**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 PDM1-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.

J Natl Compr Canc Netw 2020;18(9):1248–1269

**NCCN CATEGORIES OF EVIDENCE AND CONSENSUS**

- **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.
- **Category 3**: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise 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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**Disclosures for the NCCN Myeloid/Lymphoid Neoplasms with Eosinophilia and TK Fusion Genes Panel**

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.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.
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 \(>1.5 \times 10^9/L\) in blood and/or tissue and is divided into 4 variant types per an international consensus proposal: hereditary (familial), HEFA; primary (clonal/neoplastic), HEN; secondary (reactive), HER; and HE of undetermined significance, HEUS.\(^4\) 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.\(^5\)-\(^7\) A number of dysregulated tyrosine kinase (TK) fusion genes have been implicated in the pathogenesis of myeloid/lymphoid neoplasms with eosinophilia (MLN-Eo),\(^8\)-\(^11\) 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 PDGFRα, PDGFRβ or FGFR1*.\(^8\) In the 2017 WHO classification, myeloid/lymphoid neoplasms with *PCM1-JAK2* rearrangement was added as a provisional entity.\(^8\)-\(^11\) 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.\(^5\)-\(^7\) 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 nonspecific cytogenetic and/or molecular abnormalities, are classified as chronic eosinophilic leukemia, not otherwise specified (CEL).
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. 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).6,11

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-PDGFRA, 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, PDGFRB, 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).
tryptase, and more mast cells and/or fibrosis in the bone marrow.\textsuperscript{5,7,16} MLN-Eo with \textit{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 \textit{KIT} D816V mutation and dense clusters of mast cells typically seen in systemic mastocytosis (SM) are absent.\textsuperscript{16}

CEL is the most common clinical presentation. Blast phase MPN, 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 \textit{PDGFRB} rearrangement.\textsuperscript{5,24} This entity also has a strong male predominance.

Myeloid/Lymphoid Neoplasms With Eosinophilia and \textit{PDGFRB} Rearrangement

The diagnosis requires the presence of t(5;12)q31→q33; p13) or a variant translocation resulting in \textit{ETV6-PDGFRB} fusion gene or a \textit{PDGFRB} rearrangement with a variant fusion gene.\textsuperscript{11,23} Cases with fusion genes typically associated only with \textit{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 \textit{PDGFRB} rearrangement.\textsuperscript{5,24} This entity also has a strong male predominance.

Myeloid/Lymphoid Neoplasms With Eosinophilia and \textit{FGFR1} Rearrangement

The diagnosis requires the presence of t(8;13)(p11;q12) or a variant translocation leading to \textit{FGFR1} rearrangement demonstrated in myeloid cells, lymphoblasts, or both.\textsuperscript{11,25,26} MLN-Eo with \textit{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.\textsuperscript{5,27}

MPN or MDS/MPN with eosinophilia are the most common myeloid neoplasms associated with \textit{FGFR1}-rearranged eosinophilia. \textit{FGFR1}-ZMYM2 fusion gene and
t(8;13) are associated with high incidence of T-ALL. 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.

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.

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.

MPN or MDS/MPN with eosinophilia is the characteristic clinical presentation and de novo AML or ALL has been described in some patients. 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.

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

Clinical Presentation
Chronic phase disease may present in the bone marrow or peripheral blood, with or without eosinophilia.
Bone marrow may exhibit an atypical mast cell proliferation, often in an interstitial pattern but not the typical aggregates found in SM.1,6

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 acute leukemias with mixed-lineage disease and/or extramedullary myeloid sarcoma, T-ALL, or B-ALL. Blast phase may also present as an EMD with MPN-like features in bone marrow and 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).4

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)
HES variants (HESNs), particularly in association with the FIP1L1-PDGFRA fusion gene.\(^1\) 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).
due to the increased production of growth factors and eosinophilopoietic cytokines. 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. 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-PDGFRA–positive, the term has not been formally recognized by the WHO classification.

