Myeloid/Lymphoid Neoplasms with Eosinophilia and TK Fusion Genes, Version 3.2021

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ABSTRACT

Eosinophilic disorders and related syndromes represent a heterogeneous group of neoplastic and nonneoplastic conditions, characterized by more eosinophils in the peripheral blood, and may involve eosinophil-induced organ damage. In the WHO classification of myeloid and lymphoid neoplasms, eosinophilic disorders characterized by dysregulated tyrosine kinase (TK) fusion genes are recognized as a new category termed, *myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB or FGFR1 or with PCM1-JAK2*. In addition to these aforementioned TK fusion genes, rearrangements involving *FLT3* and *ABL1* genes have also been described. These new NCCN Guidelines include recommendations for the diagnosis, staging, and treatment of any one of the myeloid/lymphoid neoplasms with eosinophilia (MLN-Eo) and a TK fusion gene included in the 2017 WHO Classification, as well as MLN-Eo and a *FLT3* or *ABL1* rearrangement.

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Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

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All recommendations are category 2A unless otherwise noted.

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.

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At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Myeloid/Lymphoid Neoplasms with Eosinophilia and TK Fusion Genes Panel members can be found on page 1269. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

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INITIAL EVALUATION

^aThis 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.

^bGenerally, absolute eosinophil count ≥1.5 × 10⁹/L.

^cAllele-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[†].

^dThe 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^{*}).

^eAdditional 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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MLNE-1

Overview

Eosinophilic disorders and related syndromes represent a heterogeneous group of neoplastic and nonneoplastic conditions, characterized by more eosinophils in the peripheral blood, and may involve eosinophil-induced organ damage.¹⁻³

Hypereosinophilia (HE) is defined as persistent elevated eosinophil count >1.5 × 10⁹/L in blood and/or tissue and is divided into 4 variant types per an international consensus proposal: hereditary (familial), HE_{FA}; primary (clonal/neoplastic), HE_N; secondary (reactive), HE_R; and HE of undetermined significance, HE_{US}.⁴ Hypereosinophilic syndrome (HES) is the term applied for any of these HE variants with evidence of eosinophil-induced tissue/organ damage and the term *idiopathic HES* should be applied when HE with associated organ damage is detected with no apparent underlying disease or syndrome.⁴ The international consensus criteria, definition, and classification of HE, HES, and other conditions accompanied by HE are outlined in Table 1 and Table 2.

Primary (clonal/neoplastic) HE (HE_N) is characterized by neoplastic proliferation of eosinophils and can be

associated with any of the WHO-defined myeloid and/or lymphoid neoplasms.⁴ A number of dysregulated tyrosine kinase (TK) fusion genes have been implicated in the pathogenesis of myeloid/lymphoid neoplasms with eosinophilia (MLN-Eo).⁵⁻⁷

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*.⁸ In the 2017 WHO classification, myeloid/lymphoid neoplasms with *PCMI-JAK2* rearrangement was added as a provisional entity.⁹⁻¹¹ 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.⁶ Myeloproliferative neoplasms (MPNs) with peripheral blood eosinophilia (eosinophil count >1.5 × 10⁹/L) that lack all of the aforementioned TK fusion genes as well as *BCR-ABL1*, and exhibit increased blasts (5% to <20%) and/or nonspecific cytogenetic and/or molecular abnormalities, are classified as chronic eosinophilic leukemia, not otherwise specified (CEL,

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^f (RT-qPCR)
- Confirmatory FISH (PB or BM) if chromosome analysis reveals the following breakpoints: 4q12 (*PDGFRA*);^g 5q31-33 (*PDGFRB*);^h 8p11-12 (*FGFR1*); 9p24 (*JAK2*); 9q34 (*ABL1*); and 13q12 (*FLT3*)ⁱ
- T-cell immunophenotyping flow cytometry (preferred) and/or IHC and molecular analysis to confirm T-cell clonality when appropriate
- Myeloid mutation panel (next-generation sequencing [NGS])^{j,k}

Evaluation of Target Organ Involvement^k

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

- Chest x-ray
- 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)

^fTesting 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).

^gThe 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.

^hIn rare cases, cryptic *PDGFRB* rearrangements have been found, and FISH may be used to uncover, not only confirm *PDGFRB* rearrangements.

ⁱRT-PCR may be preferred over NGS for *FLT3*.

^jSee Role of NGS in the Diagnosis of Myeloid/Lymphoid Neoplasms with Eosinophilia (MLNE-D).

^kConsultation with specialized referral services is recommended for the management of relevant target end-organ damage.

