

# Acute myeloid leukemia (AML)

Recommendations from the society for diagnosis and therapy of  
haematological and oncological diseases

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## **Publisher**

DGHO Deutsche Gesellschaft für Hämatologie und  
Medizinische Onkologie e.V.

Bauhofstr. 12  
D-10117 Berlin

Executive chairwoman: Prof. Dr. med. Claudia Baldus

Phone: +49 (0)30 27 87 60 89 - 0

[info@dgho.de](mailto:info@dgho.de)

[www.dgho.de](http://www.dgho.de)

## **Contact person**

Prof. Dr. med. Bernhard Wörmann  
Medical superintendent

## **Source**

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# Acute myeloid leukemia (AML)

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**Authors:** Christoph Röllig, Francis Ayuketang Ayuk, Claudia Baldus, Jan Braess, Konstanze Döhner, Karoline Gleixner, Michael Heuser, Jan-Henning Klusmann, Markus G. Manz, Jakob Passweg, Dirk Reinhardt, Richard F. Schlenk, Armin Zebisch

**Previous authors:** Dietrich Wilhelm Beelen, Thomas Büchner, Richard Greil, Dietger Niederwieser, Markus Schaich

## 1 Summary

Acute myeloid leukemia (AML) is a biologically heterogeneous disease that leads to death within a short period of time if left untreated. Its incidence increases with age. AML is subdivided according to the WHO/ICC classifications based on cytomorphological, cytogenetic, and molecular genetic characteristics. Treatment decisions are based on the biology of the disease, comorbidity, and the treatment goals of individual patients. The goal of treatment is curative in younger patients and in older patients who are fit.

## 2 Basics

### 2.1 Definition and basic information

Acute myeloid leukemia (AML) is a neoplasm of hematopoietic stem and progenitor cells with variable myelopoietic differentiation.

Before effective drugs became available, the natural course of AML led to death in half of patients within 5 months of the first symptoms and in all patients within one year [1].

It was only after the introduction of daunorubicin and cytarabine that complete remissions and long-term success were achieved [22]. The prognosis for AML has steadily improved since the 1970s. This has been demonstrated in two registry-based studies from the US and the UK. Young patients in particular have benefited from therapeutic advances, while the prognosis for older patients aged 70 to 75 has remained almost unchanged [2, 3].

### 2.2 Epidemiology

The incidence is approximately 3.7 cases per 100,000 inhabitants per year and increases with age, with age-specific incidences of over 100 cases per 100,000 inhabitants in patients over the age of 70. The median age in a Swedish registry of adult patients was 72 years [4].

### 2.3 Pathophysiology

The origin is the pathological proliferation of clonal myeloid blood precursor cells that do not differentiate normally and usually have the immunophenotypic characteristics of the highly proliferative progenitor pool (i.e., CD34+/CD38+) or, more rarely, the stem cell pool (i.e., CD34+/CD38-). This proliferating clone overgrows the healthy bone marrow and leads to depletion of healthy hematopoiesis with the resulting clinical consequences of neutropenia (infections, sep-

sis), thrombocytopenia (bleeding), and anemia (dyspnea, reduced performance). With the advent of cytogenetic diagnostics in the 1980s, it became clear that, in contrast to CML, a wide variety of cytogenetic aberrations can be observed. In addition to gene translocations such as t(8;21), t(15;17) or inv(16), numerical changes such as trisomy 8, monosomy 7 or complex changes with more than three recurrent chromosomal aberrations in a clone were also found. It was later shown that these changes play a very important prognostic role (see chapter 5.4). With the introduction of modern molecular techniques, especially next-generation sequencing (NGS), it became apparent that even within individual patients, the disease can consist of genetically different subclones and that the proportion of the different clones can change over the course of the disease (clonal diversification/evolution). Recurrent changes can be divided into nine classes:

1. activating mutations of signal transduction (*FLT3*, *KIT*, *KRAS*, *NRAS*, etc.)
2. Mutations of myeloid transcription factors (*RUNX1*, *CEBPA*, etc.)
3. Fusions of transcription factor genes (*PML-RARA*, *MYH11-CBFB*, etc.)
4. Mutations of chromatin modifiers (*MLL-PTD*, *ASXL1*, etc.)
5. Mutations in the cohesin complex (*SMC1S*, etc.)
6. Spliceosome mutations
7. Mutations in tumor suppressor genes (*TP53*, *WT1*, etc.)
8. *NPM1* mutations
9. Mutations in DNA methylation genes (*TET1*, *TET2*, *IDH1*, *IDH2*, *DNMT3B*, *DNMT1*, *DNMT3A*)

Further investigations showed that in approximately 50% of patients, at least one additional subclone was detectable in addition to the dominant main clone; in individual patients, up to three additional leukemia clones were present. This clonal heterogeneity could be of significant importance for the response to therapy or for the development of a relapse [5]. While mutations in the *FLT3*, *NPM1*, *DNMT3A*, and *NRAS* genes are common in younger AML patients, mutations in genes such as *ASXL1*, *TET2*, *SRSF2*, and *DNMT3A* are predominant in older AML patients. Compared to patients under 60 or between 60 and 74 years of age, patients aged 75 years or older have a higher frequency of *TET2*, *SRSF2*, and *ASXL1* mutations [4]. Overall, 83% of AML patients aged 75 years or older carry at least one mutation in one of these six genes (*TET2*, *DNMT3A*, *SRSF2*, *ASXL1*, *TP53*, or *SF3B1*) associated with age-related clonal hematopoiesis. This suggests that leukemia in older people often arises from clonal hematopoiesis [6- 10].

## 2.4 Risk factors

Causes include exposure to radioactive radiation (according to Japanese data from survivors of the atomic bombs on Hiroshima and Nagasaki), benzene, tobacco, mineral oil products, paints, ethylene oxides, herbicides, and pesticides. Radiotherapy and cytostatic drugs are among the causes, typically alkylating agents with leukemia occurring 4-6 years after use and aberrations on chromosomes 5 and/or 7, as well as topoisomerase II inhibitors (anthracyclines, anthraquinones, epipodophyllotoxins) with leukemia onset 1-3 years after exposure and frequently associated chromosome aberrations of chromosome 11 band q23 but also balanced translocation t(1,17). Younger age at the time of diagnosis of the primary tumor, therapy with intercalating substances (anthracyclines, anthraquinones), and topoisomerase II inhibitors were associated with a short latency period until the onset of secondary AML in a large meta-analysis [11]. A large meta-analysis of 23 epidemiological studies with 7,746 AML cases demonstrated a clear association between smoking and the development of AML. The risk of AML is increased

by 40% in active smokers and by 25% in former smokers compared to non-smokers ( $p < 0.001$ ), correlates with the number of cigarettes smoked, and affects both sexes equally [12].

AML is often associated with myelodysplastic syndromes (MDS), for example, due to a history of MDS or MDS-typical genetics [13].

Advanced age is the biggest risk factor for developing AML. Age-associated clonal hematopoiesis of indeterminate potential (CHIP) is a risk factor for developing AML. Mutations in the following genes were found more frequently in CHIP carriers who later developed AML than in CHIP carriers who did not develop AML: *DNMT3A*, *TET2*, *SRSF2*, *ASXL1*, *TP53*, *U2AF1*, *JAK2*, *RUNX1*, and *IDH2* [14]. Similarly, a higher variant allele frequency and a higher number of CHIP mutations are associated with an increased risk of developing AML. Depending on the constellation, the 10-year AML risk is increased by 2-12.5 times [14]. In cases of familial clustering of myeloid neoplasms, suggestive cytogenetic findings, or mutations in suggestive genes (e.g., *DDX41*, *CEBPA*, or *RUNX1*), a familial germline mutation should be evaluated as the cause of AML [15].

### 3 Prevention and early detection

Apart from reducing/avoiding the modifiable risk factors mentioned above, there is no evidence for effective measures for prevention and early detection.

## 4 Clinical characteristics

### 4.1 Symptoms

The clinical presentation of AML is determined by increasing hematopoietic insufficiency as a result of blast bone marrow infiltration and by nonspecific general symptoms.

The symptoms are often nonspecific at first and later manifest as anemia (fatigue, reduced performance, paleness, etc.), neutropenia (especially bacterial infections of the lungs, throat, and skin, as well as systemic mycoses), and thrombocytopenia (petechiae, ecchymoses, menorrhagia, or epistaxis). However, an increased tendency to bleed is also possible due to disseminated intravascular coagulation and hyperfibrinolysis. Leukocytosis is found in the blood of approximately 60% of patients, and leukemic blasts are found regardless of the leukocyte count. If leukocytosis exceeds a value of approximately 100,000/ $\mu\text{l}$ , there is a risk of leukostasis with hypoxia, pulmonary opacities, retinal hemorrhages, and neurological symptoms. Leukostasis is a hematological emergency and requires a rapid reduction in the peripheral leukocyte count through chemotherapy and, in exceptional cases, through a combination of chemotherapy and leukapheresis. Aleukemic courses with normal or even decreased leukocyte counts are observed less frequently. These are more common in secondary or therapy-associated AML and in older patients. In myelomonocytic/monoblastic differentiated AML, extramedullary manifestations such as skin infiltrates, meningeal leukemia, gingival hyperplasia, and infiltration of the spleen and liver are observed with above-average frequency.

## 5 Diagnosis

Examples of microscopic diagnostics can be found in the eLearning Curriculum Hematology (eLCH), <https://ehaematology.com/>.

## 5.2 Diagnosis

### 5.2.1 Initial diagnosis

The disease is defined by a blast count of  $\geq 20\%$  in peripheral blood or bone marrow or other tissues (myelosarcoma), or by the detection of recurrent genetic changes that define AML.

According to **the current WHO classification** (2022), the following recurrent mutations and fusions define AML regardless of the blast count: *PML::RARA* fusion, *RUNX1::RUNX1T1* fusion, *CBFB::MYH11* fusion, *DEK::NUP214* fusion, *RBM15::MRTFA* fusion, *KMT2A* rearrangement, *MECOM* rearrangement, *NUP98* rearrangement, *NPM1* mutation. The diagnosis of the following genetically defined subgroups requires a blast count of  $\geq 20\%$ : CEBPA mutation, BCR::ABL, myelodysplasia-associated alterations (MR, see chapter 5.3) and "other defined genetic alterations" [16].

The **International Consensus Classification** (ICC), first published in 2022, requires a blast percentage of  $\geq 10\%$  for the above entities with the following additions: Other *RARA* rearrangements, other *KMT2A* rearrangements, "other rare recurrent translocations," and in-frame bZIP *CEBPA* mutations are also considered AML-defining [17] if the ICC-typical blast count of  $\geq 10\%$  is present, see also Table 2, Table 3, and Table 4.

Tests to confirm the diagnosis and additional tests to assess the patient's health status and plan treatment are summarized in Table 1.