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). 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+, CD7+) 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. 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. 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 PDGFRA rearrangement.

A diagnosis of a primary (clonal/neoplastic) HE (HEb) 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 (HEa). Screening for TK fusion
gene rearrangements (PDGFRA, PDGFRB, FGFR1, JAK2, ABL1, or FLT3) or other cytogenic abnormality is recommended for patients with a suspected primary (clonal/neoplastic) HE (HEN).

The diagnosis of CEL, NOS should be considered in the absence of the aforementioned TK fusion gene rearrangements, when there are other cytogenic or molecular abnormalities or increased blasts (>20% in the peripheral blood or >5% in the bone marrow, but <20% blasts in both compartments). 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 (HER) 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 (HEUS) 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 (HEN) and all possible causes of secondary (reactive) HE (HER). 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_N) from secondary (reactive) HE (HER) (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
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 CD5+, CD4+, CD7-, and CD8-. 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. 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 polyposis, and sensorineural hearing loss is recommended for patients presenting with ear, nose, and throat symptoms.2 Organ-directed biopsy (skin, lung, or liver biopsy) with appropriate IHC is needed to confirm tissue
eosinophilia and eosinophil-induced organ damage. 2 Endoscopy with relevant mucosal biopsy with IHC (CD25, CD117, and tryptase) is recommended for patients with 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 PDGFRα Rearrangement

FIP1L1-PDGFRα 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-PDGFRα rearrangement. 14,39 Nested RT-PCR and quantitative RT-PCR (RT-qPCR) are more sensitive for the detection of FIP1L1-PDGFRα fusion gene in peripheral blood. 5,15,39-41

PDGFRα fusions with other partner genes (BCR, ET6, KIF5B, CSDKR2, 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 PDGFRα have also been identified in patients with FIP1L1-PDGFRα-negative HES. 42 These alternate PDGFRα rearrangements, like FIP1L1-PDGFRα, 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. 43 Therefore, a combination of RT-PCR and FISH is the most sensitive method for the detection of FIP1L1-PDGFRα 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. 

**MLN-Eo With PDGFRB Rearrangement**

*ETV6-PDGFRB* resulting from t(5;12)(q31-33;p13) is the most common fusion gene. However, not all cases with t(5;12)(q31-33;p13) have a PDGFRB rearrangement, and these are not widely available. 

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.

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.

**FGRF1-Rearranged Eosinophilia:**

*To date, 15 partner fusion genes with *FGFR1* have been described.* 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(6;9)(p23;q33) (~1%) and t(6;9)(q27;p11) (~1%), 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.

**FLT3:**

*FLT3*-ABL1 Rearranged Eosinophilia

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

*ETV6-ABL1* t(9;12)(q34;p13) is the fusion gene involved in the majority of cases with *ABL1* rearrangement. 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.

**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. 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.\textsuperscript{5,6,26,52,53} \textit{RUNX1} mutations have also been reported in patients with acute leukemia and an \textit{FGFR1} rearrangement confirmed by FISH.\textsuperscript{26}

Conventional cytogenetic analysis for t(8;13) followed by confirmatory FISH testing using dual-color break-apart probes for \textit{FGFR1} is the effective diagnostic approach for the detection of \textit{FGFR1-ZMYM2} fusion gene and can be applied to other \textit{FGFR1} rearrangements.\textsuperscript{5,26}

MLN-Eo With JAK2 Rearrangement

\textit{PCMI-JAK2} resulting from t(8;9)(p22;p24) is the most common fusion gene.\textsuperscript{6,10,54–56} \textit{ETV6-JAK2} [t(9;12)(p24; p13)] and \textit{BCR-JAK2} [t(9;22)(p24;q11)] are the other fusion genes reported only in few patients.\textsuperscript{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.\textsuperscript{6,10}

