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Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# **Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes**

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# NCCN Guidelines Version 4.2021

## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

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# NCCN Guidelines Version 4.2021

## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

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#### [Principles of Cytogenetic and Molecular Testing in Myeloid/Lymphoid Neoplasms with Eosinophilia And Tyrosine Kinase Fusion Genes \(MLNE-C\)](#)

#### [Role of Next-Generation Sequencing \(NGS\) in the Diagnosis of Myeloid/Lymphoid Neoplasms with Eosinophilia And Tyrosine Kinase Fusion Genes \(MLNE-D\)](#)

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

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

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

See [NCCN Categories of Preference](#).

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# NCCN Guidelines Version 4.2021

## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

Updates in Version 4.2021 of the NCCN Guidelines for MLNE from Version 3.2021 include:

### [MLNE-5](#)

- Footnote "t" modified as follows: Avapritinib is approved for *advanced systemic mastocytosis (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-PDGFR*A–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.

### [MS-1](#)

- The Discussion has been updated to reflect the changes to the algorithm.

Updates in Version 3.2021 of the NCCN Guidelines for MLNE from Version 2.2021 include:

### [MLNE-7](#)

- "*Pemigatinib*" has been added as a TKI with activity against *FGFR1* under other recommended regimens for *blast phase*, with the following corresponding footnote, "*Pemigatinib (FGFR1, 2, and 3 inhibitor) is approved for the treatment of adult patients with previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma and a FGFR2 fusion or other rearrangement, as detected by an FDA-approved test. Pemigatinib has received orphan drug designation for the treatment of patients with myeloid/lymphoid neoplasms with eosinophilia and FGFR1 rearrangement and is currently being evaluated in a clinical trial for this indication. A clinical trial of pemigatinib is preferred (if available), rather than off-label use (Hoy SM. Drugs 2020;80:923-929; Verstovsek S, et al. Blood 2018;132:Abstract 690).*"

### [MS-1](#)

- The Discussion has been updated to reflect the changes to the algorithm.

Updates in Version 2.2021 of the NCCN Guidelines for MLNE from Version 1.2021 include:

### [MLNE-3](#) (Also for [MLNE-4](#), [MLNE-8](#), and [MLNE-9](#))

- The following footnote is new to the page, "*The differential diagnosis of JAK2 and ABL1 fusions with a phenotype of ALL includes Ph-like ALL.*"

### [MLNE-5](#)

- The following footnote corresponding to, If resistance mutation found, refer for clinical trial is new to this page. "*Avapritinib is approved for adult patients with 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-PDGFR*A–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."

### [MLNE-7](#)

- "*Pemigatinib*" has been added as a TKI with activity against *FGFR1* under other recommended regimens.
- The following footnote corresponding to, "clinical trial" and "pemigatinib" is new to this page. "*Pemigatinib (FGFR1, 2, and 3 inhibitor) is approved for the treatment of adult patients with previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma and a FGFR2 fusion or other rearrangement, as detected by an FDA-approved test. Pemigatinib has received orphan drug designation for the treatment of patients with myeloid/lymphoid neoplasms with eosinophilia and FGFR1 rearrangement and is currently being evaluated in a clinical trial for this indication. A clinical trial of pemigatinib is preferred (if available), rather than off-label use (Hoy SM. Drugs 2020;80:923-929; Verstovsek S, et al. Blood 2018;132:Abstract 690).*"

### [MS-1](#)

- The Discussion has been updated to reflect the changes to the algorithm.



# NCCN Guidelines Version 4.2021

## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

### **OVERVIEW**<sup>1,2,3,4,5</sup>

Clonal eosinophilia associated with tyrosine kinase (TK) fusion gene rearrangements (*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 lineage leukemias/lymphomas.

A diagnosis of myeloid/lymphoid neoplasms with eosinophilia should be suspected in the following clinical situations ([See MLNE-1](#)):

- Sustained eosinophilia ( $\geq 1.5 \times 10^9/L$ ) 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-PDGFRB*, *ETV6-ABL1*);
- Clinical features such as splenomegaly, anemia, thrombocytopenia, leukoerythroblastosis, circulating dysplastic cells, elevated serum vitamin B12 and/or 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-PDGFRB* 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-PDGFRB* 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-PDGFRB* or myeloid sarcoma. This entity has a strong male predominance and is commonly associated with marked elevation of serum vitamin B12, 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.

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

CMML, atypical 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 lineages. This entity also has a strong male predominance. Eosinophilia is not invariably present.

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

MPN with eosinophilia, AML, B-cell or T-cell lymphoma/ALL mixed phenotype acute leukemia, and/or EMD of myeloid, lymphoid, or mixed lineage. 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.

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# NCCN Guidelines Version 4.2021

## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

### **OVERVIEW**<sup>1,2,3,4,5</sup>

#### **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, 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.

#### References

<sup>1</sup>Reiter A, Gotlib J. Myeloid neoplasms with eosinophilia. *Blood* 2017;129:704-714.

<sup>2</sup>Shomali W, Gotlib J. World Health Organization-defined eosinophilic disorders: 2019 update on diagnosis, risk stratification, and management. *Am J Hematol* 2019;94:1149-1167.

<sup>3</sup>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.

<sup>4</sup>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.

<sup>5</sup>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.

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# NCCN Guidelines Version 4.2021

## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

### INITIAL EVALUATION

- Rule out secondary (reactive) eosinophilia<sup>a</sup> ([See MLNE-A](#)).
- All patients should be evaluated and managed 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<sup>b</sup> 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 bone marrow 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 fusion gene rearrangements or other cytogenetic abnormality ([See MLNE-3](#)).
- Immunohistochemistry (IHC) for tryptase/CD117/CD25 and molecular testing for *KIT* D816V<sup>c</sup>
- 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<sup>d</sup>

See Workup ([MLNE-2](#)) and Diagnostic Testing Algorithms ([MLNE-3](#))

1 major + 1 minor, or ≥3 minor criteria for SM satisfied

SM ([See NCCN Guidelines for Systemic Mastocytosis](#))

Other clonal cytogenetic or molecular abnormality or excess blasts (≥5% to <20%)

CEL-NOS<sup>e</sup>

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

<sup>a</sup>This diagnostic algorithm excludes conditions associated with secondary (reactive) eosinophilia ([see MLNE-A](#)); includes eosinophilia associated with non-myeloid malignancies such as T-cell lymphoma, Hodgkin lymphoma, and ALL.

<sup>b</sup>Generally, absolute eosinophil count ≥1.5 × 10<sup>9</sup>/L.

<sup>c</sup>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](#).

<sup>d</sup>The diagnosis is based on the 2017 WHO Classification and requires a combination of histopathologic, clinical, laboratory, and cytogenetic/molecular analyses. [See 2017 WHO Diagnostic Criteria for Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Gene Rearrangement \(MLNE-B\)](#).

<sup>e</sup>Additional cytogenetic or molecular testing may be required to confirm the differential diagnosis of clonal hematopoiesis of indeterminate potential (CHIP) vs. CEL-NOS.

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# NCCN Guidelines Version 4.2021

## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

### WORKUP

#### General Diagnostic Studies

- History and physical (H&P) 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 ([See MLNE-A](#)).
- 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, vitamin B12, 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 RT-PCR<sup>f</sup> (RT-qPCR)
- Confirmatory FISH (PB or BM) if chromosome analysis reveals the following breakpoints: 4q12 (*PDGFRA*);<sup>g</sup> 5q31~33 (*PDGFRB*);<sup>h</sup> 8p11~12 (*FGFR1*); 9p24 (*JAK2*); 9q34 (*ABL1*); and 13q12 (*FLT3*)<sup>i</sup>
- 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])<sup>i,j</sup>

#### Evaluation of Target Organ Involvement<sup>k</sup>

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

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

- See Diagnostic Testing Algorithms for Tyrosine Kinase Fusion Gene Rearrangements ([MLNE-3](#))
- See Diagnosis and Staging Considerations in Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes ([MLNE-4](#))

<sup>f</sup>Testing for imatinib-sensitive TK fusion gene rearrangements by PB is feasible and appropriate in certain clinical circumstances. [See Principles of Cytogenetic and Molecular Testing for Myeloid/Lymphoid Neoplasms with Eosinophilia \(MLNE-C\)](#).

<sup>g</sup>The overwhelming majority of *PDGFRA* fusions are represented by *FIP1L1-PDGFRB*, which is cytogenetically occult and requires FISH for the detection of *CHIC2* deletion for initial screening.

<sup>h</sup>In rare cases, cryptic *PDGFRB* rearrangements have been found, and FISH may be used to uncover, not only confirm *PDGFRB* rearrangements.

<sup>i</sup>RT-PCR may be preferred over NGS for *FLT3*.

