

# Facts About Acute Myeloid Leukemia (AML)

## Introduction

Acute myeloid leukemia (AML) is an aggressive, highly complex malignancy typically diagnosed in older adults. Patients with AML often have multiple comorbidities and may not be candidates for aggressive remission induction chemotherapy, the standard of care since the 1970s. In recent years, high throughput genetic sequencing identifying causal mutations and a better understanding of the biology of the disease have resulted in a wave of newly approved targeted therapies. These discoveries and drug approvals have resulted in better options and better outcomes for patients, particularly those who may be unable to tolerate aggressive chemotherapy.

This publication will review the updated AML subtype classifications, detail newly approved therapies, summarize current treatment recommendations, and provide information about the LLS Beat AML® Master Trial, collaborative clinical trial testing novel targeted therapies with the goal of improving outcomes for newly diagnosed patients with AML.

## Highlights

- AML is a genetically heterogeneous malignancy typically diagnosed in older adults, with a slight male predominance.
- AML was diagnosed in over 21,000 people and resulted in nearly 11,000 deaths in the US in 2019. The incidence of AML has increased 3.7% per year from 2006 to 2015.
- A multidisciplinary diagnostic approach, including both karyotype and mutation analysis, is critical to predict rates of remission, relapse, and overall survival, and to identify patients likely to benefit from targeted therapies.
- Updated classification of AML is based on clinically relevant disease information rather than morphology. Six major subtypes of AML were recognized by the World Health Organization (WHO) in 2016.
- The 2017 European Leukemia Network (ELN) Guidelines are widely used for risk stratification and determining the likelihood of treatment resistance.
- Since 2017, better understanding of the molecular basis of AML has been leveraged to produce 8 newly approved therapies for AML: for the treatment of newly diagnosed patients, those with relapsed and refractory disease, and those ineligible for aggressive induction chemotherapy.
- Updated National Comprehensive Cancer Network (NCCN) Practice Guidelines should be consulted for recommendations regarding where and when each of these therapies fits into clinical practice.
- For any patient with newly diagnosed AML, referral to a clinical trial is recommended upon diagnosis.
- The Beat AML® Master Trial sponsored by The Leukemia & Lymphoma Society is a novel, collaborative clinical trial designed to facilitate the approval of new drugs and optimize the treatment for AML by developing individualized treatment approaches.

## Background and Prevalence

AML is the most common acute leukemia in adults, with an estimated 21,450 diagnoses and nearly 11,000 deaths in the US in 2019.<sup>1</sup> It is also diagnosed at younger ages, but older adults comprise the majority of patients – the median age at diagnosis is 67 years, and 65% of patients are diagnosed at age 65 years and older.<sup>2</sup> From 2006 to 2015, the incidence of AML increased 3.7% per year, likely due to the aging population. It is more common in males by a ratio of approximately 5:3.<sup>3</sup>

AML results from genetic or epigenetic changes in hematopoietic precursor cells, resulting in a clone of myeloid precursor cells that proliferates, but can't differentiate. These immature myeloblasts expand in the bone marrow, peripheral blood, and other tissues, with a corresponding reduction in the production of normal red blood cells, platelets, and mature granulocytes.<sup>2</sup>

The great majority of AML cases arise without an apparent cause, but known and suspected risk factors for AML (other than advanced age and male gender) include those shown in **Table 1**.

**Table 1. Risk factors for AML**

Risk Factor	Examples
<b>Environmental exposures</b>	• Benzene, ionizing radiation, cigarette smoke
<b>Antecedent hematologic disorders</b>	• Myeloproliferative disorders, myelodysplastic syndromes (MDS)
<b>Genetic syndromes</b>	• Bloom syndrome, ataxia-pancytopenia syndrome, Diamond-Blackfan anemia, Fanconi anemia, MIRAGE syndrome, Noonan syndrome, Kostman syndrome, Shwachman-Diamond syndrome, Down syndrome <sup>4</sup>
<b>Previous cancer therapy (therapy-related MDS/AML or t-AML*)</b>	• Alkylating agents, topoisomerase inhibitors and radiotherapy (given as myeloablative therapy prior to autologous hematopoietic stem cell transplantation) <sup>2</sup>

\*May constitute 7% to 15% of patients with AML<sup>4</sup>

## Multidisciplinary Diagnostic Approach

A person with AML usually presents with symptoms of bone marrow failure: abnormally low levels of platelets, neutrophils, and red blood cells, and the presence of circulating blasts with the resulting complications of fatigue, pallor, weakness, increased infections, and bleeding.