MLN-Eo With FLT3 or ABL1 Rearrangement

\textit{ETV6-FLT3} resulting from t(12;13)(p13;q12) and \textit{ETV6-ABL1} resulting from t(9;12)(q34;p13) are the common fusion genes involved in the majority of cases.\textsuperscript{5,29,30,60} FLT3 fusion with other partner genes (\textit{SPTBN1, GOLGB1, TRIP11, and ZMYM2}) and complex rearrangements resulting from fusion of ABL1 with partner genes (other than \textit{ETV6}) have also been reported.\textsuperscript{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 \textit{ETV6-FLT3} and \textit{FLT3-ETV6} transcripts) can be used to confirm the presence of \textit{ETV6-FLT3} gene fusion.\textsuperscript{29} However, conventional cytogenetics is inconclusive for the detection of \textit{ETV6-ABL1}, mainly because the creation of the \textit{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.\textsuperscript{30} FISH with a combination of \textit{ETV6} and \textit{ABL1} probes, RT-PCR, or RNA sequencing are more reliable tests for the identification of an \textit{ETV6-ABL1} fusion.\textsuperscript{6,30}

**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. 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. 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. Somatic STAT3B N642H mutations were reported in 1.6% (271/1,715) of patients with eosinophilia. The presence of STAT3B 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. 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 PDGFR, PDGFBR, FGFR1, or PCM1-JAK2. In an analysis of 61 patients with MLN-Eo and rearrangement of PDGFR, PDGFBR, FGFR1, or PCM1-JAK2, at least one additional mutation in several other genes (ASXL1, BCOR, DNMT3A, TET2, RUNX1, ETF6, NRAS, STAT5B, and ZRSR2) was detected in 14 patients (23%). 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 PDGFR (14%; 5 of 35 patients), PDGFBR (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 (CSF3K M696T and KIT P155S) in patients with myeloid neoplasms with eosinophilia and FIP1L1-PDGFR rearrangement.

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.

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

<table>
<thead>
<tr>
<th>Tyrosine Kinase Gene</th>
<th>Prototypic Genetic Rearrangement</th>
<th>Chromosome Location of Tyrosine Kinase Gene</th>
<th>Rearrangement Detected by Standard Cytogenetics</th>
<th>Diagnostic Assays</th>
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<tr>
<td>PDGFRα</td>
<td>FIP1L1-PDGFRα</td>
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<td>PDGFβ</td>
<td>ETV6-PDGFBβ</td>
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<td>ZMYM2-FGFR1</td>
<td>8p11-12</td>
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<td>JAK2</td>
<td>PCM1-JAK2</td>
<td>9p24</td>
<td>Yes</td>
<td>Cytogenetics, FISH, RT-PCR</td>
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<td>FLT3</td>
<td>ETV6-FLT3</td>
<td>13q12</td>
<td>Yes</td>
<td>Cytogenetics, FISH, RT-PCR</td>
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<tr>
<td>ABL1</td>
<td>ETV6-ABL1</td>
<td>9q34</td>
<td>Yes</td>
<td>Cytogenetics, FISH, RT-PCR, RNA-sequencing</td>
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</tbody>
</table>

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

* 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. 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).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 PDGFRα, PDGFRβ, FGFR1, PCMI-JAK2, ETF6-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 PDGFRα, PDGFRβ, FGFR1, or PCMI-JAK2 identified that 14 patients (23%) had at least one mutation. The mutations detected were ASXL1, BCOR, DNMT3A, TET2, RUNX1, ETF6, NRAS, STAT5B, and ZRSR2. Multiple mutations were identified in 3 cases, and RUNX1 was found to be recurrently mutated (6 of 18 mutations detected) and was detected in 5 of 6 cases with FGFR1 rearrangements (83%). For the other groups, the mutation rates were 14% for PDGFRα, 23% for PDGFRβ, and 14% for PCMI-JAK2.