<sup>j</sup>[See Role of NGS in the Diagnosis of Myeloid/Lymphoid Neoplasms with Eosinophilia \(MLNE-D\)](#).

<sup>k</sup>Consultation with specialized referral services is recommended for the management of relevant target end-organ damage.

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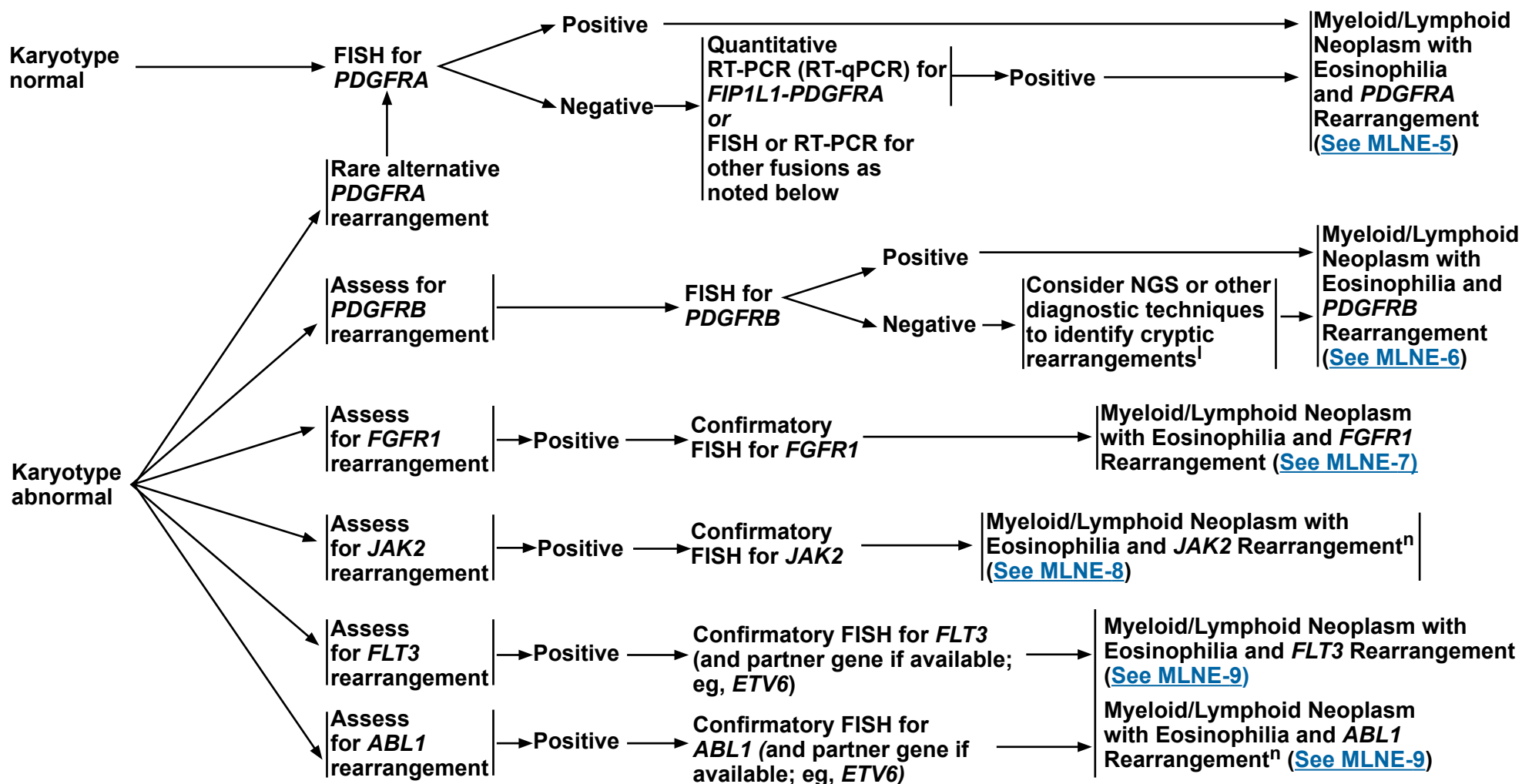




# NCCN Guidelines Version 4.2021

## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

### DIAGNOSTIC TESTING ALGORITHMS FOR TYROSINE KINASE FUSION GENE REARRANGEMENTS<sup>l,m</sup>



<sup>l</sup>See [Diagnosis and Staging Considerations in Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes \(MLNE-4\)](#).

<sup>m</sup>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 \(MLNE-C\)](#).

<sup>n</sup>The differential diagnosis of *JAK2* and *ABL1* fusions with a phenotype of ALL includes Ph-like ALL.

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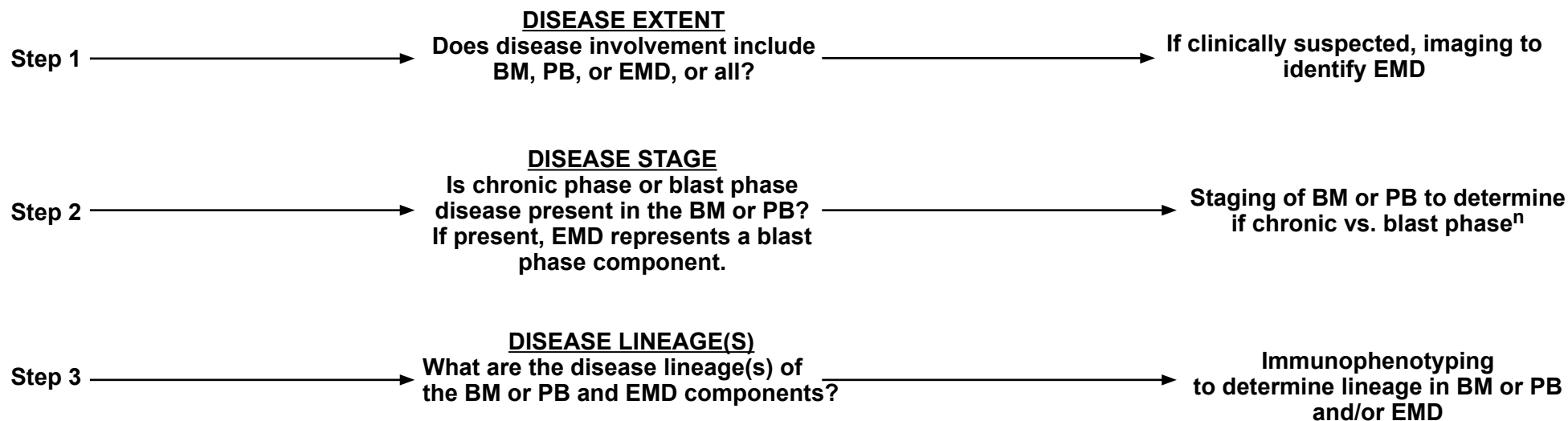


# NCCN Guidelines Version 4.2021

## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

### DIAGNOSIS AND STAGING CONSIDERATIONS IN MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND TYROSINE KINASE FUSION GENES<sup>d,o</sup>

- 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 ( $\geq 20\%$  blasts) may present in the BM or PB as AML, ALL,<sup>n</sup> or mixed lineage acute leukemia. 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."<sup>p</sup>
- EMD may present as extramedullary myeloid sarcoma, T-cell or B-cell lymphoblastic lymphoma, or myeloid/T-cell or B-cell lymphoid mixed lineage blast phase disease. 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 tyrosine kinase. This is best exemplified by the diverse phenotypes in *FGFR1*-rearranged diseases.



<sup>d</sup>The diagnosis is based on the 2017 WHO Classification and requires a combination of histopathologic, clinical, laboratory, and cytogenetic/molecular analyses. [See 2017 WHO Diagnostic Criteria for Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Gene Rearrangement \(MLNE-B\).](#)

<sup>n</sup>The differential diagnosis of *JAK2* and *ABL1* fusions with a phenotype of ALL includes Ph-like ALL.

<sup>o</sup>Eosinophilia is not invariably present.

<sup>p</sup>There is no current definition for "accelerated phase" disease; however, similar to myeloid neoplasms such as CML, 10%–19% blasts in the BM or PB have been used to define "accelerated phase."