A diagnosis is made based on the presence of  $\geq 20\%$  myeloblasts in the marrow or peripheral blood established by morphology and flow cytometry.<sup>5,6</sup> The 2019 NCCN Practice Guidelines [available [here](http://www.jnccn.org/view/journals/jnccn/17/6/article-p721.xml)] recommend a multidisciplinary diagnostic approach when AML is suspected. This approach identifies AML subtypes, stratifies pre-treatment risk and guides treatment decisions, and includes performing the following tests<sup>2</sup>:

1. Bone marrow core biopsy and aspirate analysis (including immunophenotyping by flow cytometry and cytochemistry).
2. Cytogenetic analysis: Karyotype with fluorescence in situ hybridization is needed for risk stratification and can help to confirm the diagnosis.
3. Mutational analysis: For *KIT*, *FLT3-ITD*, *FLT3-TKD*, *NPM1*, *CEBPA*, *IDH1/IDH2*, *RUNX1* and *TP53* should be performed in all patients to inform prognosis and treatment.

While identifying karyotype is critical to predict rates of remission, relapse and overall survival, mutation analysis refines risk stratification and identifies those patients likely to benefit from recently approved targeted therapies.<sup>7</sup>

## Subtype Classification and Risk Stratification Critical for Treatment Decisions

Updated classification of AML and related neoplasms by the WHO in 2016 was based on clinically relevant disease information rather than only morphology. The 6 major subtypes are shown in **Table 2**.<sup>5</sup>

In terms of risk stratification by genetics, the 2017 ELN Guidelines (**Table 3**) are widely used for determining likelihood of treatment resistance.<sup>6,8</sup>

**Table 2. AML and related neoplasms<sup>5</sup>**

• AML with recurrent genetic abnormalities
• AML with myelodysplasia-related changes
• Therapy-related myeloid neoplasms
• AML, not otherwise specified
• Myeloid sarcoma
• Myeloid proliferations related to Down syndrome

**Table 3. Risk stratification by genetics<sup>6,8</sup>**

Risk Category	Genetic Abnormality
<b>Favorable</b>	<ul style="list-style-type: none"> <li>t(8;21)(q22;q22.1); <i>RUNX1-RUNX1T1</i></li> <li>inv(16)(p13.1q22) or t(16;16)(p13.1;q22); <i>CBFB-MYH11</i></li> <li>Mutated <i>NPM1</i> without <i>FLT3-ITD</i> or with <i>FLT3-ITD</i><sup>low</sup> = allelic ratio &lt; 0.5</li> <li>Biallelic mutated <i>CEBPA</i></li> </ul>
<b>Intermediate</b>	<ul style="list-style-type: none"> <li>Mutated <i>NPM1</i> and <i>FLT3-ITD</i><sup>high</sup> = allelic ratio &gt; 0.5</li> <li>Wild-type <i>NPM1</i> without <i>FLT3-ITD</i> or with <i>FLT3-ITD</i><sup>low</sup> (without adverse-risk genetic lesions)</li> <li>t(9;11)(p21.3;q23.3); <i>MLL3-KMT2A</i></li> <li>Cytogenetic abnormalities not classified as favorable or adverse</li> </ul>
<b>Adverse</b>	<ul style="list-style-type: none"> <li>t(6;9)(p23;q34.1); <i>DEK-NUP214</i></li> <li>t(v;11q23.3); <i>KMT2A</i> rearranged</li> <li>t(9;22)(q34.1;q11.2); <i>BCR-ABL1</i></li> <li>inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); <i>GATA2,MECOM(EVI1)</i></li> <li>-5 or del(5q); -7; -17/abn(17p)</li> <li>Complex karyotype monosomal karyotype</li> <li>Wild-type <i>NPM1</i> and <i>FLT3-ITD</i><sup>high</sup></li> <li>Mutated <i>RUNX1</i></li> <li>Mutated <i>ASXL1</i></li> <li>Mutated <i>TP53</i></li> </ul>

## Treatment and Prognosis

Despite the genetic heterogeneity of AML, for decades most patients who were fit enough (generally younger patients) received aggressive induction combination chemotherapy consisting of 7 days of cytarabine and 3 days of anthracycline (“7 + 3” regimen), followed by either cytarabine-based consolidation or allogeneic hematopoietic stem cell transplant (HSCT).<sup>9</sup> This regimen results in complete remission in approximately 70% of patients younger than 60 years, and approximately 50% of those 60 years and older.<sup>7</sup>

Relapse occurs frequently, however, ranging from 30%-35% in younger patients with favorable risk factors to 70%-80% in older patients with adverse risk factors. In 2017, the overall survival (OS) rate at 5 years for patients with AML was 27.4%. Adjusted for age, 5-year OS for those younger than 65 was 39% and just 8.5% for patients 65 to 74 years of age.<sup>10</sup> Even with active therapy, the typical median OS in relapsed/refractory (r/r) AML is approximately 6 months.<sup>11</sup>

Options for patients with AML who are ineligible for aggressive chemotherapy have been limited. Less-intensive treatment approaches have included low dose cytarabine (LDAC), which is associated with poor response rates (<15%) and short median survival.<sup>12,13</sup> Hypomethylating agents have also been utilized in these patients, resulting in complete response (CR) plus CR with incomplete blood count recovery (CRi) of 20-40%.<sup>12,13</sup> Other such patients receive no chemotherapy but opt for supportive care, including hydroxyurea and transfusion support, instead.<sup>12,13</sup>