- NGS can be used to identify novel fusion gene or cryptic rearrangements when clinical suspicion is high and FISH for PDGFRα, PDGFRβ, 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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**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 PDGFRα or PDGFRβ Rearrangement**

Imatinib has resulted in high rates of durable hematologic and molecular responses in the vast majority of patients with MLN-Eo and PDGFRα or PDGFRβ rearrangement.4,24,32,71 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 FIP11-PDGFRα rearrangement. Imatinib 100 mg to 400 mg daily is the recommended dose for chronic phase in patients with PDGFRβ 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 PDGFRα 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 PDGFRβ rearrangement). Durable remissions are only rarely achieved with induction chemotherapy or allogeneic hematopoietic cell transplant (HCT). In instances
when FIP1L1-PDGFRA or a PDGFRB rearrangement is identified only after the initiation of induction chemotherapy, imatinib should be added to induction chemotherapy (ALL-type chemotherapy for lymphoid blast phase and AML-type chemotherapy for myeloid blast phase), or a return to imatinib monotherapy may also be considered.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-PDGFRA 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-PDGFRA rearrangement, and in some cases this dose range has been used only once weekly,74 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 PDGFRB 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 PDGFRB 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 PDGFRB (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 PDGFRB

| Table 1. Classification and Definition of Hypereosinophilia⁴ |
|------------------|-----------------|------------------|
| Proposed Terminology | Proposed Abbreviation | Definition and Criteria |
| Blood eosinophilia | — | >0.5 eosinophils × 10⁹/L blood |
| Hypereosinophilia | HE | >1.5 × 10⁹/L eosinophils in the blood on 2 examinations (interval ≥ 1 month⁵) and/or tissue HE defined by the following⁶: 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 | HEFA | 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 | HEUS | 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) HE⁷ | HEcl | Underlying stem cell, myeloid, or eosinophilic neoplasm, as classified by WHO criteria; eosinophils considered neoplastic cells⁸ |
| Secondary (reactive) HE⁹ | HERR | Underlying condition/disease in which eosinophils are considered nonclonal cells; HE considered cytokine-driven in most cases¹⁰ |
| Eosinophil-associated single-organ diseases | Criteria of HE fulfilled and single-organ disease |

⁴In the case of evolving life-threatening end-organ damage, the diagnosis can be made immediately to avoid delay in therapy.

⁵Validated 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.

⁶Clonality 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.

⁷In a group of patients, HER might be caused/triggered by other as yet unknown processes because no increase in eosinophilopoietic cytokine levels can be documented.

⁸In the case of evolving life-threatening end-organ damage, the diagnosis can be made immediately to avoid delay in therapy.

⁹In the case of evolving life-threatening end-organ damage, the diagnosis can be made immediately to avoid delay in therapy.

¹⁰Validated 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.
Table 2. Classification and Definition of HES and Conditions Accompanied by HE4

<table>
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<tr>
<th>Proposed Terminology</th>
<th>Proposed Abbreviation</th>
<th>Definition and Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypereosinophilic syndrome</td>
<td>HES</td>
<td>Defined as blood HE with (plus) end-organ damage attributable to tissue HE: 1. Criteria for peripheral blood HE fulfilled; and 2. Organ damage and/or dysfunction attributable to tissue HE; and 3. Exclusion of other disorders or conditions as major reason for organ damage</td>
</tr>
<tr>
<td>Idiopathic HES</td>
<td>—</td>
<td>No underlying cause of HE, no evidence of a reactive or neoplastic condition/disorder underlying HE, and end-organ damage attributable to HE</td>
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<tr>
<td>Primary (neoplastic) HES</td>
<td>HESN</td>
<td>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</td>
</tr>
<tr>
<td>Secondary (reactive) HES</td>
<td>HESR</td>
<td>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 (clonal T cells identified as the only potential cause) is a subvariant of secondary (reactive) HES</td>
</tr>
</tbody>
</table>

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.

4In the case of evolving life-threatening end-organ disease, the diagnosis can be made immediately to avoid delay in therapy.