In patients with the following anamnestic constellations, the suspicion of a predisposing germline mutation should be ruled out, especially with regard to a potential stem cell transplant from a family member [18]:

- $\geq 2$  cancers, including 1 hematological cancer
- history of hematological neoplasia plus
  - Hematological neoplasia in first- and second-degree relatives (uncles, aunts, nephews, nieces, grandparents, grandchildren, half-siblings)
  - Solid tumor at age  $\leq 50$  years in first- and second-degree relatives
  - Hematological abnormalities in first- and second-degree relatives or
- Hematological neoplasia at an unusually young age

**Table 1: Diagnosis in cases of suspected acute myeloid leukemia**

Objective	Examination
Confirmation of diagnosis	Medical history and physical examination findings
	Complete blood count and differential blood count
	Bone marrow cytology and cytochemistry
	Bone marrow biopsy (mandatory in cases of punctio sicca)
	Immunophenotyping (including CD33 on blasts, CD4, CD56, CD123, and TCL1 for differentiation of BPDCN; MPO for lineage affiliation)
	Cytogenetics Classic chromosome analysis, in particular screening for del(5q)/t(5q)/add(5q), -7/del(7q), +8, del(11q), del(12p)/t(12p)/add(12p), -13/ del(13q), i(17q), -17/add(17p) or del(17p), del(20q), and/or idic(X)(q13)
	Molecular genetics (at least the following mutations) <ul style="list-style-type: none"> <li>• <i>ASXL1</i></li> <li>• <i>BCOR</i></li> <li>• <i>CEBPA</i></li> <li>• <i>EZH2</i></li> <li>• <i>FLT3</i> (internal tandem duplications (ITD), mutant-wild-type ratio)</li> <li>• <i>FLT3 TKD</i> (codon D835 and I836)</li> <li>• <i>IDH1</i></li> <li>• <i>IDH2</i></li> <li>• <i>NPM1</i></li> <li>• <i>RUNX1</i></li> <li>• <i>SF3B1</i></li> <li>• <i>SRSF2</i></li> <li>• <i>STAG2</i></li> <li>• <i>TP53</i></li> <li>• <i>U2AF1</i></li> <li>• <i>ZRSR2</i></li> </ul>
Molecular genetics (translocations) <ul style="list-style-type: none"> <li>• <i>PML::RARA</i></li> <li>• <i>CBFB::MYH11</i></li> <li>• <i>RUNX1::RUNX1T1</i></li> <li>• <i>BCR::ABL1</i></li> <li>• <i>KMT2A::(MLL-)</i> rearrangements</li> <li>• <i>DEK-NUP214</i></li> <li>• <i>MECOM</i> rearrangements</li> <li>• <i>RBM15-MRTFA</i></li> <li>• <i>NUP98</i> rearrangement</li> </ul>	
Additional examinations/measures	General condition (ECOG/WHO score)
	Evaluation of comorbidities (e.g., HCT-CI score)
	Clinical chemistry, coagulation, urinalysis
	Pregnancy test
	Genome panel sequencing in accordance with ELN-2022 recommendations (if clinically relevant)
	HLA typing (including siblings, parents, children, if applicable) + CMV status (for patients suitable for allogeneic stem cell transplantation)
	Hepatitis and HIV serology
	Chest X-ray
	ECG
	Echocardiogram, lung function
	Additional symptom-related diagnostics: Chest CT, abdominal ultrasound

## 5.2.2 Course of the disease

The following remission criteria apply:

### **Complete remission**

#### **Morphological complete remission (CR)**

- Blast cells in bone marrow <5%
- Absence of extramedullary manifestations
- Neutrophils  $\geq 1000/\mu\text{l}$  and platelets  $\geq 100,000/\mu\text{l}$
- No blasts in peripheral blood

#### **Complete remission with partial hematological regeneration (CRh)**

- Blast cells in bone marrow <5%
- Absence of extramedullary manifestations
- Neutrophils  $\geq 500/\mu\text{l}$  and platelets  $\geq 50,000/\mu\text{l}$
- No blasts in peripheral blood

This remission category describes a state of morphological leukemia-free status without adequate blood count regeneration, thus filling a gap between morphological leukemia-free status (MLFS) and CR with incomplete regeneration of neutrophils or platelets (CRi). The CRh category takes into account the fact that, with an adequate response, the prognosis can be favorably influenced more by continuing therapy before achieving full CR than by a delay due to regeneration [19].

#### **Morphological complete remission with incomplete hematological regeneration (CRi)**

- Blasts in bone marrow <5%
- Absence of extramedullary manifestations
- Blood cell regeneration detectable based on neutrophils or thrombocytes, but not meeting CR or CRh criteria
- No blasts in peripheral blood

#### **MRD-negative complete remission (CR<sub>MRD-</sub>, CRh<sub>MRD-</sub>, CRi<sub>MRD-</sub>)**

- CR/CRh/CRi with MRD below a defined threshold (in RT-qPCR or MFC)

#### **CR/CRh/CRi with MRD in the low positive (low level) range (CR/CRh/CRi<sub>MRD-LL</sub>)**

- Defined for CBF-AML and NPM1-mutated AML
- RT-qPCR level <2% (currently under revision by ELN)

#### **CR/CRh/CRi MRD positive (CR/CRh/CRi<sub>MRD+</sub>)**

#### **Morphologically leukemia-free state (MLFS):**

- Blast cells in bone marrow <5%
- Absence of extramedullary manifestations
- No blasts in peripheral blood
- No peripheral blood regeneration required

### **Partial remission (PR)**

- Reduction of blasts in bone marrow to 5-25% AND decrease in blasts by at least 50% compared to the time of diagnosis
- Neutrophils  $\geq 1000/\mu\text{l}$  and platelets  $\geq 100,000/\mu\text{l}$
- No blasts in peripheral blood

### **Refractory disease**

- No CR/CRh/CRi at a predefined remission time point (response landmark), i.e., for example
  - After 2 cycles of intensive induction
  - After, for example, 180 days after the start of non-intensive therapy
- Formally, both PR and loss of PR fall into the category of refractory disease, but may have different implications regarding subsequent allogeneic hematopoietic stem cell transplantation.

### **Relapse after CR**

- Increase in blasts in the bone marrow to  $\geq 5\%$  or blasts in the peripheral blood that cannot be explained by reactive blood cell regeneration, or
- extramedullary AML manifestations

## **5.3 Classification**

### **5.3.1 Overview**

In 2022, two classification systems for AML were published in parallel: the updated WHO classification [16] and the newly created International Consensus Classification (ICC) [17]. Both classification systems share the primary importance of recurrent genetic changes, some of which can define AML independently of the blast count. In addition to minor differences in genetically defined entities (see chapter 5.2.1), according to the WHO, no blast threshold is necessary for the diagnosis of many of these recurrent changes, while the ICC requires a blast threshold of  $\geq 10\%$ . Patients without AML with defining recurrent genetic alterations but with 10-19% blasts are assigned to the new ICC category MDS/AML, while AML is diagnosed at 20% or above. In the WHO classification, patients without AML-defining genetic changes and 10-19% blasts are assigned to the group of myelodysplastic neoplasms with increased blast percentage 2 (MDS-IB2).

According to WHO 2022, patients with 20% or more blasts without recurrent genetic alterations will continue to be categorized according to their morphological differentiation characteristics, while the ICC summarizes this group under the name "not otherwise specified" (NOS).

Both classification systems have included documented MDS history and certain characteristic genetic changes in the group of myelodysplasia-associated AMLs, while the sole presence of multilineal dysplasia at the time of diagnosis no longer justifies assignment to the group of myelodysplasia-associated AMLs. While AML-MR (replacing AML-MRC) remains a separate entity in the WHO classification, the MDS association in the ICC classification is either part of the genetically defined entities or "only" a "diagnostic qualifier" for the actual entity.

For the classifications according to WHO and ICC 2022, see [Table 2](#) and [Table 3](#).

### 5.3.2 AML with myelodysplasia-associated changes

When approving CPX-351, the FDA and EMA linked the indication for the substance to the presence of AML-MRC according to the WHO in order to assign the heterogeneous patient population in the approval study to a standardized diagnostic group. Knowledge of the MRC subgroup after the approval of CPX-351 thus had immediate therapeutic consequences, as corresponding patients can be treated with the substance.

An AML-MRC according to WHO 2016 is present at  $\geq 20\%$  myeloblasts in BM or PB if at least one of the following criteria is met:

- MDS or MDS/MPN in the previous course
- Myelodysplasia-associated cytogenetic changes (see below)
- Multilineal dysplasia in BM at initial diagnosis of AML ( $\geq 50\%$  dysplasia in  $\geq 2$  hematopoietic lineages) in the absence of genetic markers from the WHO entity "Acute myeloid leukemia with recurrent genetic aberrations"

According to the WHO 2016, the following cytogenetic changes are considered myelodysplasia-associated:

- Complex karyotype (defined as 3 or more chromosomal aberrations without the simultaneous presence of any of the genetic markers from the WHO entity "Acute Myeloid Leukemia with recurrent genetic aberrations")
- Unbalanced aberrations: -7 or del(7q); -5 or del(5q); i(17q) or t(17p); -13 or del(13q); del(11q); del(12p) or t(12p); idic(X)(q13)
- Balanced aberrations: t(11;16) (q23.3;p13.3); t(3;21)(q26.2;q22.1); t(1;3) (p36.3;q21.2); t(2;11)(p21;q23.3); t(5;12) (q32;p13.2); t(5;7)(q32;q11.2); t(5;17) (q32;p13.2); t(5;10) (q32;q21.2); t(3;5) (q25.3;q35.1)

The new WHO classification 2022 defines the entity AML MDS-related (AML-MR) by a history of MDS or MDS/MPN or the following genetic alterations:

- Complex karyotype (defined as 3 or more chromosomal aberrations)
- Cytogenetic alterations: -7 or del(7q); -5 or del(5q); i(17q) or t(17p); **-13 or del(13q); del(11q)**; del(12p) or t(12p); idic(X)(q13)
- Somatic mutations: *ASXL1*, *BCOR*, *EZH2*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRSR2*

The ICC 2022 designates the following genetic alterations as MDS-associated (myelodysplasia-related):

- Complex karyotype (defined as 3 or more chromosomal aberrations without the simultaneous presence of a recurrent AML-defining genetic alteration)
- Cytogenetic alterations: -7 or del(7q); -5 or del(5q); i(17q) or t(17p); del(12p) or t(12p); idic(X)(q13), **+8, del(20q)**
- Somatic mutations: *ASXL1*, *BCOR*, *EZH2*, ***RUNX1***, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRSR2*

In addition, the ICC defines a history of MDS or MDS/MPN as a diagnostic qualifier.