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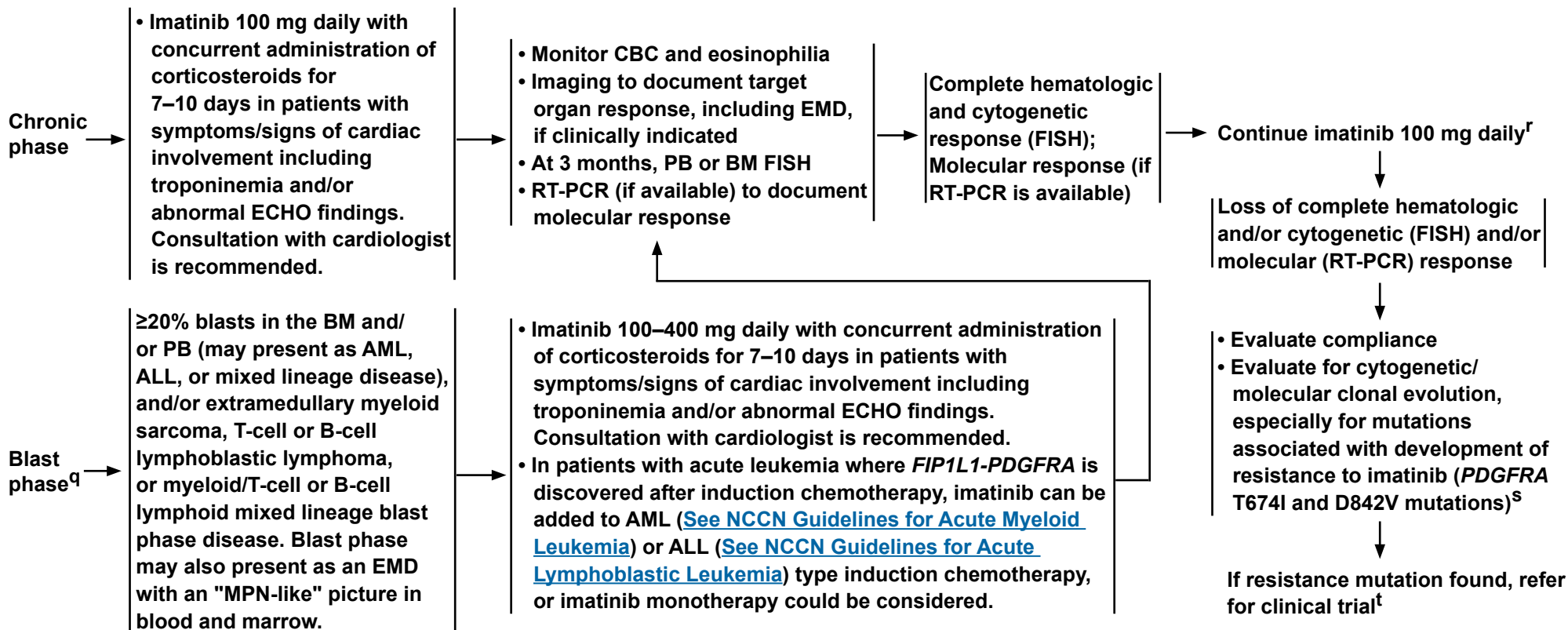
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# NCCN Guidelines Version 4.2021

## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

### MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND THE *FIP1L1-PDGFR*A REARRANGEMENT<sup>1</sup>



<sup>1</sup>See [Diagnosis and Staging Considerations in Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes \(MLNE-4\)](#).

<sup>q</sup>The *FIP1L1-PDGFR*A 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 (*PDGFR*A T674I and D842V).

<sup>r</sup>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.

<sup>s</sup>*PDGFR*A T674I and D842V mutations are resistant to imatinib.

<sup>t</sup>Avapritinib is approved for advanced systemic mastocytosis (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 *PDGFR*A exon 18 mutation, including D842V mutations. This suggests a possible role for avapritinib in patients with *FIP1L1-PDGFR*A-positive myeloid/lymphoid neoplasms with eosinophilia harboring *PDGFR*A D842V mutation resistant to imatinib. If this mutation is identified, a clinical trial of avapritinib is preferred (if available), rather than off-label use.

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

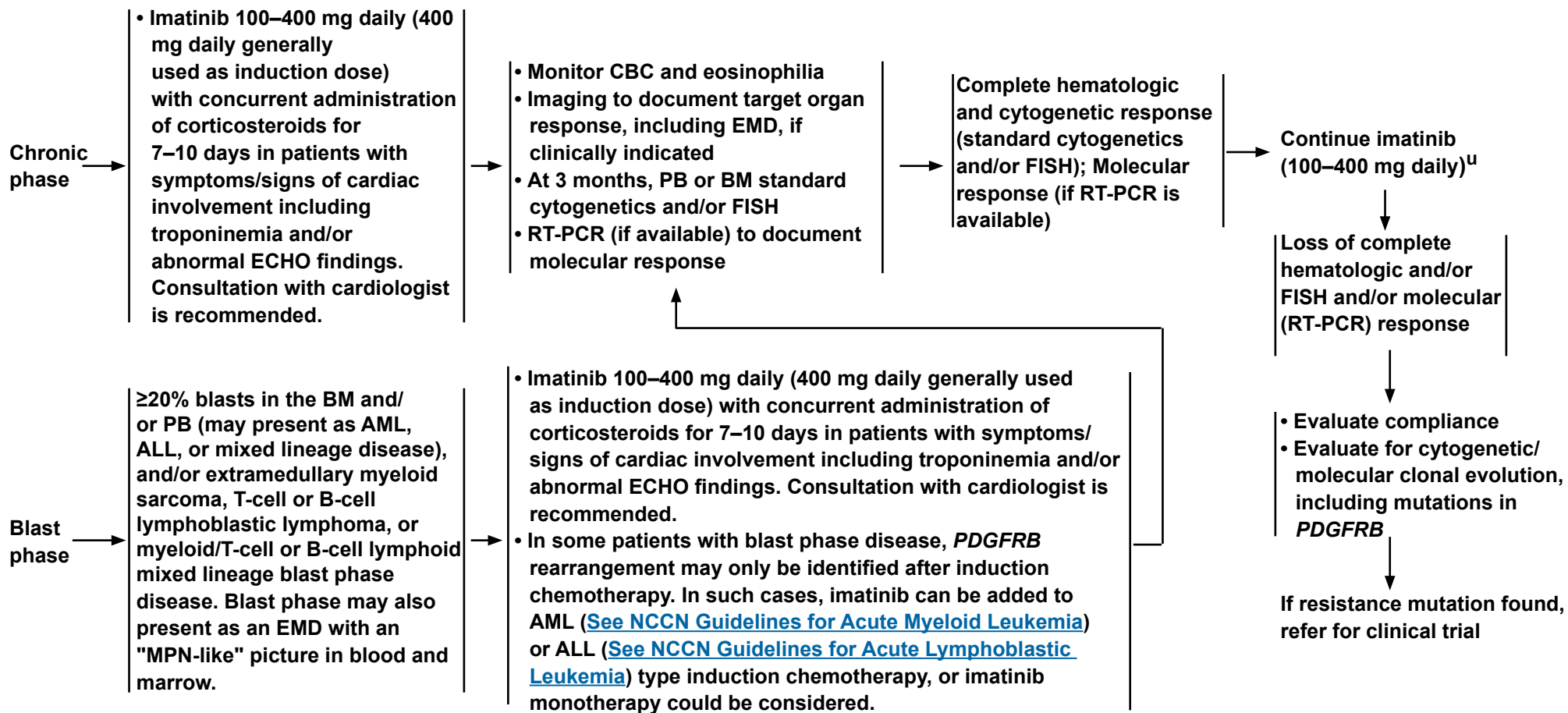
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



# NCCN Guidelines Version 4.2021

## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

### MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND *PDGFRB* REARRANGEMENT<sup>1,0</sup>



<sup>1</sup>See [Diagnosis and Staging Considerations in Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes \(MLNE-4\)](#).

<sup>0</sup>Eosinophilia is not invariably present.

<sup>u</sup>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.

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# NCCN Guidelines Version 4.2021

## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

### MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND *FGFR1* REARRANGEMENT<sup>1,0</sup>

#### 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, including cytogenetics/FISH, and if available, RT-PCR for *FGFR1* 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

#### Chronic phase

#### Blast phase

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

#### TREATMENT OPTIONS

##### Preferred regimen:

Clinical trial<sup>V</sup>

##### Other recommended regimens:

TKI with activity against *FGFR1* (eg, pemigatinib<sup>V</sup> or midostaurin or ponatinib)

Consider early referral to allogeneic HCT (if eligible)

##### Preferred regimen:

Clinical trial<sup>V</sup> and

Consider early referral to allogeneic HCT (if eligible)

##### Other recommended regimens:

Myeloid → TKI with activity against *FGFR1* (eg, pemigatinib<sup>V</sup> or midostaurin or ponatinib) ± AML-type induction chemotherapy (See [NCCN Guidelines for Acute Myeloid Leukemia](#)) followed by allogeneic HCT (if eligible)

Mixed Lineage → TKI with activity against *FGFR1* (eg, pemigatinib<sup>V</sup> or midostaurin or ponatinib) ± ALL-type induction chemotherapy (See [NCCN Guidelines for Acute Lymphoblastic Leukemia](#)) followed by allogeneic HCT (if eligible)

Lymphoid → TKI with activity against *FGFR1* (eg, pemigatinib<sup>V</sup> or midostaurin or ponatinib) ± ALL-type induction chemotherapy (See [NCCN Guidelines for Acute Lymphoblastic Leukemia](#)) followed by allogeneic HCT (if eligible)

<sup>1</sup>See [Diagnosis and Staging Considerations in Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes \(MLNE-4\)](#).