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MLNE-2

NOS) in the absence of another WHO-defined myeloid neoplasm.¹¹

The identification of specific TK fusion genes and the emergence of TK inhibitors (TKIs) has significantly improved the diagnosis and treatment of some patients with MLN-Eo.¹² 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 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.

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,” page 1259).^{8,11}

Eosinophilia is frequently observed, but it is not a prerequisite for the diagnosis of these neoplasms. Although prominent eosinophilia is present in most patients with

FIP1L1-PDGFRB, it is not invariably present in patients with a *PDGFRB*, *FGFR1*, *JAK2*, *FLT3*, or *ABL1* rearrangement.⁵ Patients also present with other blood count abnormalities, and organ damage may develop irrespective of the underlying TK fusion gene (“Clinical Presentation,” page 1252).

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.⁵⁻⁷ See “TK Fusion Genes in Myeloid/Lymphoid Neoplasms with Eosinophilia” in Table 1 in the algorithm (page 1261).

Myeloid/Lymphoid Neoplasms With Eosinophilia and *FIP1L1-PDGFRB* Rearrangement

The diagnosis requires the presence of *FIP1L1-PDGFRB* fusion gene (resulting from an interstitial deletion of *CHIC2* gene on chromosome 4q12) or a *PDGFRA* rearrangement with a variant fusion gene or an activating *PDGFRA* mutation.^{11,13-15} 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

^lSee Diagnosis and Staging Considerations in Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes (MLNE-4).

^mAlternative 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).

ⁿThe differential diagnosis of *JAK2* and *ABL1* fusions with a phenotype of ALL includes Ph-like ALL.

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MLNE-3

tryptase, and more mast cells and/or fibrosis in the bone marrow.^{5,7,16} 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.¹⁶

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.^{5,17,18} Pediatric cases have also been reported.^{19–22}

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.^{11,23} Cases with fusion genes typically associated only with *BCR-ABL1*-like B-cell lymphoblastic leukemia are specifically excluded.

Chronic myelomonocytic leukemia, atypical chronic myeloid leukemia (CML), MPN, myelodysplastic syndromes (MDS)/MPN, juvenile myelomonocytic leukemia, 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.^{5,24} This entity also has a strong male predominance.

Myeloid/Lymphoid Neoplasms With Eosinophilia and *FGFR1* Rearrangement

The diagnosis requires the presence of t(8;13)(p11;q12) or a variant translocation leading to *FGFR1* rearrangement demonstrated in myeloid cells, lymphoblasts, or both.^{11,25,26}

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.^{5,27}

MPN or MDS/MPN with eosinophilia are the most common myeloid neoplasms associated with *FGFR1*-rearranged eosinophilia. *FGFR1-ZMYM2* fusion gene and

DIAGNOSIS AND STAGING CONSIDERATIONS IN MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA
AND TYROSINE KINASE FUSION GENES^{d,e}

- Chronic phase may present in the BM or PB as an MPN or MDS/MPN with or without eosinophilia, and the BM may exhibit an atypical mast cell proliferation, often in an interstitial pattern (not typical aggregates found in SM).
- Blast phase (≥20% blasts) may present in the BM or PB as AML, ALL,^f 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."^g
- 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.

^dThe 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*).

^eThe differential diagnosis of *JAK2* and *ABL1* fusions with a phenotype of ALL includes Ph-like ALL.

^fEosinophilia is not invariably present.

^gThere 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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MLNE-4

t(8;13) are associated with high incidence of T-ALL.⁶ 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.^{5,28}

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.^{9–11}

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.^{9,10}

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

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

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.²⁹

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.⁶ 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.³⁰ The differential diagnosis of *JAK2* and *ABL1* fusions with a phenotype of ALL includes Ph like ALL.²⁹

Clinical Presentation

Chronic phase disease may present in the bone marrow or peripheral blood, with or without eosinophilia.

MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND THE *FIP1L1-PDGFR* REARRANGEMENT¹

¹See Diagnosis and Staging Considerations in Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes (MLNE-4).

²The *FIP1L1-PDGFR* 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* T674I and D842V).

³Complete 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.

⁴*PDGFR* T674I and D842V mutations are resistant to imatinib.

⁵Avapritinib is approved for adult patients with unresectable or metastatic gastrointestinal stromal tumors (GIST) harboring a *PDGFR* exon 18 mutation, including D842V mutations. This suggests a possible role for avapritinib in patients with *FIP1L1-PDGFR*-positive myeloid/lymphoid neoplasms with eosinophilia harboring *PDGFR* D842V mutation resistant to imatinib. If this mutation is identified, a clinical trial of avapritinib is preferred (if available), rather than off-label use.