### 5.3.3 Therapy-related myeloid neoplasia (tAML)

The inclusion of CPX-351 in the 2018 approval also had therapeutic implications for this group. The 2016 WHO classification defined any myeloid neoplasm that occurred after previous cytotoxic therapy as therapy-associated [20]. There were no restrictions on the substances or radia-

tion modalities and doses used, and no definition of the time sequence of AML following previous therapy.

In the current WHO classification, the entity "therapy-associated" (tAML) has been replaced by the entity "post-cytotoxic therapy" (pCT). However, the term "therapy-associated" is still found in the ICC as a diagnostic addition.

**Table 2: WHO classification of AML 2022 [16]**

<b>Acute myeloid leukemia with defining genetic alterations</b>	
	Acute promyelocytic leukemia with <i>PML::RARA</i> fusion
	Acute myeloid leukemia with <i>RUNX1::RUNX1T1</i> fusion
	Acute myeloid leukemia with <i>CBFB::MYH11</i> fusion
	Acute myeloid leukemia with <i>DEK::NUP214</i> fusion
	Acute myeloid leukemia with <i>RBM15::MRTFA</i> fusion
	Acute myeloid leukemia with <i>BCR::ABL1</i> fusion*
	Acute myeloid leukemia with <i>KMT2A</i> rearrangement
	Acute myeloid leukemia with <i>MECOM</i> rearrangement
	Acute myeloid leukemia with <i>NUP98</i> rearrangement
	Acute myeloid leukemia with <i>NPM1</i> mutation
	Acute myeloid leukemia with <i>CEBPA</i> mutation* <sup>¶</sup>
	Acute myeloid leukemia associated with myelodysplasia*
	Acute myeloid leukemia with other defining genetic alterations*
<b>Acute myeloid leukemia, defined by differentiation</b>	
	Acute myeloid leukemia with minimal differentiation
	Acute myeloid leukemia without maturation
	Acute myeloid leukemia with maturation
	Acute basophilic leukemia
	Acute myelomonocytic leukemia
	Acute monocytic leukemia
	Acute erythroleukemia
	Acute megakaryocytic leukemia

Legend:

\* Diagnosis requires a blast count  $\geq 20\%$

Either biallelic mutation (*biCEBPA*) or *bZIP* mutation in at least one allele (*smbZIP-CEBPA*)

**Table 3: International consensus classification of AML 2022 [17]**

<b>Acute myeloid leukemia with recurrent genetic alterations (requiring ≥10% blasts in bone marrow or peripheral blood)*</b>	
	APL with t(15;17)(q24.1;q21.2)/ <i>PML::RARA</i>
	AML with t(8;21)(q22;q22.1)/ <i>RUNX1::RUNX1T1</i>
	AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/ <i>CBFB::MYH11</i>
	AML with t(9;11)(p21.3;q23.3)/ <i>MLLT3::KMT2A</i>
	AML with t(6;9)(p22.3;q34.1)/ <i>DEK::NUP214</i>
	AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/ <i>GATA2, MECOM(EVI1)</i>
	AML with other rare recurrent translocations
	AML with mutated <i>NPM1</i>
	AML with in-frame <i>bZIP</i> mutated <i>CEBPA</i>
	AML with t(9;22)(q34.1;q11.2)/ <i>BCR::ABL1*</i>
<b>Acute myeloid leukemia (≥20% blasts in bone marrow or peripheral blood) or MDS/AML (10-19% blasts in bone marrow or peripheral blood)</b>	
	AML with mutated TP53#
	AML gene mutations, defined as mutations in <i>ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2</i>
	AML with myelodysplasia-associated cytogenetic alterations
	AML not otherwise specified
<b>Diagnostic additions</b>	
	Therapy-associated##: previous chemotherapy, radiotherapy, immunotherapy
	Progression from MDS: diagnostically confirmed MDS history >3 months
	Progression from MDS/MPN: diagnostically confirmed MDS/MPN history >3 months
	Germline predisposition present
	Germline predisposition (specify type)

*Legend:*

\*Exceptions: AML with *bcr::abl1* requires ≥20% to differentiate from accelerated CML

#Presence of a pathogenic somatic TP53 mutation (with a VAF of at least 10%, with or without loss of the wild-type TP53 allele) defines this entity

Previous therapy for non-myeloid neoplasms

**Table 4: Other common AML entities from WHO and ICC 2022**

Subgroup	Specification
Myeloid sarcoma	
Blastic plasmacytoid dendritic neoplasia	
Myeloid Proliferations in Down Syndrome	Myeloid leukemia in Down syndrome
	Transient abnormal myelopoiesis (syn.: transient myeloproliferative disorder)
Acute leukemias of unclear lineage	Acute undifferentiated leukemia
	Acute leukemia with mixed phenotype and t(9;22)(q34;q11.2); <i>BCR::ABL1</i>
	Acute leukemia with mixed phenotype and t(v;11q23); MLL rearranged/ <i>KMT2A</i>
	Acute leukemia with mixed phenotype, B/myeloid, NOS
	Acute leukemia with mixed phenotype, T/myeloid, NOS

### 5.3.4 Acute promyelocytic leukemia (APL) and blastic plasmacytoid dendritic cell neoplasm (BPDCN)

Acute promyelocytic leukemia (APL) occupies a special position, with the highest prognosis of all AML diseases and a long-term survival rate of over 80% if the acute initial coagulation disorder and resulting life-threatening complications can be effectively controlled. For the diagnosis and treatment of APL, please refer to [Onkopedia Acute Promyelocytic Leukemia](#). Blastic plasmacytoid dendritic cell neoplasia, which differs from AML in terms of prognosis and treatment, should be distinguished from AML; see [Onkopedia BPDCN \(German Version\)](#).

## 5.4 Prognostic factors

Age and molecular or cytogenetic changes have the strongest influence on prognosis. With increasing age, the chance of achieving complete remission decreases, while the risk of recurrence increases. In the Swedish registry (initial diagnosis date from 1997 to 2006), the 5-year survival rates were 60% for patients under 30 years of age, 43% for patients between 45 and 54 years of age, 23% for patients between 55 and 64 years of age, and continued to decline with increasing age [4]. The molecular cytogenetic changes at initial diagnosis are divided into three groups according to the ELN classification of 2022 [18] (see Table 5).

**Table 5: Molecular cytogenetic risk groups according to the European LeukemiaNet ELN 2022 classification [18]**

ELN risk group	Aberrations
Favorable	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); <i>CBFB::MYH11</i> ;† Mutated <i>NPM1</i> §,† without <i>FLT3-ITD</i> bZIP in-frame mutated <i>CEBPA</i> §
Intermediate	Mutated <i>NPM1</i> † with <i>FLT3-ITD</i> Wild-type <i>NPM1</i> with <i>FLT3-ITD</i>  Cytogenetic aberrations that were not classified as favorable or unfavorable
Unfavorable	t(6;9)(p23;q34.1); <i>DEK::NUP214</i> t(v;11q23.3); <i>KMT2A</i> rearranged#  t(8;16)(p11;p13); <i>KAT6A::CREBBP</i> inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); <i>GATA2, MECOM(EVI1)</i> t(3q26.2;v), <i>MECOM(EVI1)</i> rearranged -5 or del(5q); -7; -17/abn(17p) complex karyotype (≥3 aberrations)**; monosomic karyotype†† Mutation in <i>ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2</i> ‡‡ Mutated <i>TP53</i> ³

Legend:

†Based primarily on results from patients who received intensive therapy; initial risk assessment, may change during the course of therapy (see chapter 5.4.1)

‡Simultaneous KIT and/or FLT3 mutations do not change the risk category

§AML with NPM1 mutation and unfavorable cytogenetic changes are classified as unfavorable risk

¶Only in-frame mutations affecting the basic leucine zipper (bZIP) region of CEBPA are associated with a favorable prognosis, regardless of whether they occur monoallelically or biallelically

The presence of t(9;11)(p21.3;q23.3) trumps rare concurrent unfavorable aberrations, i.e., it tips the balance for classification in the intermediate risk group

#except KMT2A partial tandem duplication (PTD).

\*\*Complex karyotype: ≥3 separate chromosomal aberrations without the presence of other recurrent changes; hyperdiploid karyotypes with three or more trisomies (or polysomies) without structural chromosome changes are excluded from the definition of complex karyotype.

†† Monosomic karyotype: a monosomy associated with at least one other monosomy (except -X or -Y) or another structural chromosomal aberration (except CBF-AML)

‡‡ Until further notice, these changes should not be considered unfavorable if they occur together with favorable markers (see above).

aTP53 mutation with a VAF of at least 10%, regardless of TP53 allele status (mono- or biallelic mutation); TP53 mutations are significantly associated with complex or monosomic karyotypes

The ELN classification is not valid for unfit patients receiving non-intensive therapy (e.g., HMA+venetoclax). According to subgroup analyses of the VIALE-A study, the absence of a TP53 or N/KRAS or FLT3-ITD mutation during therapy with HMA+Venetoclax appears to be associated with a favorable prognosis (median OS 24 months), while mutated TP53 is associated with a poor prognosis (median OS 5.5 months). A mutation in RAS or FLT3-ITD without TP53 mutation marks an intermediate course (median OS 12 months) [21]. The corresponding ELN-2024 risk classification is shown in table 6.

Table 6: ELN risk classification for patients receiving less intensive therapy (ELN 2024 "Less-Intensive")<sup>a</sup>

Risk group	Genetic aberration
Favorable	<ul style="list-style-type: none"><li>• Mutated <b>NPM1</b> (FLT3-ITD<sup>neg</sup>, NRAS<sup>wt</sup>, KRAS<sup>wt</sup>, TP53<sup>wt</sup>)</li><li>• Mutated <b>IDH2</b> (FLT3-ITD<sup>neg</sup>, NRAS<sup>wt</sup>, KRAS<sup>wt</sup>, TP53<sup>wt</sup>)</li><li>• Mutated <b>IDH1</b><sup>b</sup> (TP53<sup>wt</sup>)</li><li>• Mutated <b>DDX41</b><sup>c</sup></li><li>• Other cytogenetic and/or molecular aberrations (FLT3-ITD<sup>ne</sup>, NRAS<sup>wt</sup>, KRAS<sup>wt</sup>, TP53<sup>wt</sup>)</li></ul>
Intermediate	<ul style="list-style-type: none"><li>• Other cytogenetic and molecular aberrations (FLT3-ITD<sup>pos</sup> and/or NRAS<sup>mut</sup> and/or KRAS<sup>mut</sup>; TP53<sup>wt</sup>)</li></ul>
Unfavorable	<ul style="list-style-type: none"><li>• Mutated TP53</li></ul>

Legend:

<sup>a</sup> This classification does not apply to patients who have previously been treated with a hypomethylating agent.