<sup>0</sup>Eosinophilia is not invariably present.

<sup>V</sup>Pemigatinib (FGFR1, 2, and 3 inhibitor) is approved for the treatment of adult patients with previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma and a *FGFR2* fusion or other rearrangement, as detected by an FDA-approved test. Pemigatinib has received orphan drug designation for the treatment of patients with myeloid/lymphoid neoplasms with eosinophilia and *FGFR1* rearrangement and is currently being evaluated in a clinical trial for this indication. A clinical trial of pemigatinib is preferred (if available), rather than off-label use (Hoy SM. *Drugs* 2020;80:923-929; Verstovsek S, et al. *Blood* 2018;132:Abstract 690).

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# NCCN Guidelines Version 4.2021

## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

### MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND *JAK2* REARRANGEMENT<sup>1,n,o,w</sup>

#### 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, 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

#### Chronic phase

#### Blast phase

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

#### TREATMENT OPTIONS

##### Preferred regimen:

Clinical trial

##### Other recommended regimens:<sup>x</sup>

TKI with activity against *JAK2* (ruxolitinib or fedratinib)

Consider early referral to allogeneic HCT (if eligible)

##### Preferred regimen:

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

##### Other recommended regimens:<sup>x</sup>

Myeloid → TKI with activity against *JAK2* (ruxolitinib or fedratinib) ± AML-type induction chemotherapy (See [NCCN Guidelines for Acute Myeloid Leukemia](#)) followed by allogeneic HCT (if eligible)

Mixed Lineage

Lymphoid → TKI with activity against *JAK2* (ruxolitinib or fedratinib) ± ALL-type induction chemotherapy (See [NCCN Guidelines for Acute Lymphoblastic Leukemia](#)) followed by allogeneic HCT (if eligible)

<sup>1</sup>See [Diagnosis and Staging Considerations in Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes \(MLNE-4\)](#).

<sup>n</sup>The differential diagnosis of *JAK2* and *ABL1* fusions with a phenotype of ALL includes Ph-like ALL.

<sup>o</sup>Eosinophilia is not invariably present.

<sup>w</sup>Only myeloid/lymphoid neoplasms with *PCM-JAK2* are included in the 2017 WHO classification as a provisional entity (see [MLNE-B](#)). Other *JAK2* rearrangements are considered variants.

<sup>x</sup>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.

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# NCCN Guidelines Version 4.2021

## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

### MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND *ABL1* OR *FLT3* REARRANGEMENT<sup>l,n,o</sup>

#### 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, 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

##### Chronic phase

##### Blast phase

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

#### TREATMENT OPTIONS

##### Preferred regimen:

Clinical trial

##### Other recommended regimens:

TKI with activity against *ABL1* or *FLT3*

Consider early referral to allogeneic HCT (if eligible)

TKI with activity against <i>ABL1</i>	TKI with activity against <i>FLT3</i>
<b>Preferred regimens:</b> <ul style="list-style-type: none"> <li>• Dasatinib<sup>y</sup></li> <li>• Nilotinib<sup>y</sup></li> </ul> <b>Other recommended regimens:</b> <ul style="list-style-type: none"> <li>• Imatinib</li> <li>• Bosutinib</li> <li>• Ponatinib</li> </ul>	<ul style="list-style-type: none"> <li>• Gilteritinib</li> <li>• Midostaurin</li> <li>• Sorafenib</li> <li>• Sunitinib</li> </ul>

##### 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 (See [NCCN Guidelines for Acute Myeloid Leukemia](#)) followed by allogeneic HCT (if eligible)
- Mixed Lineage → TKI with activity against *ABL1* or *FLT3* ± ALL-type induction chemotherapy (See [NCCN Guidelines for Acute Lymphoblastic Leukemia](#)) followed by allogeneic HCT (if eligible)
- Lymphoid → TKI with activity against *ABL1* or *FLT3* ± ALL-type induction chemotherapy (See [NCCN Guidelines for Acute Lymphoblastic Leukemia](#)) followed by allogeneic HCT (if eligible)

<sup>l</sup>See [Diagnosis and Staging Considerations in Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes \(MLNE-4\)](#).

<sup>n</sup>The differential diagnosis of *JAK2* and *ABL1* fusions with a phenotype of ALL includes Ph-like ALL.

<sup>o</sup>Eosinophilia is not invariably present.

<sup>y</sup>Schwaab J, et al. Am J Hematol 2020;95:824-833.

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# NCCN Guidelines Version 4.2021

## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

### CAUSES OF SECONDARY (REACTIVE) EOSINOPHILIA<sup>1,2</sup>

Category	Examples
<b>Infections</b>	Parasitic (strongyloidiasis, <i>Toxocara canis</i> , <i>Trichinella spiralis</i> , schistosomiasis, <i>Echinococcus</i> , entamoeba, cystoisospora, ascaris, <i>Ancylostoma duodenale</i> [hookworm], <i>Toxoplasma gondii</i> , <i>Fasciola hepatica</i> , paragonimus, clonorchis, filariasis) Viral (HIV, herpes simplex [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.
<b>Allergic/hypersensitivity diseases</b>	Asthma, rhinitis, allergic rhinitis, bronchopulmonary aspergillosis, allergic gastroenteritis
<b>Pulmonary diseases</b>	Bronchiectasis, cystic fibrosis, chronic eosinophilic pneumonia, Löffler's syndrome
<b>Cardiac diseases</b>	Tropical endocardial fibrosis, eosinophilic endomyocardial fibrosis or myocarditis
<b>Skin diseases</b>	Atopic dermatitis, urticaria, eczema, bullous pemphigoid, dermatitis herpetiformis, episodic angioedema with eosinophilia (Gleich syndrome)
<b>Connective tissue/autoimmune diseases</b>	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
<b>Medications</b>	Aspirin, NSAIDs, antimicrobials, DRESS syndrome
<b>Malignancies</b>	Solid tumors (eg, renal, lung, breast, vascular neoplasms, female genital tract cancers), Hodgkin and non-Hodgkin lymphoma, acute lymphoblastic leukemia, Langerhans cell histiocytosis, angiolymphoid hyperplasia with eosinophilia (Kimura disease)
<b>Metabolic</b>	Adrenal insufficiency
<b>Immune system diseases</b>	Hyper IgE syndrome, Omenn syndrome, Wiskott-Aldrich syndrome, IgA deficiency
<b>Other</b>	Acute/chronic graft versus host disease, solid organ rejection, cholesterol emboli, L-tryptophan ingestion, IL-2 therapy, toxic oil syndrome

<sup>1</sup>Gotlib J, Cools J, Malone JM 3rd, et al. The FIP1L1-PDGFRalpha fusion tyrosine kinase in hypereosinophilic syndrome and chronic eosinophilic leukemia: implications for diagnosis, classification, and management. *Blood* 2004;103:2879-2891.

<sup>2</sup>Shomali W, Gotlib J. World Health Organization-defined eosinophilic disorders: 2019 update on diagnosis, risk stratification, and management. *Am J Hematol* 2019;94:1149-1167.