5HE-related organ damage (damage attributable to HE): organ dysfunction with marked tissue eosinophilia and/or extensive deposition of eosinophil-derived proteins (in the presence or absence of marked tissue eosinophilia) 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.

6Clonality 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.

7The lymphoid variant of HES is regarded as a special form of secondary HES by several experts, although its exact nature and pathogenesis remain controversial.

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.26,36–99

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 reports100,101. 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.

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

<table>
<thead>
<tr>
<th>FGFR1</th>
<th>JAK2</th>
<th>FLT3</th>
<th>ABL1*</th>
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<tbody>
<tr>
<td>Pemigatinibb,100,105</td>
<td>Ruxolitinib98</td>
<td>Gilatinib99</td>
<td>Dasatinib99</td>
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<td>Midostaurin96</td>
<td>Fedratinibb</td>
<td>Midostaurin29,102</td>
<td>Nilotinibb</td>
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<td>Ponatinibb,96,105</td>
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<td>Sorafenibb,109</td>
<td>Imatinibb</td>
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<td></td>
<td></td>
<td>Sunitinibb,100</td>
<td>Bosutinibb</td>
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</table>

Abbreviation: TKI, tyrosine kinase inhibitor.

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

**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 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.

The inclusion of these TKIs is based on the extrapolation of data from myeloproliferative neoplasms (fedratinib for myeloproliferative neoplasms with eosinophilia and FGFR1 rearrangement) and a clinical trial of pemigatinib is preferred (if available), rather than off-label use.

References

22. Srinivasan A, Scordino T, Baker A. Myeloid neoplasm with eosinophilia and FIP1L1-PDGFRA rearrangement treated with imatinib mesylate: A


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<th>Panel Member</th>
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<th>Scientific Advisory Boards, Consultant, or Expert Witness</th>
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<td>Brady L. Stein, MD, PhD</td>
<td>Constellation Pharmaceuticals, Inc.; CTI BioPharma Corp.; and KIIT Pharmaceuticals</td>
<td>None</td>
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<td>Michael W. Deininger, MD, PhD</td>
<td>AstraZeneca Pharma US, Inc.; Blueprint Medicines; Cellese Corporation; Constellation Pharmaceuticals; Inc.; CTI BioPharma Corp.; Incyte Corporation; KIIT Therapeutics; Inc; NS Pharma, Inc.; Pfizer Inc.; and Promodex, Inc.</td>
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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:

Ivana G.J., MD, Windmill Therapeutics
Krishna Gundabolu, MBBS; Geron Corporation, and Portola Pharmaceuticals
Catrina Jamieson, MD, PhD; Forty Seven, Inc.
OVERVIEW

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 (≥1.5 x 10^9/L) or tissue eosinophilia (any eosinophil count) in a target organ, with the occurrence of characteristic genetic breakpoints, with some not always visible by standard cytogenetics (eg, FIP1L1-PDGFRα, 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-PDGFRα rearrangement);
- Features of chronic myelomonocytic leukemia (CMML) with eosinophilia (PDGFRα rearrangement);
- Persistent eosinophilia after intensive treatment of AML, ALL, B-cell lymphoma, or T-cell lymphoma.

Myeloid/Lymphoid Neoplasms with Eosinophilia and FIP1L1-PDGFRα 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-PDGFRα 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
OVERVIEW\textsuperscript{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.

References

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

Myeloid/Lymphoid Neoplasms with Eosinophilia Associated with FIP1L1-PDGFRα or a Variant Fusion Gene
A myeloid or lymphoid neoplasm, usually with prominent eosinophilia and
Presence of a FIP1L1-PDGFRα 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;q2) 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-PDGFRα 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 markedly elevated 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)(q34.1;q11.2)].

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

REFERENCES


2. Goldblum J, Cools J. Five years since the discovery of FIP1L1-PDGFRα: what we have learned about the fusion and other molecularly defined eosinophilic leukemias 2008;22:1999-2010.