<sup>b</sup> The favorable risk classification applies specifically to patients who have been treated with **azacitidine + ivosidenib**, regardless of the presence of activating signaling pathway mutations.

<sup>c</sup> The presence of a **DDX41 mutation** at near-heterozygous frequency should raise consideration of a **germline mutation**.

<sup>d</sup> For many cytogenetic and molecular aberrations, whether alone or in combination, there is currently insufficient data; they are provisionally classified as favorable or intermediate, depending on the absence or presence of activating signaling pathway mutations.

### 5.4.1 Measurable residual disease (MRD)

One of the strongest prognostic markers is the level of measurable residual disease (MRD). It allows for assessment during the course of therapy because it reflects the therapeutic responsiveness of the individual AML disease [22, 23]. A well-validated MRD measurement of prognostically relevant markers can thus be helpful in setting the therapeutic course, in monitoring during treatment, and in follow-up, and can serve as a surrogate endpoint in clinical studies [22].

Established MRD methods for clinical use are multicolor flow cytometry (MFC) and quantitative real-time PCR (RT-qPCR). While MFC is applicable to the majority of AML patients, it has comparatively low sensitivity and limited reproducibility of findings, whereas RT-qPCR is characterized

by higher sensitivity and reproducibility. However, due to the currently limited number of suitable molecular markers, the method is only suitable for 40-50% of AML patients (see Table 7).

NGS and dPCR are currently still in the development stage and should not be used for therapy management outside of studies. However, there is already sufficient evidence for NGS-based FLT3-ITD MRD after two cycles of intensive therapy to assess the risk of recurrence [24- 28].

**Table 7: Methods for MRD determination in AML [18]**

	Method	Target structure	Sensitivity	Applicable in % of AML	Processing time (d)	Limitations/problems
<b>Established</b>	Multi-parameter flow cytometry (MFC)	LAIP or DfN	$10^{-3}$ to $10^{-4}$	85-90	2	Lower sensitivity, evaluation with stronger subjective influence
<b>Established</b>	Real-time quantitative PCR (RT-qPCR)	Robust data: <i>NPM1</i> , <i>CBFB::MYH11</i> , <i>RUNX1::RUNX1T1</i> Less well validated: <i>KMT2A::MLL3</i> , <i>DEK::NUP214</i> , <i>BCR::ABL1</i> , <i>WT1</i>	$10^{-4}$ to $10^{-5}$	40-50 <sup>a</sup>	3-5	Limited applicability
<b>Established</b>	Next-generation sequencing (NGS) <sup>b,c</sup>	<i>FLT3-ITD</i> , <i>NPM1</i>	$\geq 10^{-4}$	~100	5-10	Lower sensitivity, expensive, technically demanding
<b>Exploratory</b>	Next-generation sequencing (NGS) <sup>b,c</sup>	Potentially any somatic mutation <sup>b</sup>	$10^{-2}$ to $10^{-4}$	~100	5-10	Lower sensitivity, expensive, technically demanding
<b>Exploratory</b>	Digital PCR (dPCR)	Specific mutations	$10^{-3}$ to $10^{-4}$	~70	3-5	Specific assay required for each mutation, limited sensitivity

Legend:

DfN, different from normal; LAIP, leukemia-associated immunophenotype.

<sup>a</sup> Less common in older AML patients.

<sup>b</sup> The NGS MRD threshold has not been defined for individual mutations; NGS MRD positivity has been provisionally defined as  $\geq 0.1\%$  VAF; clonal hematopoiesis mutations and germline mutations are excluded

<sup>c</sup> Common gene mutations associated with premalignant clonal hematopoiesis (*DNMT3A*, *TET2*, and *AXSL1*) are excluded. Further studies are needed to distinguish mutations in residual AML from mutations indicating clonal hematopoiesis.

## 5.5 Differential diagnosis

The combination of morphology, cytochemistry, immunophenotyping, cytogenetics, and molecular genetics usually allows for an unambiguous diagnosis of acute myeloid leukemia. Table 8 lists some possible differential diagnoses and the corresponding diagnostics.

**Table 8: Differential diagnosis for suspected acute myeloid leukemia**

Disease	Tests
Acute lymphocytic leukemia	Bone marrow cytochemistry (peroxidase or esterase positivity) Immunophenotyping Cytogenetics and molecular genetics
Acute leukemia of unclear lineage	Bone marrow cytochemistry (peroxidase or esterase positivity) Immunophenotyping Cytogenetics and molecular genetics
Viral infections (e.g., parvovirus B19, EBV, CMV, or HIV)	Virus detection (PCR, Ag, or serological) Absence of blasts in PB or BM immunophenotyping
Myelodysplastic syndromes	< 20% blasts in bone marrow and/or peripheral blood Cytogenetics and molecular genetics
Vitamin B12/folic acid deficiency anemia	Medical history Vitamin B12 and folic acid levels BM morphology (megaloblasts)
Aplastic anemia	BM morphology (aplasia) Cytogenetics
Leukemic lymphomas	No evidence of myeloid blasts in PB or BM Immunophenotyping Soluble interleukin-2 receptor, if applicable
Myeloproliferative syndromes	< 20% blasts in BM (exception: blast crisis of CML) Often no anemia or thrombocytopenia Cytogenetics (t(9;22)) Molecular genetics ( <i>BCR-ABL</i> , <i>JAK2</i> mutation, <i>CALR</i> mutation, <i>MPL</i> mutation)

## 6 Therapy

The entity "MDS/AML" defined by the ICC with 10-19% blasts is primarily relevant for inclusion in clinical trials, while outside of trials, AML-specific therapy is not generally recommended for this entity. This recommendation is based on the sometimes higher hematological toxicity in MDS patients and the fact that the evidence for the efficacy of established AML therapies comes from studies with AML patients and a blast count  $\geq 20\%$ .

### 6.1 Treatment structure

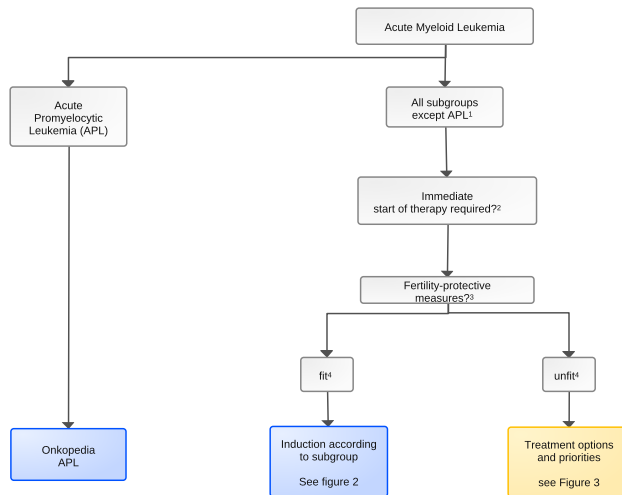
The treatment of AML should be carried out at a hematology-oncology center and as part of a treatment study. Since the 1980s, several AML study groups and multicenter studies have been formed in Germany: SAL-AMLCG (<https://www.aml-germany.com>), AMLSG (<https://www.amlsg.de/>), OSHO (<https://osho-studiengruppe.de/>). For centers that are not integrated into an AML study group, therapy based on a valid study protocol is recommended.

Immediately after the initial diagnosis, a decision must be made regarding the urgency of initiating therapy (see [Figure 1](#)).

For young patients who wish to have children or have not yet completed their family planning, the possibility of fertility preservation measures should be discussed. If possible, cryopreservation of sperm should be performed in men before the start of therapy. In women, the necessary time window of up to 2 weeks for hormonal stimulation and egg preservation is usually not available due to the urgency of AML therapy. The option of ovarian tissue preservation is also problematic due to possible complications and the risk of leukemia cell infiltration. If the patient wishes to have children, egg preservation should be discussed during the first remission before initiation of consolidation therapy; see [AYApedia Fertility and Fertility Preservation](#).

The diagnosis of AML during pregnancy poses a particular challenge. See the Onkopedia guideline [Systemic tumor therapy for pregnant women](#).

**Figure 1: Algorithm for initiating therapy**



Legend:

■ curative therapy; ■ non-curative therapy;

<sup>1</sup> APL – Acute promyelocytic leukemia

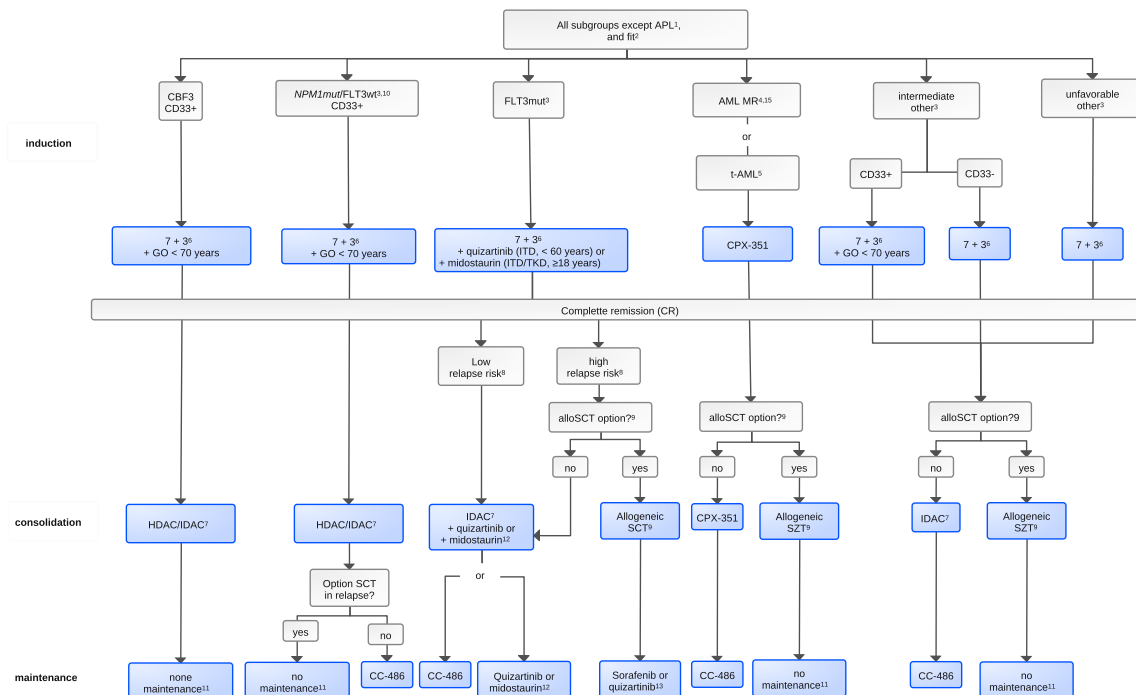
<sup>2</sup> Leukostasis or tumor lysis syndrome or derailed coagulation

<sup>3</sup> [https://www.dgho.de/publikationen/schriftenreihen/junge-erwachsene/dgho\\_gpsr\\_xi\\_de\\_0971\\_web-1](https://www.dgho.de/publikationen/schriftenreihen/junge-erwachsene/dgho_gpsr_xi_de_0971_web-1)

<sup>4</sup> Orientation based on ECOG status and comorbidity

In cases of morphological suspicion or cytogenetic (t(15;17)) or molecular biological (*PML-RARA*) evidence of acute promyelocytic leukemia (APL, FAB M3), therapy with all-trans retinoic acid (ATRA) must be initiated immediately, followed by APL-specific cytostatic therapy, see [Onkopedia Acute Promyelocytic Leukemia](#).