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**MLNE-A**





# NCCN Guidelines Version 4.2021

## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

### 2017 WHO DIAGNOSTIC CRITERIA FOR MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND REARRANGEMENT OF *PDGFRA*, *PDGFRB*, OR *FGFR1*, OR WITH *PCM1-JAK2*<sup>1</sup>

#### **Myeloid/Lymphoid Neoplasms with Eosinophilia Associated with *FIP1L1-PDGFR* or a Variant Fusion Gene\***

A myeloid or lymphoid neoplasm, usually with prominent eosinophilia

and

Presence of a *FIP1L1-PDGFR* fusion gene or a variant fusion gene with rearrangement of *PDGFRA* or an activating mutation of *PDGFRA*<sup>†</sup>

#### **Myeloid/Lymphoid Neoplasms with Eosinophilia Associated with *ETV6-PDGFRB* or Other Rearrangement of *PDGFRB*‡**

A myeloid or lymphoid neoplasm, often with prominent eosinophilia and sometimes with neutrophilia or monocytosis

and

Presence of t(5;12)q31~q33;p13) or a variant translocation<sup>¶</sup> or demonstration of an *ETV6-PDGFRB* fusion gene or other rearrangement of *PDGFRB*

#### **Myeloid/Lymphoid Neoplasms with Eosinophilia Associated with *FGFR1* Rearrangement**

A myeloproliferative or myelodysplastic/myeloproliferative neoplasm with prominent eosinophilia, and sometimes with neutrophilia or monocytosis

or

Acute myeloid leukemia or T-cell or B-cell lymphoblastic leukemia/lymphoma or mixed phenotype acute leukemia (usually associated with peripheral blood or bone marrow eosinophilia)

and

Presence of t(8;13)(p11;q12) or a variant translocation leading to *FGFR1* rearrangement demonstrated in myeloid cells, lymphoblasts, or both

#### **Myeloid/Lymphoid Neoplasms with Eosinophilia Associated with *PCM1-JAK2* Rearrangement**

A myeloid or lymphoid neoplasm, often with prominent eosinophilia

and

Presence of t(8;9)(p22;p24.1) or a variant translocation leading to *JAK2* rearrangement<sup>§</sup>

\*Patients presenting with myeloproliferative neoplasm, acute myeloid leukemia, or lymphoblastic leukemia/lymphoma with eosinophilia and a *FIP1L1-PDGFR* fusion gene are also assigned to this category.

<sup>†</sup>If appropriate molecular analysis is not possible, this diagnosis should be suspected if there is a Ph-chromosome–negative myeloproliferative neoplasm with the hematologic features of chronic eosinophilic leukemia associated with splenomegaly, a marked elevation of serum vitamin B12, elevation of serum tryptase, and an increased number of bone marrow mast cells.

<sup>‡</sup>Cases with fusion genes typically associated only with *BCR-ABL1*-like B-lymphoblastic leukemia are specifically excluded.

<sup>¶</sup>Because t(5;12)(q31;q33;p12) does not always lead to an *ETV6-PDGFRB* fusion gene, molecular confirmation is highly desirable. If molecular analysis is not possible, this diagnosis should be suspected if there is a Ph chromosome–negative myeloproliferative neoplasm associated with eosinophilia and with a translocation with a 5q31;33 breakpoint

<sup>§</sup>Other variants giving rise to a fusion gene between *JAK2* and an alternative partner include *ETV6-JAK2* [t(9;12)(p24.1;p13.2)] or *BCR-JAK2* [t(9;22)(p24.1;q11.2)].

<sup>1</sup>Reprinted from 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.

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# NCCN Guidelines Version 4.2021

## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

### PRINCIPLES OF CYTOGENETIC AND MOLECULAR TESTING IN MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND TYROSINE KINASE FUSION GENES

See Table 1. TK Fusion Genes in Myeloid/Lymphoid Neoplasms with Eosinophilia ([MLNE-C, 3 of 5](#)) and Table 2. Diagnostic Assays for the Detection of TK Fusion Genes in Myeloid/Lymphoid Neoplasms ([MLNE-C, 4 of 5](#))

#### **PDGFRA-Rearranged Eosinophilia:**

The *FIP1L1-PDGFRA* rearrangement is found in approximately 10% of patients with idiopathic eosinophilia.<sup>1-4</sup> Elevated serum vitamin B12 levels, 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*.<sup>5,6</sup> 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/or vitamin B12) and for detecting minimal residual disease (MRD). Although not widely available, chromosome genomic array testing (CGAT, also known as CMA, SNP-A, or aCGH) can readily detect submicroscopic deletions at diagnosis when a clone size is at least 20%.

Other rarer partner fusion genes for *PDGFRA* have been described (eg, *BCR*, *ETV6*, *KIF5B*, *CDK5RAP2*, *STRN*, *TNKS2*, and *FOXP1*).<sup>2,7</sup> 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.<sup>8</sup>

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 *FIP1L1-PDGFRA*-negative hypereosinophilic syndrome (HES) cases and some are implicated in disease pathogenesis and may be imatinib responsive.<sup>9</sup>

#### **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.<sup>4,6,7,10</sup> The breakpoints in *PDGFRB* are located in the chromosomal region 5q31~q33. In addition to *ETV6*, more than 30 different partner fusion genes for *PDGFRB* rearrangements have been described. Fusion genes typically associated with *BCR-ABL1*-like B-cell ALL are specifically excluded from this category (eg, *EBF1*-, *SSBP2*-, *TNIP1*-, *ZEB2*-, and *ATF7IP-PDGFRB* fusions). Rare cases with normal karyotype have been demonstrated to harbor *PDGFRB* rearrangements (eg, *TNIP1-PDGFRB* in MPN with eosinophilia).

[Continued](#)

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# NCCN Guidelines Version 4.2021

## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

### PRINCIPLES OF CYTOGENETIC AND MOLECULAR TESTING IN MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND TYROSINE KINASE FUSION GENES

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

Not all cases 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 fusion 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.<sup>3,6</sup>

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 fusion 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, 15 partner fusion genes with *FGFR1* have been described.<sup>4,6,7</sup> 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.<sup>4,6,7</sup>

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

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

*ETV6-ABL1* [t(9;12)(q34;p13)] is the fusion gene involved in the majority of cases with *ABL1* rearrangement.<sup>7</sup> Other complex rearrangements have also been reported. Routine karyotyping can be inconclusive and FISH can miss small insertions. FISH with *ETV6* and *ABL1* probes, RT-PCR, or RNA sequencing are more reliable for the identification of *ETV6-ABL1* rearrangement.<sup>7,11</sup>

[Continued](#)

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# NCCN Guidelines Version 4.2021

## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

### PRINCIPLES OF CYTOGENETIC AND MOLECULAR TESTING IN MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND TYROSINE KINASE FUSION GENES

Table 1. TK Fusion Genes in Myeloid/Lymphoid Neoplasms with Eosinophilia

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

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

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

**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



# NCCN Guidelines Version 4.2021

## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

### PRINCIPLES OF CYTOGENETIC AND MOLECULAR TESTING IN MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND TYROSINE KINASE FUSION GENES

Table 2. Diagnostic Tests for the Detection of TK Fusion Genes in Myeloid/Lymphoid Neoplasms

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

<sup>a</sup>FISH for the *CHIC2* deletion is used to diagnose the *FIP1L1-PDGFRA* fusion.

<sup>b</sup>*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.

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# NCCN Guidelines Version 4.2021

## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

### PRINCIPLES OF CYTOGENETIC AND MOLECULAR TESTING IN MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND TYROSINE KINASE FUSION GENES

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- <sup>3</sup>Boyer DF. Blood and bone marrow evaluation for eosinophilia. *Arch Pathol Lab Med* 2016;140:1060-1067.
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# NCCN Guidelines Version 4.2021

## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

### ROLE OF NGS IN THE DIAGNOSIS OF MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND TYROSINE KINASE FUSION GENES

- **NGS studies have identified driver mutations involving a broad spectrum of genes most frequently involved in DNA methylation/chromatin modification.**<sup>1-3</sup> 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).<sup>1,4,5</sup>
- **Mutations detected by NGS may also provide a means to identify primary (clonal/neoplastic) eosinophilia from secondary (reactive) eosinophilia, including in cases 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.**<sup>6</sup>
- **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.**<sup>7</sup> The mutations detected were *ASXL1*, *BCOR*, *DNMT3A*, *TET2*, *RUNX1*, *ETV6*, *NRAS*, *STAT5B*, and *ZRSR2*. Multiple mutations were identified in 3 cases, and *RUNX1* was found to be recurrently mutated (6 of 19 mutations detected) and was detected in 5 of 6 cases 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 fusion gene 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 needs to be determined, including whether specific variants could be CHIP mutations.**

#### References

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- <sup>7</sup>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.**

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# NCCN Guidelines Version 4.2021

## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

### NCCN Categories of Evidence and Consensus

<b>Category 1</b>	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
<b>Category 2A</b>	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
<b>Category 2B</b>	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
<b>Category 3</b>	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

### NCCN Categories of Preference

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

All recommendations are considered appropriate.





# NCCN Guidelines Version 4.2021 Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

This discussion corresponds to the NCCN Guidelines for Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes. Last updated: July 9<sup>th</sup>, 2021.

## Discussion

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## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

### 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.<sup>1-3</sup>

Hypereosinophilia (HE) is defined as persistent elevated eosinophil count  $>1.5 \times 10^9/L$  in blood and/or tissue and is divided into four variant types per an international consensus proposal: hereditary (familial), HE<sub>FA</sub>; primary (clonal/neoplastic), HE<sub>N</sub>; secondary (reactive), HE<sub>R</sub>; and HE of undetermined significance, HE<sub>US</sub>.<sup>4</sup> 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.<sup>4</sup> The international consensus criteria, definition and classification of HE, HES and other conditions accompanied by HE are outlined in [Table 1](#) and [Table 2](#).