## Therapies Approved Since 2017

Recently, better understanding of the molecular basis of AML has been leveraged to produce 8 approved therapies from 2017 to 2019 – either as single agents or in combination with other therapies (**Table 4**). These approvals have provided welcome treatment options for patients with AML, particularly older patients. A brief description of each is found below. Updated 2019 NCCN Practice Guidelines [available [here](https://www.nccn.org/view/journals/jnccn/17/6/article-p721.xml)] ([www.nccn.org/view/journals/jnccn/17/6/article-p721.xml](https://www.nccn.org/view/journals/jnccn/17/6/article-p721.xml)) should be consulted for detailed recommendations regarding where and when each of these therapies fits into clinical practice for the treatment of patients with AML.<sup>2</sup> The full Prescribing Information for each of these therapies should be consulted to learn about associated toxicities.

**Table 4. Therapies for AML approved since 2017**

Therapy	Mechanism of Action	Indication(s)
<b>Daunorubicin and cytarabine liposome</b> (VYXEOS®) <sup>14</sup> [Approved 2017]	Fixed molar ratio of daunorubicin and cytarabine in a liposomal formulation	<ul style="list-style-type: none"> <li>Adults with newly diagnosed therapy-related AML (t-AML)</li> <li>AML with myelodysplasia-related changes (AML-MRC)</li> </ul>
<b>Gemtuzumab ozogamicin</b> (MYLOTARG™) <sup>15</sup> [Approved 2017]	Anti CD-33 antibody linked to N-acetyl gamma calicheamicin, a cytotoxic agent	<ul style="list-style-type: none"> <li>Adults with newly diagnosed CD33-positive AML either as single agent or in combination with 7+3</li> <li>Relapsed/refractory (r/r) CD33-positive AML in patients &gt;2 years</li> </ul>
<b>Midostaurin</b> (RYDAPT®) <sup>16</sup> capsules [Approved 2017]	FMS-like tyrosine kinase 3 (FLT3) inhibitor	<ul style="list-style-type: none"> <li>FLT3-positive newly diagnosed AML in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation</li> </ul>
<b>Gilteritinib</b> (XOSPATA®) <sup>17</sup> oral tablets [Approved 2018]	FMS-like tyrosine kinase 3 (FLT3) inhibitor	<ul style="list-style-type: none"> <li>Adults with r/r AML with <i>FLT3</i> mutation</li> </ul>
<b>Enasidenib</b> (IDHIFA®) <sup>18</sup> oral tablets [Approved 2017]	IDH2 inhibitor	<ul style="list-style-type: none"> <li>Adults with r/r AML with <i>IDH2</i> mutation</li> </ul>
<b>Ivosidenib</b> (TIBSOVO®) <sup>19</sup> oral tablets [Approved 2018]	IDH1 inhibitor	<p>For treatment of AML with a susceptible <i>IDH1</i> mutation in:</p> <ul style="list-style-type: none"> <li>Adults ≥75 years with newly diagnosed AML or who have comorbidities that preclude use of intensive induction chemotherapy</li> <li>Adults with r/r AML</li> </ul>
<b>Venetoclax</b> tablets (VENCLEXTA®) <sup>20</sup> [Approved 2018]	BCL-2 inhibitor	With hypomethylating agents or low dose cytarabine (LDAC) for treatment of newly diagnosed AML in adults ≥75 years or who have comorbidities that preclude use of intensive induction chemotherapy
<b>Glasdegib</b> (DAURISMO™) <sup>21</sup> tablets [Approved 2018]	Hedgehog pathway inhibitor	With LDAC for treatment of newly diagnosed AML in adults ≥75 years or who have comorbidities that preclude use of intensive induction chemotherapy

### **Daunorubicin and cytarabine liposome for injection (VYXEOS®) [approved in 2017]**

The “7 + 3” regimen of cytarabine and daunorubicin has been used for the treatment of AML for over 40 years. Studies have demonstrated that cytarabine and daunorubicin are maximally effective against malignant cells when 5 times as much cytarabine as daunorubicin is present, however, separate infusion of these agents does not serve to maintain this 5:1 molar ratio.<sup>22</sup>

The recently approved liposome formulation maintains a 5:1 molar ratio of cytarabine/daunorubicin within the liposome after injection, stabilizes both drugs and preferentially targets leukemic cells.<sup>22</sup> In clinical studies in older adults (ages 60-75 years) with AML, OS was significantly longer in patients receiving VYXEOS® (9.6 months) than those receiving traditional 7 + 3 cytarabine and daunorubicin (5.9 months).<sup>14</sup>

VYXEOS® is approved for adults with newly diagnosed AML that develops secondarily to other chemotherapeutic regimens (t-AML) or myelodysplastic syndrome (AML-MRC). It has a Boxed Warning for dosing errors, due to dosing that differs from daunorubicin or cytarabine administered separately.<sup>14</sup>