**Figure 2: Therapy algorithm for the initial decision at first diagnosis**



**Legend:**

  curative therapy;

<sup>1</sup> APL - acute promyelocytic leukemia excluded

<sup>2</sup> Fit for intensive therapy, based on ECOG status and comorbidity

<sup>3</sup> See Table 5 [18]

<sup>4</sup> AML MR: following the removal of the AML-MRC subgroup in the revisions of the AML definitions by the WHO and ICC, the indication group for CPX-351 in myelodysplasia-associated AML largely corresponds to the entity "AML myelodysplasia-associated (AML-MR)" according to WHO 2022, or the entities "AML with myelodysplasia-associated gene mutations," "AML with myelodysplasia-associated cytogenetic alterations," and "AML with progression from MDS or MDS/MPN" according to ICC 2022  
Moderate non-randomized evidence for the superior efficacy of CPX-351 over 7+3 for patients <60 years of age; randomized evidence for superiority in molecularly defined AML-MR (myelodysplasia-related gene mutations MRG) and no superiority in TP53 mutation

<sup>5</sup> t-AML - Therapy-associated AML

<sup>6</sup> 7+3 - Treatment regimen with Ara-C on 7 days, daunorubicin on 3 days

<sup>7</sup> HDAC - high-dose Ara-C; IDAC - intermediate-dose Ara-C;

<sup>8</sup> Low risk of recurrence:

- FLT3-TKD + NPM1mut

- FLT3-TKD + NPM1wt + MFC-MRD in KM <0.1%

High risk of recurrence: all others, i.e.

- FLT3-ITD

- FLT3-TKD + NPM1wt + MFC-MRD in BM ≥0.1% after 2 cycles of intensive therapy (2 x induction or 1 x induction + 1 x consolidation)

<sup>9</sup> allo SCT - allogeneic stem cell transplantation

<sup>10</sup> This recommendation includes bZIP inframe CEBPA-mutated patients

<sup>11</sup> MRD monitoring if possible

<sup>12</sup> Same TKI as in induction therapy

<sup>13</sup> If sorafenib is contraindicated, quizartinib can be used as an alternative maintenance therapy after alloSCT

In general, intensive curative therapy for AML is divided into induction therapy with the goal of complete remission (CR) and post-remission therapy to maintain CR. The chance of achieving CR after intensive induction therapy is determined primarily by the genetic background of the AML and less by the age of the patient [29]. It is around 80-90% in patients with favorable cytogenetic or molecular genetic aberrations (including t(8;21), inv(16), NPM1 mutation, CEBPA bZIP inframe) is >80-90% compared to <30% in patients with unfavorable aberrations (including TP53 mutation, monosomal karyotype). Since comprehensive diagnostics, including genetic analysis, form the basis of modern subgroup-specific therapy, it is advisable to wait until these data are available before starting therapy [30], see Figure 2.

Emergency initiation of intensive therapy should be considered in patients with signs of leukostasis syndrome with or without hyperleukocytosis and/or tumor lysis syndrome or uncontrolled coagulation. Therapy then consists of administering hydroxyurea and, if necessary, cytarabine if symptom control cannot be achieved [31]. It should be noted that effective therapy of hyperleukocytosis (>50-100 Gpt/l) may require a dosage of hydroxyurea of 4-5 g per day. Cytarabine can be administered as a preliminary phase or as part of a 7+3 regimen. Anthracyclines should only be administered once the leukocyte count has fallen below 30 Gpt/l in order to avoid negatively affecting the rheological properties of the blood [32].

If a wait-and-see approach was decided upon at the time of diagnosis due to a clinically stable situation and the patient develops the above-mentioned life-threatening clinical symptoms before the results are received, intensive therapy should be determined on the basis of the findings available to date and started immediately.

Older patients with a biological age over 75 years and/or significant comorbidities should not be offered intensive, curative therapy due to high toxicity and early mortality with only about a 10% chance of long-term remission [33]. The goal of therapy is to prolong life with the best possible quality of life. The basis for this is supportive care (best supportive care, BSC) with the addition of potentially life-prolonging cytostatic treatment, see chapter 6.1. 1. 3.

### **6.1.1 First-line therapy**

#### **6.1.1.1 Patients who can be treated intensively with curative therapy ("fit")**

This group includes patients who have a biological age of up to 75 years and have no or few comorbidities.

For young patients who wish to have children or have not yet completed their family planning, fertility-preserving measures should be considered depending on the urgency of the treatment.

##### **6.1.1.1.1 Induction therapy**

###### **6.1.1.1.1.1 7+3**

This therapy is used in patients who cannot be assigned to any of the following subgroups or who have an immediate indication for therapy at initial diagnosis and for whom the results of genetic diagnostics are not yet available.

Standard induction therapy (3+7 regimen) involves a combination of three days of anthracycline/anthracenedione (e.g., daunorubicin 60 mg/m<sup>2</sup>, idarubicin 10-12 mg/m<sup>2</sup>, or mitoxantrone 10-12 mg/m<sup>2</sup>) and 7 days of cytarabine (100-200 mg/m<sup>2</sup> continuously), see [Appendix Therapy Protocols \(German Version\)](#).

An alternative induction regimen is recommended for patients classified into the following subgroups:

- Patients with CD33-positive core-binding factor AML (CBF-AML), patients with CD33-positive NPM1 mutation in FLT3wt and with CD33-positive AML and bZIP in-frame mutated CEBPA
- Patients with FLT3 mutation
- Patients with myelodysplasia-associated and patients with therapy-associated AML (tAML) in FLT3wt

- Patients with CD33-positive intermediate-risk AML in FLT3wt

For all patients undergoing intensive chemotherapy, if the blast count is <5% in the early puncture or remission check after the first induction cycle, no second induction therapy is required before starting post-remission therapy [34].

#### 6.1.1.1.1.2 Patients with CD33-positive core-binding factor AML (CBF-AML), patients with CD33-positive NPM1 mutation in FLT3wt, and patients with CD33-positive AML and bZIP in-frame mutated CEBPA

For patients in this subgroup, the addition of gemtuzumab ozogamicin (GO) to the first cycle of standard induction therapy with 7+3 is recommended. Gemtuzumab ozogamicin (GO), a conjugate of CD33 antibody and cytotoxin calicheamicin, was approved by the EMA in 2018 for primary therapy in combination with standard chemotherapy based on the published results of the French ALFA-0701 study and other randomized studies and their meta-analysis [35, 36] for primary therapy in combination with standard chemotherapy based on the ALFA-0701 study. CD33 positivity is a prerequisite for the use of this substance, as stipulated in the approval of GO. The meta-analysis of randomized therapy intervention studies shows a clear advantage in overall survival for the CBF-AML patient group through the addition of GO to standard induction with DA (HR 0.5; 5-year survival 77.5% versus 55%) [35]. The advantage does not appear to result from an increase in CR rates [35, 37], but rather from a greater reduction in the leukemic burden in CR patients (deeper remission of CR or higher remission quality) and a resulting reduced risk of relapse [38].

The majority of patients in the above meta-analysis came from the MRC/NCRI studies AML15 and AML16 and received GO at a dose of 3 mg/m<sup>2</sup> as a single dose, as did those in the AMLSG 09-09 study. The NCRI-AML18 study has now demonstrated greater efficacy with two doses of GO compared to one dose in older patients aged 60 years and above (median age 69 years), and the GnG study showed a trend toward higher remission rates and longer survival with three doses of GO compared to one dose [39]. However, this efficacy could no longer be demonstrated in patients over 70 years of age [40]. Based on the greater effect size for recurrence risk, EFS/RFS, and OS in the three-time administration in the ALFA study, as well as the greater MRD reduction demonstrated by GO in the ALFA and AMLSG studies, three-time administration is recommended in accordance with the approval. According to the approval, GO should only be administered in the first, not a possible second induction therapy.

In the randomized AMLSG 09-09 study, this was also demonstrated for NPM1-mutated patients. CR rates were similarly high with and without GO, but in patients in CR, relapse-free survival was significantly and clinically relevant prolonged, based on a greater reduction in MRD by GO [41]. This effect was particularly pronounced in patients up to 60 years of age. A significant prolongation of EFS was observed in the age group up to 60 years (HR 0.71), numerically also in patients aged 61-70 years (HR 0.75), while a negative trend was observed in the age group >70 years (HR 1.42) [42]. In patients >70 years, the rate of induction deaths was increased, which is why the primary endpoint EFS in the overall population could not be improved by GO. The cause of the increased early mortality is thought to be the increased toxicity of the combination due to the addition of etoposide to 7+3/DA. In the ALFA-0701 study, early mortality was not significantly different, but the upper patient age was limited to 70 years.

Based on an overview of the data, GO is recommended for NPM1-positive AML due to its significant antileukemic effect, but its use in patients over 70 years of age is not recommended. The significance of GO during consolidation therapy is less clearly established [43], but its use is possible within the scope of the approval, see [Drug Evaluation Gemtuzumab Ozogamicin \(German Version\)](#) and [Appendix Acute Myeloid Leukemia approval status \(German Version\)](#).

#### 6.1.1.1.1.3 Patients with FLT3 mutation

Patients with FLT3-ITD or FLT3-TKD mutation should receive a tyrosine kinase inhibitor (TKI) from day 8 to 21 of induction therapy. In the presence of an FLT3-ITD mutation, the TKIs midostaurin and quizartinib are available following positive study results from RATIFY and QuANTUM-First. Both studies were placebo-controlled. To date, there has been no direct comparison between the two substances.

According to data from a randomized placebo-controlled study, midostaurin in combination with standard chemotherapy can significantly prolong EFS, RFS, and OS in FLT3-mutated AML patients up to 60 years of age [44]. Based on this study, midostaurin was approved by the EMA in 2017 for combination with standard induction chemotherapy, chemoconsolidation, and as maintenance therapy for twelve 28-day cycles in patients with newly diagnosed FLT3-mutated AML, see [Drug Evaluation Midostaurin \(German Version\)](#).

