of other disorders or conditions as major reason for organ damage
• Idiopathic HES	—	No underlying cause of HE, no evidence of a reactive or neoplastic condition/disorder underlying HE and end-organ damage attributable to HE.
• Primary (neoplastic) HES	HES_N	Underlying stem cell, myeloid, or eosinophilic neoplasm classified according to WHO guidelines and end-organ damage attributable to HE, and eosinophils are considered (or shown) neoplastic (clonal) cells.[c]
• Secondary (reactive) HES	HES_R	Underlying condition/disease in which eosinophils are considered nonclonal cells; HE is considered cytokine driven, and end-organ damage is attributable to HE. Lymphoid variant HES[d] (clonal T-cells identified as the only potential cause) is a subvariant of secondary (reactive) HES.
Other conditions and syndromes		
Specific syndromes accompanied by HE		Specific syndromes in which the effect of eosinophilia remains unclear but the clinical presentation is distinct and accompanied by HE
Other conditions accompanied by HE		Mostly organ-restricted conditions in which the effect of eosinophilia remains unclear

a. In the case of evolving life-threatening end-organ damage, the diagnosis can be made immediately to avoid delay in therapy.

b. HE-related organ damage (damage attributable to HE): organ dysfunction with marked tissue eosinophil infiltrates and/or extensive deposition of eosinophil-derived proteins (in the presence or absence of marked tissue eosinophils) and 1 or more of the following: (1) fibrosis (lung, heart, digestive tract, skin, and others); (2) thrombosis with or without thromboembolism; (3) cutaneous (including mucosal) erythema, edema/ angioedema, ulceration, pruritus, and eczema; and (4) peripheral or central neuropathy with chronic or recurrent neurologic deficit. Less commonly, other organ system involvement (liver, pancreas, kidney, and other organs) and the resulting organ damage can be judged as HE-related pathology, so that the clinician concludes the clinical situation resembles HES. Note that HES can manifest in 1 or more organ systems.

c. Clonality of eosinophils is often difficult to demonstrate or is not examined. However, if a myeloid or stem cell neoplasm known to present typically with clonal HE is present or a typical molecular defect is demonstrable (eg, *PDGFR* or *FGFR* mutations or *BCR/ABL1*), eosinophilia should be considered clonal.

d. The lymphoid variant of HES is regarded as a special form of secondary HES by several experts, although its exact nature and pathogenesis remain controversial.

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