### **Gemtuzumab ozogamicin (MYLOTARG™) for injection [approved in 2017]**

CD33 is expressed in immature myeloblasts but not in either mature hematopoietic stem cells or non-hematopoietic cells, making it a prime target for therapy in AML.<sup>10</sup> Gemtuzumab ozogamicin is a humanized anti-CD33 antibody linked to N-acetyl gamma calicheamicin, a cytotoxic agent. It is internalized after binding to CD33-expressing cells and induces cell cycle arrest and cell death by apoptosis.<sup>10,15</sup>

In 2000, gemtuzumab ozogamicin received FDA approval through an accelerated process as a monotherapy for older patients with r/r CD33-positive AML. It was voluntarily withdrawn from the market after subsequent data failed to show clinical benefit and revealed an increase in treatment-related mortality. FDA re-approval in 2017 was prompted by data from clinical studies using a different dosing regimen and a new patient population showing significant clinical benefit in<sup>10,15</sup>:

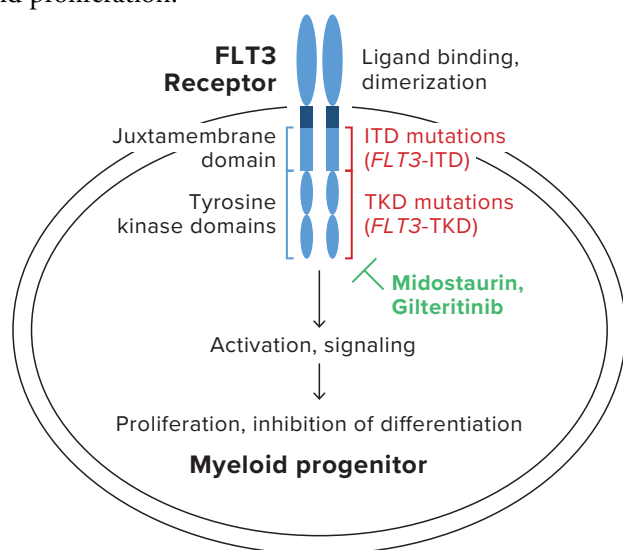
- Adults with newly diagnosed, CD33-positive AML as a single agent or in combination with 7 + 3
- Adults and children (>2 years) with r/r CD33-positive AML as a single agent

In a meta-analysis of 5 clinical trials, 5-year OS of all patients who received gemtuzumab ozogamicin with standard 7 + 3 induction chemotherapy as frontline therapy was 34.6%, compared to 30.7% in those that received standard chemotherapy alone. When restricted to just those patients with favorable risk, OS was 77.5% in those patients receiving gemtuzumab ozogamicin and 55% in those receiving standard induction chemotherapy alone.<sup>23</sup>

Gemtuzumab ozogamicin has a Boxed Warning for hepatotoxicity, including severe or fatal hepatic veno-occlusive disease (VOD).

### FMS-like Tyrosine Kinase 3 (FLT3) Inhibitors

FLT3 is a tyrosine kinase receptor expressed on myeloid and lymphoid progenitor cells. Upon binding its ligand, the receptor dimerizes and activates downstream signaling pathways mediating differentiation and growth<sup>24</sup> (Figure 1). Mutations in *FLT3*-ITD occur in ~30% of all AML cases, resulting in the activation of tyrosine kinase activity, signaling and proliferation.<sup>25</sup>



**Figure 1. FLT3 mutations in AML.** Simplified schematic of the FLT3 receptor and its role in the pathogenesis of AML. Upon ligand binding, the FLT3 receptor dimerizes, autophosphorylates, and activates downstream signaling pathways resulting in the proliferation of myeloid progenitor cells and an inhibition of differentiation. Gain-of-function mutations in the juxtamembrane region (*FLT3*-ITD) and in the tyrosine kinase domains (*FLT3*-TKD) resulting in ligand-independent FLT3 receptor activation are common driver mutations in AML.

ITD: internal tandem duplication; TKD: tyrosine kinase domain

Internal tandem duplication (ITD) mutations (*FLT3*-ITD) (Figure 1) are common driver mutations in AML, accounting for ~25% of all cases. Patients with *FLT3*-ITD mutations typically present with high leukemic burden and have a higher risk of relapse and shorter OS.<sup>24,25</sup>

Another 10% of AML patients carry mutations in the tyrosine kinase domain of FLT3 (*FLT3*-TKD), but the prognostic value of these mutations is not clear. It's also been shown that mutations can evolve from diagnosis to

relapse, suggesting mutation testing may be necessary at multiple timepoints.<sup>25</sup>

Multiple small molecules targeting FLT3 have been developed, and to date 2 have received FDA approval for the treatment of *FLT3*-mutated AML: midostaurin and gilteritinib.