Contrary to the study population (age 18-59 years), approval was granted without an upper age limit. Data for patients between the ages of 60 and 70 are available from a phase II study [45]. In patients scheduled for hematopoietic stem cell transplantation, midostaurin should be discontinued 48 hours prior to conditioning therapy. When used concomitantly with strong CYP3A4 inhibitors (e.g., ketoconazole, posaconazole, voriconazole, ritonavir, or clarithromycin), close attention should be paid to the risk of midostaurin level increases and toxicity, especially in patients aged >60 years [45]. Strong CYP3A4 inducers (e.g., carbamazepine, rifampicin, enzalutamide, phenytoin, St. John's wort) should not be administered concomitantly due to the reduction in midostaurin levels.

In patients with internal tandem duplication (FLT3-ITD), the randomized QuANTUM-First study investigated the second-generation tyrosine kinase inhibitor quizartinib in combination with standard induction, consolidation, and maintenance therapy for 3 years in a randomized, placebo-controlled trial. Compared to placebo, quizartinib increased the CR rate from 64.9% to 71.6% and reduced the cumulative recurrence incidence after 2 years from 43.3% to 31.2%. As a result, quizartinib significantly prolonged median overall survival compared to placebo from 15.1 to 31.9 months (HR 0.78; p=0.0324) [26].

In younger patients <60 years of age with FLT3-ITD mutation, a comparison of the hazard ratios for overall survival shows a value of 0.68 for quizartinib and 0.8 for midostaurin, suggesting that quizartinib is at least equally or more effective. In older patients aged 60 years and older, a subgroup analysis of the QuANTUM-First study shows no survival benefit for the addition of quizartinib. In contrast, older patients in the AMLSG 16-10 study treated with midostaurin have a survival advantage over a historical comparison group not treated with midostaurin [45].

Outside of studies, the addition of quizartinib is therefore recommended for patients with FLT3-ITD <60 years of age, and the addition of midostaurin is recommended for patients aged 60 years and older undergoing intensive induction.

Patients with FLT3-TKD mutation should be treated with midostaurin.

#### 6.1.1.1.4 Patients with myelodysplasia-associated AML and patients with therapy-associated AML (tAML)

For this subgroup, the use of CPX-351 (a liposomal formulation of cytarabine and daunorubicin in a fixed molar ratio) is approved as a substitute for the classic combination of cytarabine and anthracycline in induction therapy. The approval is based on a significant survival benefit of 9.6 months versus 5.9 months after 7+3 in the randomized approval study (HR 0.69) [46]. The patients included were between 60 and 75 years of age and belonged to the following different subgroups.

- Previous MDS (47%) or CMML (7.5%)
- De novo AML with MDS karyotype (25%)

- tAML (20%)

Deviating from the study population, approval was granted for patients with AML-MRC (including patients with multilineage dysplasia) and tAML and for all age groups  $\geq 18$  years.

With regard to the above-mentioned study population and the current AML classifications of 2022, the indication group for CPX-351 in myelodysplasia-associated AML largely corresponds to the entity "AML myelodysplasia-associated (AML-MR)" according to WHO 2022 or the entities "AML with myelodysplasia-associated gene mutations," "AML with myelodysplasia-associated cytogenetic alterations," and "AML with progression from MDS or MDS/MPN" according to ICC 2022. Based on smaller retrospective analyses, the new defining genetic alterations compared to the AML-MRC classification appear to be associated with a favorable response to CPX-351 [47 - 49].

Since younger patients were excluded from the CPX-351 approval study, there is a lack of randomized evidence of its efficacy in this age group. Recently published retrospective real-world data on CPX-351 predominantly describe mixed age groups without exclusion of younger patients, with comparable response rates and comparable to slightly longer median survival compared to the approval study [47, 50-58]. Retrospective comparative data with standard chemotherapy (7+3, Ida-FLAG) show similar survival times [47, 50, 51, 58]. A smaller subgroup analysis of the NCRI-AML19 study with predominantly younger patients showed a survival advantage of CPX-351 over Ida-FLAG for patients with molecularly defined myelodysplasia-associated genetic alterations and no advantage in TP53 mutation. Due to a high proportion of TP53 mutations in cytogenetically defined myelodysplasia-associated AMLs, CPX-351 was not superior in this group [49]. A subgroup analysis of the CPX-351 approval study in comparison to 7+3 confirms the superiority of CPX-351, especially in the subgroup of patients with molecularly defined myelodysplasia-associated AML (myelodysplasia-related gene mutations, MRG), and shows a lack of superiority in the presence of TP53 mutation [59]. In summary, there is moderate evidence for the efficacy of CPX-351 in younger patient groups (evidence level 3-4), but its superiority over 7+3 has not yet been prospectively demonstrated [47, 51]. Based on the randomized evidence of superiority in MRG from the NCRI-AML-19 study, which included predominantly younger patients, and based on increasing non-randomized evidence of superiority over 7+3 in patients  $< 60$  years of age, and the assumption of a biological continuum beyond the age limit of 60 years, the recommendation restriction for CPX-351 to patients  $\geq 60$  years of age no longer applies. The AMLSG 30-18 study is a randomized comparison between CPX-351 and 7+3, including in younger patients with intermediate- and high-risk AML (NCT03897127).

It should be noted that the liposomal formulation is associated with higher bone marrow toxicity, which manifests itself in an approximately 7-day prolongation of the post-therapeutic cytopenia phase. This did not lead to an increase in infectious complications, but to a 15% increase in bleeding in the CPX-351 arm. Within the approval study, the survival benefit from the use of CPX-351 was greatest in patients with consolidating allogeneic stem cell transplantation [46], see Appendix [Acute Myeloid Leukemia – Approval Status \(German Version\)](#), see Chapter 6.1.1.1.1 and [Drug Daunorubicin Cytarabine \(German Version\)](#)

#### 6.1.1.1.1.5 Patients with CD33-positive intermediate-risk AML with FLT3wt

For patients with intermediate cytogenetic risk, the meta-analysis on the effect of GO in combination with standard chemotherapy also demonstrated a survival benefit, with NPM1-mutated patients included in the intermediate risk group. The CR rate was not significantly increased by GO (OR 0.91), but overall survival was prolonged; the corresponding hazard ratio was 0.85. The corresponding 15% risk reduction at any time point and increase in 5-year survival from 35.5% to 40.7% is thus significantly lower than for patients with a favorable genetic constellation (see

above). Based on the overall data, GO is therefore recommended as optional in this patient group.

#### 6.1.1.1.1.6 Patients not assigned to the above subgroups

Patients who, according to the available specific diagnostics, cannot be assigned to any of the subgroups mentioned above, or who require immediate initiation of therapy upon initial diagnosis and for whom the results of genetic diagnostics are not yet available, receive standard induction therapy with 7+3.

Patients who do not respond to one or two cycles of induction therapy are considered primarily refractory and are treated with salvage chemotherapy, see chapter [6.1.2](#).

#### 6.1.1.1.2 Post-remission therapy

Patients who achieve CR require consolidation therapy, as otherwise a rapid relapse of AML is to be expected. Consolidation therapy can generally be carried out with higher-dose cytarabine or an allogeneic blood stem cell transplant. The choice of consolidation therapy is based on the risk profile or the corresponding AML subgroup, the general condition of the patient, and, in some cases, the MRD.

High-dose cytarabine (HDAC) is associated with a significantly prolonged RFS in the CBF-AML group compared to intermediate-dose cytarabine (IDAC), whereas it does not offer any RFS advantage over IDAC in cases of intermediate and unfavorable cytogenetic risk and generally makes no difference to OS [[60](#), [61](#)].

Myeloablative high-dose chemotherapy with autologous transplantation has a similarly low treatment-related mortality rate as higher-dose cytarabine and is occasionally used as an alternative consolidation option. However, the risk of relapse is significantly increased compared to allogeneic transplantation, and superiority in overall survival compared to higher-dose cytarabine has not yet been demonstrated. Nevertheless, this treatment principle appears to be particularly important in low-risk patients (CEBPA bZIP-inf, CBF-AML) [[62](#)].

##### 6.1.1.1.2.1 Patients with CD33-positive core-binding factor AML (CBF-AML) and patients with CD33-positive NPM1 mutation in FLT3wt and patients with CD33-positive AML and bZIP in-frame mutated CEBPA – consolidation

The risk of relapse in these subgroups is comparatively low at 20-40% [[63](#), [64](#)], so that post-remission therapy with high-dose cytarabine leads to a relatively high proportion of long-term remissions. Outside of studies, patients with cytogenetically favorable risk, i.e., t(8;21) or inv(16), should therefore receive chemotherapy consolidation with high-dose cytarabine (HDAC), as this is highly likely to achieve long-term remission [[64](#)], see [Appendix Acute Myeloid Leukemia Therapy Protocols \(German Version\)](#). This also applies to patients with AML and normal karyotype as well as NPM1 mutation without accompanying FLT3-ITD mutation [[65](#), [66](#)]. The disease in these patients can be monitored by measuring minimal/measurable residual disease (MRD) based on mutated *NPM1* and, in the event of molecular relapse or molecular persistence, a salvage concept can be implemented, if possible involving allogeneic stem cell transplantation.

A possible standard chemotherapy for younger patients outside of studies is the adapted CALGB protocol [[67](#)] with a high cytarabine dose of 3 g/m<sup>2</sup> twice daily for 3 days, see [Appendix Therapy Protocols \(German Version\)](#). Since cytarabine is associated with high toxicity in the older patient group, intermediate-dose cytarabine is used for better tolerability in older patients, see [Appendix Therapy Protocols \(German Version\)](#).

The significance of GO in post-remission therapy is unclear and, contrary to its approval, is not explicitly recommended, as in randomized studies GO was either only used in induction or all patients who received GO during induction were also treated with it in post-remission therapy. The approval status includes the administration of GO in two post-remission therapies in combination with daunorubicin and cytarabine based on the approval study. However, two randomized studies failed to demonstrate any advantage of GO in post-remission therapy.

Due to the lack of data on efficacy and the low risk of relapse in CBF-AML, maintenance therapy with oral azacitidine (CC-486) is not recommended in this patient group.

In NPM1-mutated AML, maintenance therapy with oral azacitidine (CC-486) is effective and, according to subgroup analyses of the approval study, led to an extension of median overall survival from 26.2 to 48.6 months in MRD-negative patients from 10.3 to 39.4 months [68]. Based on these data, maintenance therapy with oral azacitidine is recommended for patients who are not eligible for allogeneic transplantation during primary therapy or who would refuse it in the event of relapse. All other patients with NPM1-mutated AML and the option of allogeneic SCT in case of relapse should be closely monitored for NPM1 MRD instead of receiving CC-486 maintenance therapy in order to receive allogeneic SCT promptly in case of molecular relapse [69]. RT-qPCR-based NPM1 or CBF MRD >2% at the end of chemotherapy consolidation is associated with an increased risk of relapse [22, 65, 66]. A significantly lower threshold is currently being discussed in the ELN.