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MLNE-5

Bone marrow may exhibit an atypical mast cell proliferation, often in an interstitial pattern but not the typical aggregates found in SM.¹⁶

There is no current definition for accelerated phase disease; however, the presence of 10% to 19% blasts in the bone marrow or peripheral blood has been used to define accelerated phase similar to myeloid neoplasms such as CML. Blast phase (≥20% blasts in the bone marrow and/or peripheral blood) may present as AML or ALL, or acute leukemias with mixed-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).⁶

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.² The most common presenting signs and symptoms include weakness and fatigue, cough, dyspnea, myalgias or angioedema, rash or fever, and rhinitis.⁷ In addition, patients also present with various blood count abnormalities depending on the underlying neoplasm (eg, neutrophilia, basophilia, thrombocytosis, monocytosis, myeloid immaturity, and both mature and immature eosinophils with varying degrees of dysplasia and anemia and/or thrombocytopenia with or without increased blast cells or dysplasia).^{2,7}

Organ damage may occur in HES irrespective of the underlying subtype of HE due to the increased production and/or persistent accumulation of eosinophils in tissue.² The skin, lungs, gastrointestinal tract, heart, and nervous system are the most commonly involved organ systems, although all organ systems may be susceptible to eosinophilia.^{2,7} Endomyocardial thrombosis and fibrosis are often documented in primary (neoplastic)

MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND *PDGFRB* REARRANGEMENT^{1,0}

¹See Diagnosis and Staging Considerations in Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes (MLNE-4).

⁰Eosinophilia is not invariably present.

^uCHR 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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MLNE-6

HES variants (HES_N), particularly in association with the *FIP1L1-PDGFR* fusion gene.^{2,7} Imaging studies and organ-directed biopsy are useful for the documentation of target organ involvement.² See “Evaluation of Target Organ Involvement,” page 1258.

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_R) caused by the reactive expansion of eosinophils that can be associated with a wide range of nonneoplastic (ie, allergies, infections, autoimmune or inflammatory disorders) or neoplastic (hematologic or solid malignancies) conditions.^{1,3} Differential diagnoses of the nonneoplastic 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 on page 1258).

Allergic disorders (eg, allergic asthma, food allergy, atopic dermatitis, drug reactions) are the most common

cause of secondary (reactive) HE (HE_R) occurring in about 80% of cases, and parasitic infections represent the second most common cause.^{1,3} Strongyloidiasis due to *Strongyloides stercoralis* exposure is generally the most common parasitic infection, although infections due to several other organisms have also been reported. If exposure to an infectious agent is suspected, initiation of appropriate treatment is necessary to prevent superinfection and consultation with an infectious agent specialist is recommended.

HE may also be present in individuals with certain immunodeficiency syndromes associated with abnormal immunoglobulin 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 [also known as Churg-Strauss syndrome]).^{1,3} HES may also be associated with a wide spectrum of dermatologic conditions (eg, atopic dermatitis, urticaria, eczema).³

Secondary (reactive) HE (HE_R) is frequently observed in patients with solid tumors and lymphoid malignancies (eg, Hodgkin lymphoma, B-cell and T-cell lymphomas)

MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND *FGFR1* REARRANGEMENT^{1,9}

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 EMD with an "MPN-like" picture in blood and marrow.

TREATMENT OPTIONS

Preferred regimen:

Clinical trial^v

Other recommended regimens:

TKI with activity against *FGFR1* (eg, pemigatinib^v or midostaurin or ponatinib)

Consider early referral to allogeneic HCT (if eligible)

Preferred regimen:

Clinical trial^v and

Consider early referral to allogeneic HCT (if eligible)

Other recommended regimens:

Myeloid → TKI with activity against *FGFR1* (eg, pemigatinib^v 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^v or midostaurin or ponatinib) ± ALL-type induction chemotherapy (See NCCN Guidelines for Acute Lymphoblastic Leukemia) followed by allogeneic HCT (if eligible)

Lymphoid

¹See Diagnosis and Staging Considerations in Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes (MLNE-4).

⁹Eosinophilia is not invariably present.

^vPemigatinib (*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).

[†]To view the most recent version of these guidelines, visit NCCN.org.