#### Midostaurin (RYDAPT®) capsules [approved in 2017]

Midostaurin inhibits signaling by wild-type FLT3, *FLT3*-ITD and *FLT3*-TKD, in addition to other kinases. Disruption of FLT3 signaling by midostaurin inhibits proliferation and induces apoptosis in leukemic cells harboring ITD and TKD mutant FLT3, in addition to cells that overexpress wild-type FLT3.<sup>16,24</sup>

In a phase 3 trial, 717 patients with newly diagnosed *FLT3*-mutated AML were stratified by *FLT3* mutational status and randomized 1:1 to receive midostaurin or placebo in combination with standard 7 + 3 induction and consolidation chemotherapy, followed by maintenance with midostaurin or placebo for up to 1 year.

Midostaurin plus standard 7 + 3 chemotherapy was found to be superior to placebo plus standard chemotherapy – 4-year OS in the midostaurin arm was 51% compared to 44% in the control arm.<sup>24</sup>

Midostaurin capsules are indicated for *FLT3*-positive (both ITD and TKD mutated) newly diagnosed AML as detected by an [FDA-approved test](http://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools) (www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools) in combination with standard 7 + 3 cytarabine and daunorubicin induction and cytarabine consolidation.<sup>16</sup>

#### Gilteritinib (XOSPATA®) oral tablets [approved in 2018]

Gilteritinib is a second-generation FLT3 inhibitor with more FLT3 specificity and less off-target activity against other kinases than midostaurin.<sup>26</sup> It inhibits wild-type FLT3 in addition to *FLT3*-ITD and *FLT3*-TKD.<sup>17</sup> Gilteritinib was approved as a single agent for adults with r/r AML with *FLT3* mutations as detected by an [FDA-approved test](http://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools). (www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools)

In the phase 3 trial, 371 adults with r/r AML with a *FLT3* mutation were randomized 2:1 to receive either 120 mg gilteritinib daily over continuous 28-day cycles or salvage chemotherapy (either intensive or low-intensity regimen). In the final analysis, 14.2% of patients in the gilteritinib arm achieved CR vs 10.5% in the chemotherapy arm. Patients receiving gilteritinib survived significantly longer than those assigned to the chemotherapy arm (median 9.3 months vs 5.6 months).<sup>17</sup>

Gilteritinib has a Boxed Warning for differentiation syndrome, which occurred in 11 of 319 patients treated with gilteritinib in clinical trials.<sup>17</sup>



## Isocitrate Dehydrogenase (IDH) Inhibitors

The IDH enzymes comprise 3 enzymes (IDH1, IDH2 and IDH3) involved in the citric acid cycle – the central driver of cellular respiration – converting isocitrate to  $\alpha$ -ketoglutarate. Gain-of-function mutations in IDH1 and IDH2 generate excess 2-hydroxyglutarate (2-HG) instead of  $\alpha$ -ketoglutarate, which is likely an early, critical contributor to oncogenesis due to its disruption of metabolic and epigenetic mechanisms involved in cellular differentiation.<sup>27-29</sup>

*IDH1* and *IDH2* mutations have been implicated in several malignancies, including glioma, cholangiocarcinoma, chondrosarcoma, myelodysplastic syndromes and AML. In fact, nearly 20% of AML cases are *IDH*-mutant, with *IDH2*-mutations being more prevalent than *IDH1*. Characteristics associated with *IDH*-mutant AML include increased patient age and intermediate risk cytogenetics.<sup>27,28</sup>

In vitro studies have established that inhibiting mutant IDH in leukemic cells reduces 2-HG production, reverses epigenetic changes and releases the myeloid differentiation block.<sup>29</sup> Multiple small molecule inhibitors of mutant IDH are in development, and 2 have been approved by the FDA for the treatment of adults with AML with demonstrated *IDH* mutations. Both products are approved for r/r AML, and one is approved for newly diagnosed patients  $\geq 75$  years or who have comorbidities that preclude use of intensive induction chemotherapy.

### Enasidenib (IDHIFA®) oral tablets [approved in 2017]

In vitro studies reveal enasidenib selectively inhibits mutant IDH2 variants R140Q, R172S and R172K at 40-fold lower concentrations than wild type IDH. Enasidenib was approved in 2017 for the treatment of adults with r/r AML with an *IDH2* mutation as identified by an [FDA-approved test](#).<sup>18</sup> (www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools)

In a single-arm trial, 199 adults with r/r AML were given enasidenib daily until disease progression or unacceptable toxicity. Efficacy was determined based on CR + CR with hematologic improvement (CRh) percentage, duration of response, and the rate of conversion from transfusion dependence to transfusion independence. After a median follow-up of 6.6 months, 23% of patients achieved CR/CRh with a median duration of response of 8.2 months. Of 157 patients dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 34% became independent of these transfusions during any 56-day post-baseline period.<sup>18</sup>

Enasidenib has a Boxed Warning for differentiation syndrome, which occurred in 14% of patients in clinical trials.<sup>18</sup> In November 2018, the FDA released a Safety Announcement warning that signs and symptoms of differentiation syndrome are not being recognized in patients receiving enasidenib and encouraged healthcare professionals to be alert for initial symptoms, which can be difficult to distinguish from cardiogenic pulmonary edema, pneumonia or sepsis.<sup>30</sup>