#### 6.1.1.1.2.2 Patients with FLT3 mutation – consolidation

When deciding on the optimal post-remission therapy, the FLT3 mutation type (ITD versus TKD), NPM1 comutation status, NGS-based sensitive FLT3-ITD MRD, and multicolor flow cytometry (MFC) MRD should be taken into account in addition to the patient's physical suitability and donor availability.

Patients with FLT3-TKD and NPM1 mutation or with FLT3-TKD and MFC-MRD in KM <0.1% have a comparatively **low risk of recurrence** and can be treated with chemotherapy consolidation plus TKI. The findings after 2 cycles of intensive chemotherapy are decisive for the MFC MRD level, whereby this can be either two intensive induction cycles or one induction cycle and one consolidation therapy. Intermediate-dose cytarabine plus TKI is recommended for chemotherapy consolidation, which should be identical to that used during induction therapy.

Quizartinib, midostaurin, or oral azacitidine (CC-486) are also available for maintenance therapy after completion of chemotherapy consolidation. In the approval study for midostaurin, midostaurin maintenance was only used in patients who had already received midostaurin during induction and consolidation, i.e., there was no re-randomization after completion of chemotherapy. A landmark analysis from the start of maintenance therapy showed no significant effect of midostaurin maintenance on disease-free or overall survival [70]. In the approval study for oral azacitidine, patients were randomized at the start of maintenance therapy to receive either placebo or oral azacitidine. The FLT3-mutated subgroup was small, with 63 patients. Maintenance with CC-486 significantly prolonged median relapse-free survival from 4.6 to 23.1 months, while median overall survival was non-significantly prolonged from 9.7 to 28.2 months [68]. It should be noted that the data on the efficacy of CC-486 were collected from a group of older patients aged 55 years and older, while the midostaurin data were collected from patients between 18 and 60 years of age. In the QuANTUM-First study, patients were not re-randomized for maintenance therapy. In patients without primary allogeneic SCT who received quizartinib maintenance therapy, the risk of death was significantly reduced by 60% compared to placebo (HR 0.4) [71].

Based on these data, maintenance therapy with quizartinib after prior quizartinib treatment or oral azacitidine is recommended for patients without transplantation options after completion

of chemotherapy consolidation until disease progression or in case of contraindications or intolerance, alternatively with midostaurin.

Patients with FLT3-ITD have a **higher risk of recurrence**, especially with high unmutated NPM1 and positive NGS-based sensitive FLT3-ITD MRD in the bone marrow after 2 cycles of intensive chemotherapy. In cases of FLT3-TKD without NPM1 mutation and MRD positivity in MFC-based measurement (threshold  $\geq 0.1\%$ ) in the bone marrow after two cycles of intensive chemotherapy, an increased risk of relapse must also be assumed. However, the inclusion of MFC-MRD requires extensive experience on the part of the laboratory performing the test.

Patients with a higher risk of recurrence should receive allogeneic stem cell transplantation as post-remission therapy if possible. For patients with the option of allogeneic transplantation, the risk of recurrence in FLT3-ITD-AML is increased despite allogeneic stem cell transplantation. In the randomized, placebo-controlled SORMAIN study, maintenance therapy with sorafenib significantly reduced the risk of relapse or death by 61% and prolonged overall survival (HR 0.52) in FLT3-ITD-positive patients who underwent allogeneic stem cell transplantation in first CR [72]. Further publications confirm the significant antileukemic effect of sorafenib after allogeneic SCT [73, 74]. Based on these results, sorafenib maintenance therapy for 2 years, starting between day +60 and +100 after transplantation, is recommended for FLT3-ITD patients after allogeneic transplantation. Attention should be paid to toxicities and, if necessary, dose reductions.

An analysis of all patients in the QuANTUM-First study who received maintenance therapy after allogeneic SCT showed no survival benefit for quizartinib over placebo, although the small numbers and study design do not allow a definitive conclusion to be drawn about efficacy in the maintenance phase. The small group of 33 patients with positive FLT3-ITD MRD before the start of maintenance showed a numerically insignificant survival benefit with quizartinib maintenance (HR 0.606; 95% CI 0.225-1.633) [71]. Based on the similar results of a beneficial effect of maintenance with gilteritinib after allogeneic SCT in patients with positive MRD [75], the fact that the quizartinib arm of the QuANTUM-First study, including patients with maintenance therapy after allogeneic SCT was superior to the placebo arm and quizartinib is therefore approved as maintenance therapy after allogeneic SCT, the use of quizartinib is recommended as maintenance therapy in cases of contraindications for sorafenib, especially in cases of FLT3-ITD MRD positivity after allogeneic SCT.

No survival benefit could be demonstrated for midostaurin maintenance after allogeneic SCT [76].

#### 6.1.1.1.2.3 Patients with myelodysplasia-associated AML and patients with therapy-associated AML (tAML) - Consolidation

Patients with myelodysplasia-associated AML ("AML myelodysplasia-associated (AML-MR)" according to WHO 2022 or "AML with myelodysplasia-associated gene mutations," "AML with myelodysplasia-associated cytogenetic changes" and "AML with progression from MDS or MDS/MPN" according to ICC 2022) have a high risk of recurrence, which is why allogeneic stem cell transplantation is recommended as post-remission therapy for suitable patients in remission after CPX-351 or 7+3 standard induction and with a available donor. If transplantation is not an option, CPX-351 is also available for consolidation, although its value in the approval study was not compared with the usual standard high-dose cytarabine, but with 7+3, which is unusual in consolidation [46]. For patients without a transplant option, maintenance therapy with oral azacitidine is recommended after chemoconsolidation.

The prognosis for patients with t(AML) depends on the genetic profile, so the best post-remission therapy should be selected according to the ELN risk stratification.

#### 6.1.1.1.2.4 Patients with intermediate or poor prognosis

Due to the relevant risk of relapse, allogeneic SCT is recommended as post-remission therapy for both subgroups if the patients are suitable and a suitable donor is available [63, 77]. Since transplant outcomes depend on disease risk, transplant risk, and comorbidities, these patients should be referred to a transplant center at an early stage, even if they have reduced AZ or comorbidities, so that the indication can be determined together with the transplant team.

Even in patients with **intermediate cytogenetic risk**, allogeneic SCT should be sought outside of studies if an HLA-identical sibling or HLA-identical unrelated donor is available. Alternatively, in suitable patients without an HLA-identical donor, allogeneic stem cell transplantation with an HLA-haploidentical family donor should also be considered, see [Onkopedia allogeneic stem cell transplantation - indications \(German Version\)](#).

In cases of intermediate risk and difficult indication for SCT due to patient preference or borderline physical fitness at the time of first remission, primary chemoconsolidation may be considered if a donor is available, and SCT may be reserved for the event of recurrence. The randomized ETAL1 study shows that in cases of intermediate risk, the risk of relapse is significantly reduced by SZT in 1st CR. With lower initial therapy-associated mortality of chemoconsolidation and good SCT results in relapse, overall survival with a therapy concept involving delayed SCT is approximately the same as with transplantation in first remission [78].

Non-randomized data from the HOVON-SAKK-132 study indicate that in the presence of a valid flow cytometric MRD marker in MRD-negative intermediate-risk patients with chemoconsolidation, relapse-free survival is slightly shorter than with allogeneic SCT and overall survival does not differ significantly [79]. In the GIMEMA1301 study, MRD-positive intermediate-risk patients who underwent allogeneic SCT had similar relapse-free and overall survival rates as MRD-negative intermediate-risk patients who underwent chemoconsolidation [80].

In older, fit patients who were not suitable for intensive induction at initial diagnosis due to leukemia-related physical impairment, who have been successfully treated with hypomethylating agents and venetoclax, and who have achieved a physical condition in remission that allows for SCT, such a procedure should also be considered.

Patients without donors, with significant comorbidities, or in poor clinical condition should, if possible, receive chemoconsolidation with 2-3 cycles of intermediate-dose cytarabine [67]. For these patients, maintenance therapy with oral azacitidine is recommended after chemoconsolidation. The data are based on the results of the randomized QUAZAR registration study. Older patients  $\geq 55$  years of age with intermediate or unfavorable genetic risk who achieved CR/CRi after intensive induction therapy with or without prior consolidation therapy but were not eligible for allogeneic stem cell transplantation were treated with the oral azacitidine formulation CC-486 versus placebo until disease progression, death, or intolerable toxicity. CC-486 resulted in a significant prolongation of median overall survival to 24.7 months compared to 14.8 months with placebo (HR 0.69;  $p=0.0009$ ) [81]. After 3 years, 37.4% of patients in the CC-486 arm were still alive, compared with 27.9% in the placebo arm [82].

#### **6.1.1.2 Older fit patients.**

This age group includes patients who are over 65 years of age and have no or few comorbidities. Since both remission rates and long-term remissions decrease with increasing age and the risk of therapy-associated complications increases at the same time [1, 4, 83], the opportunities and risks in this age group must be weighed particularly carefully and discussed with the patients. In this context, it can be helpful to estimate the individual genetic risk constellation and CR probability as well as the risk of early mortality using scores, e.g., [www.amlcompositemodel.org](http://www.amlcompositemodel.org) [29, 84]. In addition to clinical characteristics, the Multistage Prediction Tool also includes genetic information in the risk prediction and compares the outcome

with and without allogeneic stem cell transplantation (<https://cancer.sanger.ac.uk/aml-multi-stage/>).

To assess the optimal treatment strategy, newly diagnosed AML patients should be referred to an experienced treatment center.

In the following constellation, palliative therapy with cytoreductive outpatient chemotherapy (see chapter 6.1.1.3) or best supportive care (BSC) should be considered because the expected complications of intensive therapy outweigh the potential benefits:

- Biological age >75 years
- comorbidities
  - Late diabetic syndrome
  - Severe liver or kidney disease
  - Heart failure (EF <30%)
- ECOG  $\geq$ 3
- Low chances of recovery (e.g., in the case of TP53 mutation), high risk of early mortality during induction

All other patients should be evaluated for intensive curative therapy. The therapy does not differ fundamentally from the therapy for younger patients as described in chapter 6.1.1.1. Modifications between younger (usually up to a biological age of 65) and older fit patients only concern the reduced cytarabine dose in consolidation therapy, see Appendix Therapy Protocols.

### **6.1.1.3 Older patients without intensive therapy options**

For patients with a biological age over 75 years or with significant comorbidities such as late diabetic syndrome, liver or kidney disease, heart failure (EF <30%), ECOG  $\geq$ 3, or poor chances of recovery due to unfavorable cytogenetics (unfit, fragile, or frail), the therapeutic goal is to prolong life with the highest possible quality of life [83]. In addition to BSC, these patients should be offered cytoreductive outpatient chemotherapy in addition to purely symptomatic administration of hydroxyurea to reduce the leukocyte count.