Primary (clonal/neoplastic) HE (HE<sub>N</sub>) is characterized by neoplastic proliferation of eosinophils and can be associated with any of the WHO-defined myeloid and/or lymphoid neoplasms.<sup>4</sup> A number of dysregulated tyrosine kinase (TK) fusion genes have been implicated in the pathogenesis of myeloid/lymphoid neoplasms with eosinophilia (MLN-Eo).<sup>5-7</sup>

In 2008, the WHO classification of eosinophilic disorders was revised to include clonal/neoplastic eosinophilia resulting from TK fusion gene rearrangements as a new category termed, “Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB* or *FGFR1*.”<sup>8</sup> In the 2017 WHO classification, myeloid/lymphoid neoplasms with *PCM1-JAK2* rearrangement was added as a provisional entity.<sup>9-11</sup> In addition to these aforementioned TK fusion genes, rearrangements

involving *FLT3* and *ABL1* genes have also been described in MLN-Eo, but have not yet been formally added to the WHO classification.<sup>6</sup>

Myeloproliferative neoplasms (MPNs) with peripheral blood eosinophilia (eosinophil count  $>1.5 \times 10^9/L$ ) that lack all of the aforementioned TK fusion genes 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, not otherwise specified (CEL, NOS) in the absence of another WHO-defined myeloid neoplasm.<sup>11</sup>

The identification of specific TK fusion genes and the emergence of tyrosine kinase inhibitors (TKIs) has significantly improved the diagnosis and treatment of some patients with MLN-Eo.<sup>12</sup> The management of patients with MLN-Eo requires a multidisciplinary team approach, preferably in specialized medical centers.

The NCCN Guidelines® for Myeloid/Lymphoid Neoplasms with Eosinophilia and TK Fusion Genes include recommendations for the diagnosis, staging, and treatment of any one of the MLN-Eo associated with a TK fusion gene included in the 2017 WHO Classification, as well as MLN-Eo with a *FLT3* or *ABL1* rearrangement.

### Literature Search Criteria and Guidelines Update Methodology

Prior to the development of NCCN Guidelines® for Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase fusion genes, an electronic search of the PubMed database was performed to obtain key literature in the last 10 years, 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 only peer-reviewed biomedical literature.<sup>13</sup>



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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; 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 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.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN [webpage](#).

### Diagnostic Criteria

The diagnosis requires the presence of a TK fusion gene rearrangement confirmed by cytogenetic and/or molecular testing (See *Cytogenetic and Molecular Testing* in this discussion on MS-8).<sup>11</sup>

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-PDGFR*, it is not invariably present in patients with a *PDGFRB*, *FGFR1*, *JAK2*, *FLT3*, or *ABL1* rearrangement.<sup>5</sup> Patients also present with other blood count abnormalities, and organ damage may develop irrespective of the underlying TK fusion gene. See *Clinical Presentation* in this discussion on MS-4.

The clinical phenotype of MLN-Eo is driven by the TK (eg, *PDGFRA*, *PDGFRB*, *FGFR1*, *JAK2*, *FLT3*, *ABL1*) as well as the partner gene. A large number of variant fusion partner genes (>70) have been characterized to date.<sup>5-7</sup> See *Table 1. TK Fusion Genes in Myeloid/Lymphoid Neoplasms with Eosinophilia* in the algorithm.

### Myeloid/Lymphoid Neoplasms with Eosinophilia and *FIP1L1-PDGFR* Rearrangement

The diagnosis requires the presence of *FIP1L1-PDGFR* fusion gene (resulting from an interstitial deletion of *CHIC2* gene on chromosome 4q12) or a *PDGFR* rearrangement with a variant fusion gene or an activating *PDGFR* mutation.<sup>11,14-16</sup> 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, a marked elevation of serum vitamin B12, elevation of serum tryptase, and an increased number of mast cells and/or fibrosis in the bone marrow.<sup>5,7,17</sup> MLN-Eo with *FIP1L1-PDGFR* 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 absent.<sup>17</sup>

CEL is the most common clinical presentation. Blast phase MPN, acute myeloid leukemia (AML), and rarely T-cell acute lymphoblastic lymphoma (T-ALL) or myeloid sarcoma have also been described.<sup>5,18,19</sup> Pediatric cases have also been reported.<sup>20-23</sup>

### 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 *ETV6-PDGFRB* fusion gene or a *PDGFRB* rearrangement with a variant fusion gene.<sup>11,24</sup> Cases with fusion genes typically associated only with *BCR-ABL1*-like B-cell lymphoblastic leukemia are specifically excluded.



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## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

Chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia (CML), MPN, MDS/MPN, juvenile myelomonocytic leukemia (JMML), and blast-phase disease involving the bone marrow and/or extramedullary disease (EMD) involving myeloid, lymphoid, or mixed lineages are the clinical presentations associated with MLN-Eo and *PDGFRB* rearrangement.<sup>5,25</sup> 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.<sup>11,26,27</sup>

MLN-Eo 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.<sup>5,28</sup>

MPN or MDS/MPN with eosinophilia are the most common myeloid neoplasms associated with *FGFR1*-rearranged eosinophilia. *FGFR1-ZMYM2* fusion gene and t(8;13) are associated with high incidence of T-ALL.<sup>6</sup> De novo AML, B-cell lymphoblastic leukemia/lymphoma or mixed phenotype acute leukemia (usually associated with peripheral blood or bone marrow eosinophilia), and/or EMD of myeloid, lymphoid, or mixed lineage have also been described in some cases.<sup>5,29</sup>

### Myeloid/Lymphoid Neoplasms with Eosinophilia and *PCM1-JAK2* Rearrangement

This is 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.<sup>9-11</sup>

MLN-Eo with *PCM1-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.<sup>9,10</sup>

MPN or MDS/MPN with eosinophilia is the characteristic clinical presentation and de-novo AML or ALL has been described in some patients.<sup>9,10</sup> 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

This category has not been formally added to the WHO classification. 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.<sup>30</sup>

MLN-Eo with *FLT3* or *ABL1* rearrangement is generally associated with an aggressive clinical course, disease progression, or relapse. CEL-NOS is the characteristic clinical presentation in MLN-Eo with *FLT3* rearrangement. Peripheral T-cell lymphoma or T-ALL have also been described.<sup>6</sup> De novo ALL is the most common clinical presentation associated with *ABL1* rearrangement in children; AML and chronic myeloid/lymphoid phenotypes have been described in adults.<sup>31</sup> The differential diagnosis of *JAK2* and *ABL1* fusions with a phenotype of ALL includes Ph-like ALL.<sup>30</sup>

### 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.<sup>17</sup>



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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 ( $\geq 20\%$  blasts in the bone marrow and/or peripheral blood) may present as AML or ALL, or acute leukemias with mixed-lineage disease and/or extramedullary myeloid sarcoma, T-ALL, or B-cell acute lymphoblastic lymphoma (B-ALL). Blast phase may also present as an EMD with MPN-like features in bone marrow or peripheral blood. TK fusion genes have been identified in a number of cases where eosinophilia is concurrently diagnosed with T-cell lymphomas or blast phase acute leukemias of myeloid, lymphoid, or mixed lineage (de novo or secondary).<sup>6</sup>

EMD may present as extramedullary myeloid sarcoma, T-ALL or B-ALL, or myeloid/T- or B-cell lymphoid mixed-lineage 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.

MLN-Eo with TK fusion gene rearrangements are associated with a variety of symptoms related to the overproduction of cytokines, growth factors, and eosinophil-derived mediators.<sup>2</sup> The most common presenting signs and symptoms include weakness and fatigue, cough, dyspnea, myalgias or angioedema, rash or fever, and rhinitis.<sup>7</sup> 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).<sup>2,7</sup>

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.<sup>2</sup> 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.<sup>2,7</sup>

Endomyocardial thrombosis and fibrosis are often documented in primary (neoplastic) HES variants (HES<sub>N</sub>), particularly in association with the *FIP1L1-PDGFR*A fusion gene.<sup>2,7</sup> Imaging studies and organ-directed biopsy are useful for the documentation of target organ involvement.<sup>2</sup> See *Evaluation for Target Organ Involvement* in this discussion on MS-8.

### 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 secondary (reactive) HE (HE<sub>R</sub>) 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.<sup>1,3</sup> 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 secondary (reactive) HE (HE<sub>R</sub>) occurring in about 80% of cases, and parasitic infections represent the second most common cause.<sup>1,3</sup> 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.