### Ivosidenib (TIBSOVO®) oral tablets [approved in 2018]

Ivosidenib is a potent inhibitor of the mutant IDH1 enzyme (the most common mutations leading to increased levels of 2-HG are R132H and R132C). In vitro studies show that ivosidenib inhibits these mutations at much lower concentrations than wild type IDH1. Ivosidenib is approved for treatment of adults with AML and *IDH1* mutation as identified by an [FDA-approved test](#).<sup>19</sup> (www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools) This includes both r/r AML and patients 75 years and older with newly diagnosed AML or who have comorbidities that preclude use of intensive induction chemotherapy.

Ivosidenib was studied in a single-arm trial of 28 adults with newly diagnosed AML with an *IDH1* mutation. Subjects were over 75 years of age or had comorbidities that precluded the use of intensive induction chemotherapy. They received 500 mg ivosidenib daily until disease progression, unacceptable toxicity, or stem cell transplant (2 patients proceeded to transplant). After a median follow-up of 8.1 months, 42.9% achieved CR/CRh (the median duration of response could not be estimated). Of 17 patients dependent on RBC and/or platelet transfusion at baseline, 41.2% became independent of these transfusions during any 56-day post-baseline period.<sup>19</sup>

The efficacy and safety of ivosidenib were also evaluated in a single arm trial in 174 adults with r/r AML, who were given 500 mg ivosidenib daily until disease progression, unacceptable toxicity, or stem cell transplant (12% proceeded to transplant). After a median follow-up of 6.6 months, 32.8% achieved CR/CRh with a median duration of response of 8.2 months. Of 110 patients dependent on RBC and/or platelet transfusion at baseline, 37.3% became independent of these transfusions during any 56-day post-baseline period.<sup>19</sup>

Like enasidenib, ivosidenib has a Boxed Warning for differentiation syndrome, which occurred in 25% of patients with newly diagnosed AML and 19% of those with r/r AML in clinical trials. The FDA Safety Announcement mentioned above warns healthcare providers to be alert for symptoms of differentiation syndrome in patients receiving ivosidenib as well as enasidenib.<sup>30</sup>

## BCL-2 Inhibitor: Venetoclax tablets (VENCLEXTA®) [approved in 2018]

B-cell leukemia/lymphoma-2 (BCL-2) family members are proteins that bind and sequester pro-apoptotic proteins in cancer cells. It has been demonstrated that BCL-2 mediates chemoresistance and promotes survival of leukemic blast and progenitor cells,<sup>9,13,31</sup> and BCL-2 overexpression is a common finding in hematologic malignancies.<sup>32</sup>

Venetoclax is a potent and selective BCL-2 inhibitor that has been investigated in combination with other therapies in multiple hematologic malignancies, including chronic lymphocytic leukemia, small lymphocytic lymphoma, non-Hodgkin lymphoma, and AML. Scores of clinical trials are underway.<sup>32</sup>

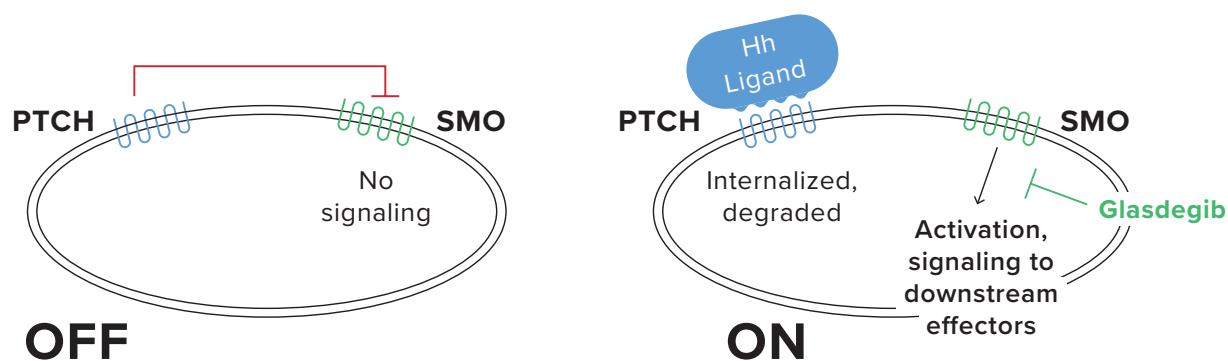
In 2018, venetoclax received approval for the front-line treatment of AML in combination with hypomethylating agents (azacitidine or decitabine) or low dose cytarabine in adults 75 years or older or who have comorbidities that preclude intensive induction chemotherapy. The indication was granted under accelerated approval based on the response rates in phase 2 studies, and continued approval is contingent upon confirmatory trials.<sup>20</sup>