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due to the increased production of growth factors and eosinophilopoietic cytokines.³ In solid tumors, the incidence of HE is generally limited to advanced stage disease, and among the lymphoid malignancies, the incidence of HE is more frequent in T-cell lymphomas.³ In myeloid malignancies (eg, CML, AML, advanced SM), HE may similarly develop. In some 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. Although many of these cases are *FIP1L1-PDGFR*A-positive, the term has not been formally recognized by the WHO classification.⁷

Lymphocyte-variant HES (L-HES) is characterized by clonal T-cells with an aberrant immunophenotype and is associated with increased number of eosinophils, elevated serum thymus and activation-related chemokine (TARC), and IgE levels (although these findings are neither sensitive nor specific).^{3,7,16} 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.¹⁶ 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 nonspecific and can also be identified in patients with HES of undetermined significance or even in patients with a *PDGFR*A rearrangement.^{31,32}

A diagnosis of a primary (clonal/neoplastic) HE (HE_N) should be suspected in patients with elevated serum tryptase level, abnormal T-cell population, increased blasts, cytogenetic or molecular abnormality, and/or bone marrow fibrosis, splenomegaly, and/or lymphadenopathy, after ruling out all possible causes of secondary (reactive) HE (HE_R). Screening for TK fusion

MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND JAK2 REARRANGEMENT^{1,n,o,w}

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:^x

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:^x

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)

¹See Diagnosis and Staging Considerations in Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes (MLNE-4).ⁿThe differential diagnosis of JAK2 and ABL1 fusions with a phenotype of ALL includes Ph-like ALL.^oEosinophilia is not invariably present.^wOnly 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.^xRuxolitinib 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.[†]Available in the supplemental online content at JNCCN.org.[‡]To view the most recent version of these guidelines, visit NCCN.org.

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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_N).

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 nonspecific cytogenetic abnormality (trisomy 8 or isochromosome 17) or increased blast cells (>2% in the peripheral blood or >5% in the bone marrow, but <20% blasts in both compartments).¹¹ Bone marrow morphology might be helpful to distinguish CEL, NOS from idiopathic HES.³³

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* has

been proposed to describe such situations.³⁴ In patients with eosinophilia in whom causes for secondary (reactive) HE (HE_R) have been excluded, additional cytogenetic or molecular testing and morphologic evaluation of the bone marrow and peripheral blood may be useful to confirm the differential diagnosis of clonal hematopoiesis of indeterminate potential 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_{US}) per international consensus criteria and HES (organ damage present) with no apparent underlying disease or syndrome is referred to as idiopathic HES.⁴ These are diagnoses of exclusion that are assigned after ruling out primary (clonal/neoplastic) HE (HE_N) and all possible causes of secondary (reactive) HE (HE_R). 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

¹See Diagnosis and Staging Considerations in Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes (MLNE-4).

ⁿThe differential diagnosis of *JAK2* and *ABL1* fusions with a phenotype of ALL includes Ph-like ALL.

^oEosinophilia is not invariably present.

^ySchwaab J, et al. Am J Hematol 2020;95:824-833.

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identify primary (clonal/neoplastic) HE (HE_N) from secondary (reactive) HE (HE_R) (see "Role of NGS," page 1261).

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 nonspecific finding in many of the underlying conditions (allergies, infections, and L-HES) related to secondary or reactive eosinophilia.^{5,16} 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.^{5,7,16} 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.³⁵⁻³⁷ *Aspergillus*-specific

immunoglobulins and increased serum IgE are characteristic findings of ABPA.³

Laboratory testing should include 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).¹⁶

Additional laboratory testing may be considered based on the patient's history, symptoms, and findings on physical examination.⁷ This includes serology testing for Strongyloides and other parasitic infections; testing for antineutrophil cytoplasmic antibodies and antinuclear antibodies; stool ova and parasites test and gastrointestinal polymerase chain reaction (PCR); quantitative serum immunoglobulin levels (including IgE), erythrocyte sedimentation rate, and/or C-reactive protein; 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