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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]).<sup>1,3</sup> HES may also be associated with a wide spectrum of dermatologic conditions (eg, atopic dermatitis, urticaria, eczema).<sup>3</sup>

Secondary (reactive) HE (HE<sub>R</sub>) 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.<sup>3</sup> 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.<sup>3</sup> In myeloid malignancies (eg, CML, AML, advanced SM), HE may similarly develop. In some cases, 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 cases with MPN features such as splenomegaly or an increased serum tryptase or vitamin B12 level. While many of these cases are *FIP1L1-PDGFR*–positive, the term has not been formally recognized by the WHO classification.<sup>7</sup>

Lymphocyte-variant HES (L-HES) is characterized by clonal T-cells with an aberrant immunophenotype and is associated with increased number of eosinophils, elevated serum thymus and activation-related chemokine (TARC), and IgE levels (although these findings are neither sensitive nor specific).<sup>3,7,17</sup> 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 cases 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.<sup>17</sup> 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.<sup>32,33</sup>

A diagnosis of a primary (clonal/neoplastic) HE (HE<sub>N</sub>) 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 secondary (reactive) HE (HE<sub>R</sub>). Screening for TK fusion gene rearrangements (*PDGFRA*, *PDGFRB*, *FGFR1*, *JAK2*, *ABL1*, or *FLT3*) or other cytogenetic abnormality is recommended for patients with a suspected primary (clonal/neoplastic) HE (HE<sub>N</sub>).

The diagnosis of CEL, NOS should be considered in the absence of the aforementioned TK fusion gene rearrangements, 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).<sup>11</sup> Bone marrow morphology might be helpful to distinguish CEL, NOS from idiopathic HES.<sup>34</sup>



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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.<sup>35</sup> In patients with eosinophilia in whom causes for secondary (reactive) HE (HE<sub>R</sub>) 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.

A diagnosis of idiopathic HE (organ damage absent) is equivalent to the respective term, HE of undetermined significance (HE<sub>US</sub>) per international consensus criteria and HES (organ damage present) with no apparent underlying disease or syndrome is referred to as idiopathic HES.<sup>4</sup> These are diagnoses of exclusion that are assigned after ruling out primary (clonal/neoplastic) HE (HE<sub>N</sub>) and all possible causes of secondary (reactive) HE (HE<sub>R</sub>). NGS via myeloid mutation panels may also be useful to establish the clonality in selected circumstances where no TK fusion gene rearrangements are detected. Mutations detected by NGS may also provide a means to identify primary (clonal/neoplastic) HE (HE<sub>N</sub>) from secondary (reactive) HE (HE<sub>R</sub>). See *Role of NGS* below on MS-10.

### 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 exam, 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.<sup>5,17</sup> As previously noted, an elevated serum tryptase and/or vitamin B12 level is commonly observed in myeloproliferative variants of HE, particularly in myeloid neoplasms with a *PDGFRA* fusion gene.<sup>5,7,17</sup> 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.<sup>36-38</sup> Aspergillus-specific immunoglobulins and increased serum IgE are characteristic findings of ABPA.<sup>3</sup>

Laboratory testing should include complete blood count (CBC) with differential, comprehensive metabolic panel with uric acid, lactate dehydrogenase, and liver function tests, serum tryptase levels, and vitamin B12 levels. Peripheral blood smear should be reviewed for the evidence of other blood count abnormalities (eg, eosinophilia, dysplasia, monocytosis, circulating blasts).<sup>17</sup>

Additional laboratory testing may be considered based on the patient's history, symptoms, and findings on physical examination.<sup>7</sup> 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 fusion gene rearrangement; and confirmatory FISH testing



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to identify breakpoints associated with TK fusion gene rearrangements is recommended for all patients to confirm the diagnosis of myeloid/lymphoid neoplasms.<sup>11,17</sup>

The diagnostic testing algorithms for TK fusion gene rearrangements are outlined in MLNE-3. See also the section below on *Cytogenetic and Molecular Testing* (MS-8). 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-.<sup>17</sup> 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.<sup>17</sup> *STAT3* mutation has also been recently identified in the CD3-, CD4+ T-cells in a patient with L-HES.<sup>39</sup>

### Evaluation of Target Organ Involvement

Electrocardiogram (ECG), cardiac troponin, and/or 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 distinguish eosinophilic cardiac disease from other etiologies.<sup>2</sup>

Pulmonary function tests, chest x-ray, and bronchoscopy with bronchoalveolar lavage are useful to confirm lung involvement in patients with respiratory symptoms.<sup>2</sup> Electromyography (EMG) 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 (ENT) symptoms.<sup>2</sup>

Organ-directed biopsy (skin, lung, or liver biopsy) with appropriate IHC is needed to confirm tissue eosinophilia and eosinophil-induced organ damage.<sup>2</sup> 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

#### *MLN-Eo with PDGFRA Rearrangement*

*FIP1L1-PDGFR*A is the most common fusion gene in MLN-Eo and results from an interstitial deletion of *CHIC2* gene on chromosome 4q12.<sup>14-16</sup> *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-PDGFR*A rearrangement.<sup>15,40</sup> Nested RT-PCR and quantitative RT-PCR (RT-qPCR) are more sensitive for the detection of *FIP1L1-PDGFR*A fusion gene in peripheral blood.<sup>5,16,40-42</sup>

*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 fusion gene rearrangements.<sup>5,6,16</sup> In addition to these rearrangements, several novel imatinib-sensitive point mutations in *PDGFRA* have also been identified in patients with *FIP1L1-PDGFR*A–negative HES.<sup>43</sup> These alternate *PDGFRA* rearrangements, like *FIP1L1-PDGFR*A, are associated with an excellent prognosis when treated with imatinib.





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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.<sup>44</sup> 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.<sup>45</sup> Therefore, a combination of RT-PCR and FISH is the most sensitive method for the detection of *FIP1L1-PDGFRB* 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.<sup>5</sup>

### ***MLN-Eo with PDGFRB Rearrangement***

*ETV6-PDGFRB* resulting from t(5;12)(q31-33;p13) is the most common fusion gene.<sup>24</sup> However, not all cases with t(5;12)(q31-33;p13) have a *PDGFRB* rearrangement, and fusion gene rearrangements involving non-TK genes in the 5q31~q33 region (eg, *IL-3* or *ACSL6*) have also been reported in cases with t(5;12)(q31-33;p13).<sup>46</sup> Identification of the fusion genes 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.<sup>5,47-49</sup> While the presence of *PDGFRB* fusion gene rearrangements 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 fusion gene.<sup>50</sup> 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.<sup>42,51</sup> However, the use of RT-PCR is limited by the large number of partner fusion genes. RNA sequencing may also be considered in cases with complex/cryptic fusions.<sup>52</sup>

### ***MLN-Eo with FGFR1 Rearrangement***

*FGFR1-ZMYM2* resulting from t(8;13)(p11;q12) is the most common fusion gene occurring in approximately 50% of cases.<sup>6,26,27</sup> Several other partner genes have been described. *FGFR1-CNTRL* [t(8;9)(p11;q33)], *FGFR1-FGFR1OP* [t(6;8)(q27;p11)], and *FGFR1-BCR* [t(8;22)(p11.2;q11.2)] are the other common fusion gene rearrangements occurring in about 10% to 29% of cases.<sup>5,6,27,53,54</sup> *RUNX1* mutations have also been reported in patients with acute leukemia and an *FGFR1* rearrangement confirmed by FISH.<sup>27</sup>

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* fusion gene and can be applied to other *FGFR1* rearrangements.<sup>5,27</sup>

### ***MLN-Eo with JAK2 Rearrangement***

*PCM1-JAK2* resulting from t(8;9)(p22;p24) is the most common fusion gene.<sup>6,10,55-57</sup> *ETV6-JAK2* [t(9;12)(p24;p13)] and *BCR-JAK2* [t(9;22)(p24;q11)] are the other fusion genes reported only in few patients.<sup>6,10,58-60</sup>



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As with other fusion gene rearrangements 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.<sup>6,10</sup>

### **MLN-Eo 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 fusion genes involved in the majority of cases.<sup>6,30,31,61</sup> *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.<sup>6,47,62-64</sup>

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.<sup>30</sup> However, conventional cytogenetics is inconclusive for the detection of *ETV6-ABL1*, mainly because the creation of the *ETV6-ABL1* fusion gene requires at least three chromosomal breaks and the fusion gene rearrangement is not uniform across cases and typically involves cryptic insertions that can be missed with routine cytogenetics.<sup>31</sup> 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.<sup>6,31</sup>

### **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.<sup>65-68</sup> In one study, myeloid neoplasm-related somatic mutations involving a single gene or  $\geq 2$  genes have been identified in 28%

of patients (14 out 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.<sup>66</sup> In another study, 53% of patients (16 out 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.<sup>67</sup> Somatic *STAT5B* N642H mutations were reported in 1.6% (27/1715) of patients with eosinophilia.<sup>68</sup> 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.<sup>68</sup> 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 MLN-Eo and rearrangement of *PDGFRA*, *PDGFRB*, *FGFR1*, or *PCM1-JAK2*.<sup>69-71</sup> In an analysis of 61 patients with MLN-Eo 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%).<sup>69</sup> Patients with *FGFR1* rearrangement had a significantly higher frequency of additional mutations (83%; 5 out of 6 patients; all had *RUNX1* mutation) in comparison to those with *PDGFRA* (14%; 5 out of 35 patients), *PDGFRB* (23%; 3 out of 13 patients), or *PCM1-JAK2* (14%; 1 out of 7 patients) rearrangements. NGS-based fusion gene 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-PDGFR* rearrangement.<sup>70</sup>



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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 managed by a multidisciplinary team (including engagement of other sub-specialists 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 IV 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 MLN-Eo and *PDGFRA* or *PDGFRB* rearrangement.<sup>19,25,33,72-84</sup> 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.<sup>75</sup>

Imatinib 100 mg daily is the recommended dose for induction therapy for chronic phase disease in patients with *FIP1L1-PDGFRB* rearrangement. Imatinib 100 mg to 400 mg daily is the recommended dose for chronic

phase 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.<sup>73</sup>

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-PDGFRB* 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.<sup>25,78</sup>

### 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.<sup>85</sup>

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-PDGFRB* 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.