Venetoclax was evaluated in a non-randomized phase 1b dose escalation and expansion trial in combination with azacitidine or decitabine in newly diagnosed AML in patients who were ineligible for intensive chemotherapy. With a median follow-up of 8.9 months, 67% of patients (all doses) achieved CR + CRi. The median duration of response was 11.3 months, and median OS was 17.5 months.<sup>31</sup> In comparison, response rates for decitabine or azacitidine monotherapy in this population ranged from 20% to 40%.<sup>31</sup>

Venetoclax in combination with LDAC was evaluated in a non-randomized, open-label phase 1b/2 study in older patients ( $\geq 60$  years) with AML who were ineligible for intensive chemotherapy. CR + CRi was 54% with a median OS of 10.1 months. These rates compare favorably with LDAC monotherapy, with CR/CRi rates of 11%-19% and median OS of 5.5 months.<sup>13</sup>

## Hedgehog pathway inhibitor: Glasdegib (DAURISMO™) tablets [approved in 2018]

The hedgehog (Hh) pathway is a signaling pathway that plays a key role in embryonic development of vertebrates. It is controlled by two cellular membrane receptors, Patch (PTCH) and Smoothed (SMO). SMO transmits activating signals to downstream components (**Figure 2**), and PTCH normally functions to inhibit signaling by SMO when not bound to its ligand. When the hedgehog ligand binds to PTCH, PTCH is internalized and degraded, allowing SMO to activate downstream effectors. Abnormal activation of Hh pathway signaling has been identified in several leukemias and leukemia stem cells.<sup>33</sup>



**Figure 2. The Hedgehog Pathway.** The Hh pathway is controlled by Patch (PTCH) and Smoothed (SMO), two transmembrane receptors. OFF: When PTCH is not bound to its ligand, it functions to inhibit signaling by SMO. ON: When Hh is bound, PTCH is internalized and degraded, allowing SMO to accumulate and signal downstream effectors, including inducing gene expression.

Glasdegib is an orally bioavailable small molecule that binds to and inhibits signaling by SMO. It gained FDA approval in 2018 in combination with LDAC for the treatment of newly diagnosed AML in adults 75 years and older, or who have comorbidities that preclude use of intensive induction chemotherapy.<sup>21</sup>

The efficacy of glasdegib was evaluated in a randomized, open-label study of 132 patients with newly diagnosed AML or high-risk MDS not eligible for intensive chemotherapy. The trial compared glasdegib with LDAC vs LDAC alone. Median OS was 8.8 months for glasdegib + LDAC, vs 4.9 months for LDAC alone. The CR rate was 18.2% in the glasdegib + LDAC arm vs 2.6% for LDAC alone.<sup>21</sup>

Glasdegib has a Boxed Warning for embryo-fetal toxicity.<sup>21</sup>

## Recommendations

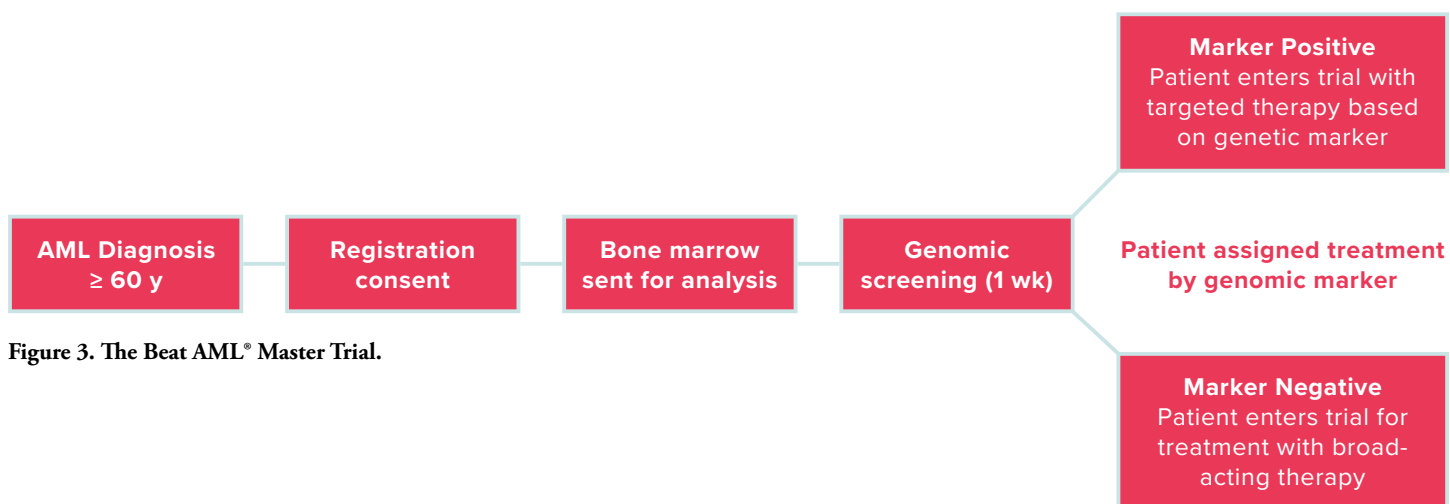
For any patient with AML, NCCN Guidelines strongly encourage enrollment in a clinical trial. For patients not enrolled in a trial, cytogenetics and risk stratification guide treatment decisions.<sup>2</sup> NCCN Practice Guidelines are available [here](http://www.jnccn.org/view/journals/jnccn/17/6/article-p721.xml). (www.jnccn.org/view/journals/jnccn/17/6/article-p721.xml)