CAUSES OF SECONDARY (REACTIVE) EOSINOPHILIA^{1,2}

Category	Examples
Infections	Parasitic (strongyloidiasis, <i>Toxocara canis</i> , <i>Trichinella spiralis</i> , schistosomiasis, <i>Echinococcus</i> , <i>Entamoeba</i> , <i>Cystoisospora</i> , <i>ascaris</i> , <i>Ancylostoma duodenale</i> [hookworm], <i>Toxoplasma gondii</i> , <i>Fasciola hepatica</i> , <i>paragonimus</i> , <i>clonorchis</i> , <i>filariasis</i>) Viral (HIV, herpes simplex [HSV], human T-cell leukemia virus type 2 [HTLV-2]) Fungal (<i>coccidioides</i> , <i>histoplasma</i> , <i>cryptococcus</i> , <i>pneumocystis</i>) Bacterial/Mycobacterial Consultation with infectious disease specialist is recommended for the management of complications related to specific infections.
Allergic/hypersensitivity diseases	Asthma, rhinitis, allergic rhinitis, bronchopulmonary aspergillosis, allergic gastroenteritis
Pulmonary diseases	Bronchiectasis, cystic fibrosis, chronic eosinophilic pneumonia, Löfller's syndrome
Cardiac diseases	Tropical endocardial fibrosis, eosinophilic endomyocardial fibrosis or myocarditis
Skin diseases	Atopic dermatitis, urticaria, eczema, bullous pemphigoid, dermatitis herpetiformis, episodic angioedema with eosinophilia (Gleich syndrome)
Connective tissue/autoimmune diseases	Inflammatory bowel disease, celiac disease, eosinophilic granulomatosis with polyangiitis, rheumatoid arthritis, systemic lupus erythematosus, polyarteritis nodosa, sarcoidosis, systemic sclerosis, Sjögren's syndrome, bullous pemphigoid, IgG4-related disease, eosinophilic fasciitis
Medications	Aspirin, NSAIDs, antimicrobials, DRESS syndrome
Malignancies	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)
Metabolic	Adrenal insufficiency
Immune system diseases	Hyper IgE syndrome, Omenn syndrome, Wiskott-Aldrich syndrome, IgA deficiency
Other	Acute/chronic graft versus host disease, solid organ rejection, cholesterol emboli, L-tryptophan ingestion, IL-2 therapy, toxic oil syndrome

¹Gottlieb 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.

²Shomali W, Gottlieb 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

nested reverse transcription PCR (RT-PCR) to detect the TK fusion gene rearrangement; and confirmatory FISH testing to identify breakpoints associated with TK fusion gene rearrangements is recommended for all patients to confirm the diagnosis of myeloid/lymphoid neoplasms.^{11,16}

The diagnostic testing algorithms for TK fusion gene rearrangements are outlined in the algorithm (see MLNE-3, page 1251). See also the section on "Cytogenetic and Molecular Testing" (page 1259). 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 the algorithm (see MLNE-4, page 1252).

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-.¹⁶ 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.¹⁶ *STAT3* mutation has also been recently identified in the CD3-, CD4+ T-cells in a patient with L-HES.³⁸

Evaluation of Target Organ Involvement

Electrocardiogram, cardiac troponin, and/or NT-proBNP measurement and echocardiogram 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.²

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

Organ-directed biopsy (skin, lung, or liver biopsy) with appropriate IHC is needed to confirm tissue

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-PDGFR*A rearrangement is found in approximately 10% of patients with idiopathic eosinophilia.¹⁻⁴ Elevated serum vitamin B12 levels, serum tryptase level, and/or mast cell proliferation in the BM are surrogate markers for *FIP1L1-PDGFR*A 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-PDGFR*A rearrangement results from an approximately 800-kb submicroscopic deletion in chromosome 4q12 leading to the fusion of *FIP1L1* and *PDGFRA* genes. Metaphase karyotype is unrevealing and the diagnosis is made by FISH and/or RT-PCR. The FISH probe used to identify these rearrangements detects loss of the intervening material, such as the gene *CHIC2*.^{5,6} An alternative approach is a nested RT-PCR or RT-qPCR assay. Although the breakpoints in *PDGFRA* occur exclusively in exon 12, the breakpoints in *FIP1L1* are more variable but still amenable to detection by RT-qPCR. The sensitivity of this assay in most labs is 0.01%–0.001%, but as the fusion can be difficult to detect in some patients a combination strategy of FISH and RT-PCR is the most sensitive method for the detection of this rearrangement, particularly in patients where clinical suspicion is high (eg, male, elevation of serum tryptase and/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*).^{2,7} Detection of these alternate *PDGFRA* rearrangements is critical due to the excellent prognosis these patients have when they are treated with imatinib. Conventional cytogenetics will detect these rearrangements, but these other rearrangements can be best detected by FISH with the break-apart *PDGFRA* FISH probe. The break-apart FISH can detect a rearrangement with any gene partner and is more sensitive than karyotype analysis. RT-PCR for specific gene rearrangements is also informative, if available.⁸

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

Lastly, focused sequencing of exons 9–19 can detect mutations. Activating point mutations in *PDGFRA* have been identified in *FIP1L1-PDGFR*A–negative hypereosinophilic syndrome (HES) cases and some are implicated in disease pathogenesis and may be imatinib responsive.⁹