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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 mg to 200 mg daily have been sufficient to maintain molecular remission in the majority of patients with *FIP1L1-PDGFR*A rearrangement, and in some cases this dose range has been used only once weekly,<sup>74</sup> higher doses (maximum of 400 mg daily) may be required for some patients.<sup>75,76</sup>

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 *PDGFR*A T674I and D842V mutations has been reported in few patients with blast phase disease.<sup>73,86</sup> Nilotinib, ponatinib, and sorafenib have shown limited activity in patients with *PDGFR*A T674I and D842V mutations.<sup>86-89</sup> *PDGFR*B 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 *PDGFR*B mutations has been described only in two case reports.<sup>90-92</sup> Evaluation for cytogenetic/molecular clonal evolution can identify *PDGFR*A (T674I and D842V) or *PDGFR*B mutations conferring resistance to imatinib in patients with loss of response. Referral to clinical is recommended, if resistance mutation found.

Avapritinib is approved for 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 *PDGFR*A exon 18 mutation, including D842V mutations.<sup>93-97</sup> This suggests a possible role for avapritinib in patients with MLN-Eo and

*PDGFR*A rearrangement harboring *PDGFR*A 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 MLN-Eo and *PDGFR*A rearrangement who have achieved CMR has been demonstrated mostly in retrospective studies in a limited number of patients.<sup>33,72,98,99</sup> 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. The feasibility of discontinuation of imatinib in patients with MLN-Eo and a *PDGFR*B 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 *FLT3* or *ABL1* Rearrangement

MLN-Eo with the above-mentioned TK fusion gene rearrangements are generally associated with an aggressive clinical course, relapse, or disease progression to blast phase and allogeneic HCT is the only potentially curative option.<sup>9,10,28,31,100</sup>

Clinical trial is the preferred treatment option for patients with chronic phase disease. 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 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.



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In the absence of a suitable clinical trial, TKI ± induction chemotherapy followed by allogeneic HCT is the appropriate treatment approach.



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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-lineage blast phase disease).

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 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.<sup>27,100-103</sup>

TKI with Activity Against <i>FGFR1</i>	TKI with Activity Against <i>JAK2</i>	TKI with Activity Against <i>FLT3</i>	TKI with Activity Against <i>ABL1</i> <sup>a</sup>
Pemigatinib <sup>b,104,105</sup> Midostaurin <sup>106</sup> Ponatinib <sup>27,89,102,107,108</sup>	Ruxolitinib <sup>103,109-111</sup> Fedratinib <sup>c</sup>	Gilteritinib <sup>c</sup> Midostaurin <sup>c</sup> Sorafenib <sup>101,112</sup> Sunitinib <sup>112</sup>	Dasatinib <sup>103</sup> Nilotinib <sup>103</sup> Imatinib <sup>103</sup> Bosutinib <sup>c</sup> Ponatinib <sup>c</sup>

a. Dasatinib or nilotinib are more effective than imatinib to induce durable complete remissions in patients with *ETV6-ABL1* fusion gene.<sup>103</sup>

b. Pemigatinib (FGFR inhibitor) is approved for the treatment of previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma with a *FGFR2* fusion or other rearrangement, (as detected by an FDA-approved test). It has received orphan drug designation for the treatment of patients with MLN-Eo and *FGFR1* rearrangement. It is currently being evaluated in a clinical trial for this indication and a clinical trial of pemigatinib is preferred (if available), rather than off-label use.

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 and ponatinib for CML).

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 rearrangement to document response (hematologic, cytogenetic, or molecular response) should be considered for all patients after initiation of treatment. However, it should be noted that there are no consensus response criteria for assessment of response.

Monitoring minimal residual disease (MRD) after allogeneic HCT and maintenance therapy with TKI (eg, ponatinib) or hypomethylating agent (eg, 5-azacytidine) has been shown to be effective for MLN-Eo with *FGFR1* rearrangement in single case reports.<sup>108,113</sup> 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.



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## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

**Table 1. Classification and Definition of Hypereosinophilia<sup>4</sup>**

Proposed Terminology	Proposed Abbreviation	Definition and Criteria
<b>Blood eosinophilia</b>	—	>0.5 eosinophils × 10 <sup>9</sup> /L blood
<b>Hypereosinophilia</b>	<b>HE</b>	>1.5 × 10 <sup>9</sup> /L eosinophils in the blood on 2 examinations (interval ≥1 month <sup>a</sup> ) and/or tissue HE defined by the following <sup>b</sup> <ol style="list-style-type: none"> <li>Percentage of eosinophils in bone marrow exceeds 20% of all nucleated cells; and/or</li> <li>Pathologist is of the opinion that tissue infiltration by eosinophils is extensive; and/or</li> <li>Marked deposition of eosinophil granule proteins is found (in the absence or presence of major tissue infiltration by eosinophils).</li> </ol>
• Hereditary (familial) HE	HE <sub>FA</sub>	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 <sub>US</sub>	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 <sup>c</sup>	HE <sub>N</sub>	Underlying stem cell, myeloid, or eosinophilic neoplasm, as classified by WHO criteria; eosinophils considered neoplastic cells <sup>d</sup>
• Secondary (reactive) HE <sup>c</sup>	HE <sub>R</sub>	Underlying condition/disease in which eosinophils are considered nonclonal cells; <sup>d</sup> HE considered cytokine-driven in most cases <sup>e</sup>
<b>Eosinophil-associated single-organ diseases</b>		Criteria of HE fulfilled and Single-organ disease

- In the case of evolving life-threatening end-organ damage, the diagnosis can be made immediately to avoid delay in therapy.
- 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.
- HE<sub>N</sub> and HE<sub>R</sub> are prediagnostic checkpoints that should guide further diagnostic evaluations but cannot serve as final diagnoses.
- 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.
- In a group of patients, HE<sub>R</sub> might be caused/triggered by other as yet unknown processes because no increase in eosinophilopoietic cytokine levels can be documented.

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## Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

**Table 2. Classification and Definition of Hypereosinophilic syndrome and conditions accompanied by HE<sup>a</sup>**

Proposed Terminology	Proposed Abbreviation	Definition and Criteria
<b>Hypereosinophilic syndrome</b> <ul style="list-style-type: none"> <li>• Idiopathic HES</li> <li>• Primary (neoplastic) HES</li> <li>• Secondary (reactive) HES</li> </ul>	<p style="text-align: center;"><b>HES</b></p> <p style="text-align: center;">—</p> <p style="text-align: center;">HES<sub>N</sub></p> <p style="text-align: center;">HES<sub>R</sub></p>	<p>Defined as blood HE with (plus) end-organ damage attributable to tissue HE:</p> <ol style="list-style-type: none"> <li>1. Criteria for peripheral blood HE fulfilled<sup>a</sup>; and</li> <li>2. Organ damage and/or dysfunction attributable to tissue HE;<sup>b</sup> and</li> <li>3. Exclusion of other disorders or conditions as major reason for organ damage</li> </ol> <p>No underlying cause of HE, no evidence of a reactive or neoplastic condition/disorder underlying HE and end-organ damage attributable to HE.</p> <p>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.<sup>c</sup></p> <p>Underlying condition/disease in which eosinophils are considered nonclonal cells; HE is considered cytokine driven, and end-organ damage is attributable to HE.</p> <p>Lymphoid variant HES<sup>d</sup> (clonal T-cells identified as the only potential cause) is a subvariant of secondary (reactive) HES</p>
<b>Other conditions and syndromes</b>		
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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