## Beat AML® Master Trial

The Leukemia & Lymphoma Society’s (LLS’s) Beat AML® Master Trial is a groundbreaking clinical trial designed to facilitate the approval of new drugs and optimize the treatment for AML by developing individualized treatment approaches. The protocol is designed to facilitate a collaborative and responsive consortium that can serve as a model for future cancer clinical trials.

The trial is a collaboration between LLS (the trial sponsor), academic researchers, pharmaceutical companies, a genomic provider, and a clinical research organization. It is open to patients 60 years and older with newly diagnosed AML, with some studies allowing younger adult patients.

Upon diagnosis, enrolled patients receive a genomic screen via bone marrow biopsy. Based on the results of the screen, each patient will be assigned a personalized therapy on one of several sub-studies. Sites and arms of the trial are expected to increase as data accumulate with the potential to test novel drug combinations (**Figure 3**). To date, over 700 patients have been enrolled at 17 sites. More information, including how to enroll patients, can be found [here](http://www.lls.org/beat-aml/beat-aml-for-healthcare-professionals). (www.lls.org/beat-aml/beat-aml-for-healthcare-professionals)



**Figure 3. The Beat AML® Master Trial.**

LLS Clinical Trial Nurse Navigators are registered nurses with expertise in blood cancers. They are available to provide individualized clinical trial searches. Information about the LLS Clinical Trial Support Center can be found [here](http://www.jnccn.org/view/journals/jnccn/17/6/article-p721.xml). (www.jnccn.org/view/journals/jnccn/17/6/article-p721.xml) Additional resources are listed below.



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## We're Here to Help

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services.

### The Leukemia & Lymphoma Society

3 International Drive, Suite 200

Rye Brook, NY 10573

Phone Number: (800) 955-4572

(M-F, 9 a.m. to 9 p.m. ET)

Website: [www.lls.org](http://www.lls.org)

Email: [infocenter@LLS.org](mailto:infocenter@LLS.org)

LLS offers free information and services for patients and families touched by blood cancers as well as for healthcare professionals. The resources listed below are available to you and your patients.

**Consult with an Information Specialist.** Information Specialists are master's level oncology social workers, nurses and health educators. They offer up-to-date disease and treatment information. Language services are available. For more information, please

- Call: (800) 955-4572 (M-F, 9 a.m. to 9 p.m. ET)
- Email: [infocenter@LLS.org](mailto:infocenter@LLS.org)
- Visit: [www.lls.org/clinicaltrials](http://www.lls.org/clinicaltrials)

**Clinical Trial Support Center.** Patients and caregivers can work one-on-one with a Clinical Trial Nurse Navigator who will provide personalized clinical trial searches, help overcome barriers to trial enrollment and personally assist patients through the entire clinical trial journey.

If you have a patient who is looking for, or may be a candidate for a clinical trial, encourage them to call LLS at (800) 955-4572 or learn more at [www.lls.org/navigation](http://www.lls.org/navigation).

## Web, Telephone and In-person Education Programs for Healthcare Professionals and Patients.

- CME/CE education programs: [www.lls.org/CE](http://www.lls.org/CE)
- Patient/caregiver education programs: [www.lls.org/webcasts](http://www.lls.org/webcasts)

**Education Videos.** LLS offers education videos on blood cancer treatment and support for patients and caregivers. Please visit: [www.lls.org/educationvideos](http://www.lls.org/educationvideos).

**LLS Community.** LLS Community is an online social network and registry for patients, caregivers, and healthcare professionals. It is a place to ask questions, get informed, share your experience, and connect with others. To join visit: [www.lls.org/community](http://www.lls.org/community)

**LLS Chapters.** LLS offers community support and services in the United States and Canada including the Patti Robinson Kaufmann First Connection Program (a peer-to-peer support program), in-person support groups, and other helpful resources. For more information about these programs or to contact your chapter, please

- Call: (800) 955-4572
- Visit: [www.lls.org/chapterfind](http://www.lls.org/chapterfind)

## Additional Resource

### The National Cancer Institute (NCI)

[www.cancer.gov](http://www.cancer.gov)

(800) 422-6237

The National Cancer Institute, part of the National Institutes of Health, is a national resource center for information and education about all forms of cancer, including Acute Myeloid Leukemia (AML). The NCI also provides a clinical trial search feature, the PDQ® Cancer Clinical Trials Registry, at [www.cancer.gov/clinicaltrials](http://www.cancer.gov/clinicaltrials), where healthcare professionals and patients can look for clinical trials.