PDGFRB-Rearranged Eosinophilia:

The *ETV6-PDGFRB* [t(5;12)(q31~33;p13.2)] is the most common abnormality with a hematologic presentation similar to CMML.^{4,6,7,10} The breakpoints in *PDGFRB* are located in the chromosomal region 5q31~q33. In addition to *ETV6*, more than 30 different partner 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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eosinophilia and eosinophil-induced organ damage.² Endoscopy with relevant mucosal biopsy with IHC (CD25, CD117, and tryptase) is recommended for patients with gastrointestinal 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 4q12.¹³⁻¹⁵ *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.^{14,39} Nested RT-PCR and quantitative RT-PCR (RT-qPCR) are more sensitive for the detection of *FIP1L1-PDGFR*A fusion gene in peripheral blood.^{5,15,39-41}

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.^{5,6,15} 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.⁴² These alternate *PDGFRA* rearrangements, like *FIP1L1-PDGFR*A, are associated with an excellent prognosis when treated with imatinib.

Peripheral blood or bone marrow FISH have similar sensitivities and the diagnosis can be made from either source. However, peripheral blood FISH may not robustly detect the deletion due to low clone size, and false-negative results have also been reported with bone marrow FISH.⁴³ 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.⁴⁴ Therefore, a combination of RT-PCR and FISH is the most sensitive method for the detection of *FIP1L1-PDGFR*A rearrangement.

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.^{3,6}

Sensitive RT-PCR has the benefit of small clone detection, in addition to the ability to detect complex and/or cryptic cases not evident by conventional cytogenetics. However, outside of *ETV6-PDGFRB*, the feasibility of RT-PCR is limited by the large number of partner 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.^{4,6,7} The most common rearrangement is t(8;13)(p11;q12), which results in the fusion of *ZMYM2* with *FGFR1* in about 50% of cases. This entity is associated with a high incidence of T-cell lymphoblastic lymphoma/leukemia. Two other common rearrangements include t(8;9)(p11;q33) (~15%) and t(6;8)(q27;p11) (~10%), which result in the fusions of *CNTRL* and *FGFR1OP* with *FGFR1*, respectively.

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

***JAK2*-Rearranged Eosinophilia:**

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

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

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

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

Continued

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

MLN-Eo With PDGFRB Rearrangement

ETV6-PDGFRB resulting from t(5;12)(q31-33;p13) is the most common fusion gene.²³ 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).⁴⁵ 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.^{5,46-48} 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.⁴⁹ 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.^{41,50} 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.⁵¹

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.^{6,25,26} 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

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.

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about 10% to 29% of cases.^{5,6,26,52,53} *RUNX1* mutations have also been reported in patients with acute leukemia and an *FGFR1* rearrangement confirmed by FISH.²⁶

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.^{5,26}

MLN-Eo With *JAK2* Rearrangement

PCM1-JAK2 resulting from t(8;9)(p22;p24) is the most common fusion gene.^{6,10,54-56} *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.^{6,10,57-59}

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.^{6,10}

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.^{6,29,30,60} *FLT3* fusion with other partner genes (*SPTBN1*, *GOLGB1*, *TRIP11*, and *ZMYM2*) and complex rearrangements resulting from fusion of *ABL1* with partner genes (other than *ETV6*) have also been reported.^{6,46,61-63}

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.²⁹ However, conventional cytogenetics is inconclusive for the detection of *ETV6-ABL1*, mainly because the creation of the *ETV6-ABL1* fusion gene requires at least 3 chromosomal breaks and the fusion gene rearrangement is not uniform across cases and typically involves cryptic insertions that can be missed with routine cytogenetics.³⁰ FISH with a combination of *ETV6* and *ABL1* probes, RT-PCR, or RNA sequencing are more reliable tests for the identification of an *ETV6-ABL1* fusion.^{6,30}

Role of NGS

NGS studies have also identified driver mutations involving a broad spectrum of genes most frequently

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 ^a , 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 ^b	Cytogenetics, ^b FISH, ^b RT-PCR, RNA-sequencing

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

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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.⁶⁴⁻⁶⁷ In one study, myeloid neoplasm-related somatic mutations involving a single gene or ≥ 2 genes have been identified in 28% of patients (14 of 51) with idiopathic HES, with *ASXL1* (43%), *TET2* (36%), *EZH2* (29%), *SETBP1* (22%), *CBL* (14%), and *NOTCH1* (14%) being the most frequently mutated genes.⁶⁵ In another study, 53% of patients (16 of 30) had at least one candidate mutation with *NOTCH1* (27%), *SCRIB* and *STAG2* (17%), and *SH2B3* (13%) being the most frequently mutated genes; clonal *TCR* rearrangement was present in 13% of patients.⁶⁶ Somatic *STAT5B* N642H mutations were reported in 1.6% (27/1,715) of patients with eosinophilia.⁶⁷ The presence of *STAT5B* N642H mutation as a sole abnormality was associated with a shorter overall survival compared with published series in patients with HES, suggesting that these cases should be reclassified as CEL, NOS.⁶⁷ Thus, targeted NGS studies will be helpful to establish clonality in a subset of patients with idiopathic HES leading to reclassification 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*.⁶⁸⁻⁷⁰ 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%).⁶⁸ Patients with *FGFR1* rearrangement had a significantly higher frequency of additional mutations (83%; 5 out of 6 patients; all had *RUNX1* mutation) in comparison with those with *PDGFRA* (14%; 5 of 35 patients), *PDGFRB* (23%; 3 of 13 patients), or *PCM1-JAK2* (14%; 1 of 7 patients) rearrangements. NGS-based 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-PDGFRA* rearrangement.⁶⁹

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.

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.¹⁻³ The rate of mutation detection is variable (11%, 28%, and 53% in 3 different studies) and the number of genes screened in these studies was also variable (23, 45, and 88, respectively).^{1,4,5}
- Mutations detected by NGS may also provide a means to identify primary (clonal/neoplastic) eosinophilia from secondary (reactive) eosinophilia, including in 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.⁶
- A recent survey of 61 patients with WHO-defined myeloid/lymphoid neoplasms associated with eosinophilia and harboring *PDGFRA*, *PDGFRB*, *FGFR1*, or *PCM1-JAK2* identified that 14 patients (23%) had at least one mutation.⁷ The mutations detected were *ASXL1*, *BCOR*, *DNMT3A*, *TET2*, *RUNX1*, *ETV6*, *NRAS*, *STAT5B*, and *ZRSR2*. Multiple mutations were identified in 3 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.

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MLNE-D

Treatment Considerations

All patients should be evaluated and managed by a multi-disciplinary team (including engagement of other subspecialists based on clinical presentation and organ involvement) in specialized centers. Assessment for clinical situations that may require urgent intervention is recommended for all patients. Immediate institution of oral or high-dose intravenous corticosteroids may be necessary as clinically indicated, especially in patients in whom eosinophil-mediated cardiac damage/heart failure is present or suspected.

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

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

Imatinib has resulted in high rates of durable hematologic and molecular responses in the vast majority of patients with MLN-Eo and *PDGFRA* or *PDGFRB* rearrangement.^{18,24,32,71-83} 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 echocardiogram findings.⁷⁴

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 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.⁷²

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

Table 1. Classification and Definition of Hypereosinophilia⁴

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

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

^bValidated 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.

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

^dClonality 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.

^eIn a group of patients, HE_R might be caused/triggered by other as yet unknown processes because no increase in eosinophilopoietic cytokine levels can be documented. Reprinted from Valent P, Klion AD, Horny HP, et al. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. *J Allergy Clin Immunol*, 2020;130(3):607-612, with permission from Elsevier.

when *FIP1L1-PDGFR*A 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.^{24,77}

Monitoring Response and Additional Treatment

Complete hematologic response (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.⁸⁴

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-PDGFR*A because standard karyotyping cannot detect the fusion; standard cytogenetics and/or FISH for *PDGFRB*) are recommended at 3 months after initiation of imatinib. RT-PCR (if available) can be considered to document molecular response.

Continuation of imatinib at the initial dose is recommended for patients achieving a complete response (complete hematologic response, CCyR, or complete molecular response). Although low doses of 100 to 200 mg daily have been sufficient to maintain molecular remission in most patients with *FIP1L1-PDGFR*A rearrangement, and in some cases this dose range has been

used only once weekly,⁷³ higher doses (maximum of 400 mg daily) may be required for some patients.^{74,75}

Monitoring hematologic response, cytogenetic response (FISH), and molecular response (if RT-qPCR is available) every 3 and 6 months is recommended for patients experiencing 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 before initiation of additional treatment of 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.^{72,85} Nilotinib, ponatinib, and sorafenib have shown limited activity in patients with *PDGFR*A T674I and D842V mutations.^{85–88} *PDGFRB* T681I has been shown to confer resistance to imatinib in vitro, but has not yet been identified in patients treated with imatinib; acquired resistance to imatinib mediated by other *PDGFRB* mutations has been described only in 2 case reports.^{89–91} Evaluation for cytogenetic/molecular clonal evolution can identify *PDGFR*A (T674I and D842V) or *PDGFRB* mutations conferring resistance to imatinib in patients with loss of response. Referral to clinical is recommended, if resistance mutation found.

Avapritinib is approved for unresectable or metastatic gastrointestinal stromal tumors harboring a *PDGFR*A

Table 2. Classification and Definition of HES and Conditions Accompanied by HE⁴

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

Abbreviation: HE, hypereosinophilia.

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

^bHE-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 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 organ systems.

^cClonality 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.

^dThe lymphoid variant of HES is regarded as a special form of secondary HES by several experts, although its exact nature and pathogenesis remain controversial. Reprinted from Valent P, Klion AD, Horny HP, et al. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. *J Allergy Clin Immunol*, 2020;130(3):607-612, with permission from Elsevier.

exon 18 mutation, including D842V mutations.^{92,93} This suggests a possible role for avapritinib in patients with MLN-Eo and *PDGFRA* rearrangement harboring *PDGFRA* D842V mutation resistant to imatinib. If this mutation is identified, a clinical trial of avapritinib is preferred (if available), rather than off-label use.

The feasibility of discontinuation of imatinib in patients with MLN-Eo and *PDGFRA* rearrangement who have experienced complete molecular response has been shown mostly in retrospective studies in a limited number of patients.^{32,71,94,95} Substantial variability has been seen 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 *PDGFRB* rearrangement has not been evaluated. At the present time, there are no definite criteria to identify patients suitable for discontinuation of imatinib and it is therefore not recommended outside the context of clinical trials.

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

MLN-Eo with the previously 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.^{9,10,27,30,96}

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. In the absence of a suitable clinical trial, TKI $\pm$ induction chemotherapy followed by allogeneic HCT is the appropriate treatment approach. 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*, *ABL1*, or *FLT3* are listed Table 3. Given the rare nature of this disease, available evidence is mainly from case reports and/or their potential clinical activity is extrapolated

Table 3. TKIs With Activity Against FGFR1, JAK2, FLT3, and ABL1

FGFR1	JAK2	FLT3	ABL1 ^a
Pemigatinib ^{b,102,103} Midostaurin ¹⁰⁴ Ponatinib ^{26,88,98,100,105}	Ruxolitinib ^{99,106–108} Fedratinib ^c	Gilteritinib ^c Midostaurin ^c Sorafenib ^{97,109} Sunitinib ¹⁰⁹	Dasatinib ⁹⁹ Nilotinib ⁹⁹ Imatinib ⁹⁹ Bosutinib ^c Ponatinib ^c

Abbreviation: TKI, tyrosine kinase inhibitor.

^aDasatinib or nilotinib are more effective than imatinib to induce durable complete remissions in patients with *ETV6-ABL1* fusion gene.⁹⁹

^bPemigatinib (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 myeloid/lymphoid neoplasms with eosinophilia 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.

^cThe inclusion of these TKIs is based on the extrapolation of data from myeloproliferative neoplasms (fedratinib for myelofibrosis) and other myeloid neoplasms (gilteritinib and midostaurin for acute myeloid leukemia; bosutinib and ponatinib for chronic myeloid leukemia).

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.^{26,96–99}

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 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.^{100,101} The role for TKI as maintenance therapy after 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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Individual Disclosures for the NCCN Myeloid/Lymphoid Neoplasms with Eosinophilia and TK Fusion Genes Panel

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The NCCN Guidelines Staff have no conflicts to disclose.

*The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty:

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Supplemental online content for:

NCCN Guidelines: Myeloid/Lymphoid Neoplasms with Eosinophilia and TK Fusion Genes, Version 3.2021

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OVERVIEW^{1,2,3,4,5}

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

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MLNE/INTRO-1

OVERVIEW^{1,2,3,4,5}

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

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

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

Myeloid and/or lymphoid neoplasm with eosinophilia, 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.

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MLNE/INTRO-2

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

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*[†]

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[¶] 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[§]

*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.

[†]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.

[‡]Cases with fusion genes typically associated only with *BCR-ABL1*-like B-lymphoblastic leukemia are specifically excluded.

[¶]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

[§]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)].

¹Reprinted 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.

PRINCIPLES OF CYTOGENETIC AND MOLECULAR TESTING IN MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA
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