In the randomized, placebo-controlled VIALE-A study, the combination of 5-azacitidine with the bcl2 inhibitor venetoclax led to a significant increase in remission rates (CR/CRi) from 28.3% to 66.4%. Venetoclax significantly prolonged overall survival in combination with azacitidine from 9.6 to 14.7 months. This positive effect was demonstrated in all genetic subgroups [85].

Based on the available data, this combination is recommended as the first-line treatment of choice in patients who cannot undergo intensive therapy. The evidence for azacitidine is more robust, but similar efficacy can be assumed for decitabine as a combination partner [86].

The clinical management for combination therapy with venetoclax differs significantly from that of monotherapy with HMA:

To reduce the risk of tumor lysis, venetoclax combination therapy should only be started when the leukocyte count is below 25,000/ $\mu$ l, with dosing over 3 days and supportive measures taken to prevent tumor lysis. In addition, drug interactions must be taken into account. The following is recommended:

- Cycle 1 should be started under inpatient conditions
- The venetoclax dosage must be adjusted when co-administered with moderate or strong CYP3A inhibitors. These include azoles, ciprofloxacin, and macrolides. When co-adminis-

tered with the strong CYP3A inhibitor posaconazole, the dose should be reduced to 50-100 mg per day.

- The more pronounced cytopenia compared to monotherapy with hypomethylating agents (HMA), associated with a higher probability of infectious complications, requires close monitoring with bone marrow diagnostics after cycle 1 (between days 21 and 28) and timely dose adjustments depending on remission status and blood count. Once blast clearance has been achieved, G-CSF can be used in cases of delayed regeneration.

In the randomized, placebo-controlled combination study with venetoclax and LDAC, the response to venetoclax increased from 13% to 48%. The predefined primary analysis of the primary study endpoint after a median follow-up of 12 months showed a survival difference of 7.2 versus 4.1 months, which did not reach statistical significance. Only after a further 6 months and a difference in overall survival of 8.4 versus 4.1 months was statistical significance achieved [87]. Based on the data mentioned, the EMA did not approve the combination of LDAC plus venetoclax.

If a venetoclax combination is not possible, a hypomethylating agent (HMA), i.e., 5-azacitidine and decitabine alone, can be used as an alternative. HMAs can achieve higher response rates and prolong survival compared to the historical standard of low-dose cytarabine [88], see [Appendix Therapy Protocols \(German Version\)](#).

With the combination of decitabine and the oral cytidine deaminase inhibitor cedazuridine, a purely oral HMA formulation has also been available for primary therapy since 2023. Approval was granted after evidence of equivalent plasma availability between intravenous decitabine and oral decitabine-cedazuridine administration [89].

Due to the mechanism of action of HMA, a delayed response may occur with HMA monotherapy, so that an assessment of efficacy is only recommended after 3-4 months [90]. The therapy should be administered every four weeks until progression, as relapses occur rapidly after discontinuation [91]. Although there are no randomized direct comparisons of the two substances, their efficacy can be considered equivalent [92]. Their use is therefore also based on practical considerations.

As a further option for combination with LDAC in unfit patients was approved in June 2020. In a randomized, non-placebo-controlled study, this hedgehog inhibitor led to an increase in CR/CRi rates from 5.3% to 24.3% and a median significant prolongation of survival from 4.3 to 8.3 months compared to LDAC monotherapy [93]. There is currently no direct comparison of this combination with the efficacy of LDAC plus venetoclax.

In cases of contraindications to HMA or progressive disease, low-dose cytarabine (LDAC) can be used as an alternative. LDAC is more effective than hydroxyurea in this situation [94].

For unfit patients with newly diagnosed IDH1-mutated AML, the IDH1 inhibitor ivosidenib was evaluated in combination with azacitidine in the randomized, placebo-controlled AGILE study. Compared to azacitidine and placebo, the addition of ivosidenib increased the CR rate from 15% to 47%. The duration of response was significantly longer with ivosidenib-azacitidine therapy than with azacitidine plus placebo. As a result, patients receiving the ivosidenib combination achieved a median overall survival of 24.0 months compared to 7.9 months in the placebo arm (HR 0.44; p=0.001) [95]. Based on these results, the EMA granted approval for the combination of substances in May 2023 for first-line therapy in patients with IDH1 R132 mutation who are not suitable for standard induction therapy. This provides patients with IDH1 mutation with another treatment option in addition to the combination of HMA plus venetoclax. There is no direct comparison of the two options. In the small IDH1 cohort from the venetoclax approval study (VIALE-A), the CR rate is 27% versus 47% in the ivosidenib study (AGILE), while the combined CR/CRh rate with venetoclax is 61% versus 53% in the AGILE study. The median OS was

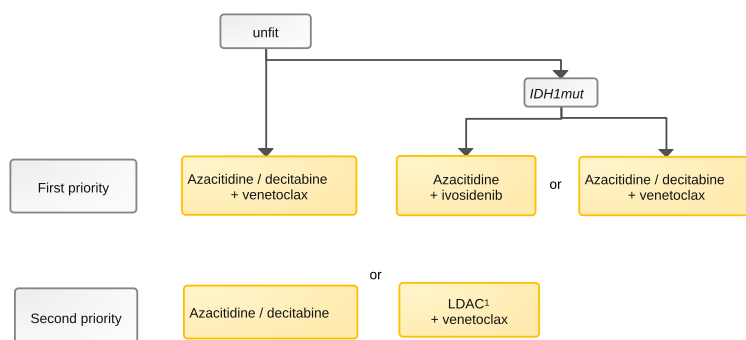
29.3 months in the AGILE study and 15 months in the IDH1 subgroup of the VIALE-A study, while the relative risk reduction (HR) with venetoclax is expressed as an HR of 0.19, compared to 0.42 in the AGILE study with ivosidenib. In the ivosidenib study, the rate of severe cytopenias and febrile neutropenia is lower than with venetoclax [95, 96]. Due to the lack of a direct comparison, both treatment options are recommended as equally suitable for first-line therapy.

For a summary of the therapeutic options for first-line therapy in unfit patients and their prioritization, see [Figure 3](#).

A small proportion of newly diagnosed patients may be so impaired by leukemia-related organ damage (e.g., leukemic infiltration of the liver), neutropenic infectious complications, or B symptoms that intensive therapy is not possible or justifiable at the time of initial diagnosis. Successful treatment of AML with HMA or LDAC, possibly in combination with venetoclax, can improve the condition to such an extent that SCT appears feasible and can be performed successfully.

Due to the far-reaching prognostic consequences for or against intensive curative or palliative cytoreductive therapy, newly diagnosed AML patients should be referred to an experienced treatment center for assessment of the optimal treatment strategy.

**Figure 3: Treatment options for primary therapy in unfit patients**



Legend:

  non-curative therapy;

<sup>1</sup> Decitabine can be used if<sup>there are</sup> contraindications to azacitidine

<sup>2</sup> HMA - hypomethylating agents

<sup>3</sup> LDAC - low-dose Ara-C;

## 6.1.2 Recurrence therapy

A relevant MRD level at the end of chemotherapy consolidation is associated with an increased risk of relapse in patients treated curatively (MFC-MRD  $>10^{-4}$ , NPM1/CBF-RT-qPCR  $>2\%$ ). MRD conversion (CR<sub>(MRD-)</sub> → CR<sub>(MRD+)</sub>) or a log increase in MRD over time usually precedes hematological relapse and allows for the rapid initiation of relapse therapy.

For fit patients who are to be treated with **curative intent** in relapse, allogeneic stem cell transplantation remains the only procedure with the possibility of long-term remission. If neither an HLA-identical family donor nor a suitable unrelated donor is available ( ), alternative stem cell sources, in particular HLA-haploidentical family donors, can also be used (see [Onkopedia guideline Allogeneic Stem Cell Transplantation Donor Selection \(German Version\)](#)).

If, at the time of recurrence diagnosis, an SCT cannot be performed within 6 weeks, re-induction for disease control remains the treatment of choice. If donor availability allows for an SCT within 4-6 weeks after the recurrence diagnosis, a watch-and-wait strategy or, if necessary, low-dose chemotherapy for disease control and transplantation as soon as possible is the preferred treatment option. The randomized controlled ETAL3 study demonstrated that remission rates after SZT and overall survival did not differ between patients who received re-induction

versus no re-induction prior to relapse SZT and instead received dose-intensified conditioning with median SZT performed within 4 weeks. Instead, the incidence of side effects and length of hospital stay were significantly higher in the re-induction arm [97].

Any re-induction therapy that may be required should include intermediate- or high-dose cytarabine.

The approval of the second-generation type I FLT3 inhibitor gilteritinib for monotherapy in relapsed/refractory AML with FLT3 mutation opens up an additional third pathway to allogeneic SCT. In the 2:1 randomized controlled approval study, relapsed/refractory FLT3-mutated AML patients were treated either with a predetermined standard therapy (60.5% intensive and 39.5% non-intensive) versus gilteritinib as oral monotherapy (ADMIRAL study). The remission rate was higher in the gilteritinib arm (CR 21.1% versus 10.5%, CR/CRi 25.5% versus 11.3%, CR/CRh 34% versus 15.3%). In the gilteritinib arm, 63/247 (25.5%) patients underwent allogeneic stem cell transplantation, compared with 19/124 (15.3%) in the standard arm. Patients in the gilteritinib arm were able to receive the drug as maintenance therapy after allogeneic SCT until progression. Including patients who underwent allogeneic transplantation, the median overall survival in the gilteritinib arm was 9.3 versus 5.6 months in the control arm (HR 0.64;  $p < 0.001$ ); after censoring transplanted patients at the time of allogeneic SCT, the difference was 8.3 versus 5.3 months (HR 0.58). In terms of both response and median overall survival, the results of gilteritinib were superior to those of intensive standard relapse chemotherapy (CR 24.8% versus 16.0%, median survival 10.5 versus 6.9 months) [98]. The significantly better efficacy of gilteritinib compared to standard chemotherapy has now been confirmed in a second randomized study with an almost identical design and very similar results. In the COM-MODORE study, overall survival in the gilteritinib arm was 9 months versus 4.7 months in the control arm (HR 0.549,  $p = 0.00126$ ) [99]. Non-randomized data suggest that gilteritinib is also effective after prior sorafenib or midostaurin therapy [100]. In patients with relapsed/refractory disease and FLT3 mutation, gilteritinib is therefore recommended as the first-line relapse therapy, even if the patient is suitable for intensive salvage therapy and allogeneic SCT is planned. If gilteritinib fails, intensive standard salvage therapy may be considered.

In cases of relapse after allogeneic SCT, repeat SCT may be considered in individual cases of chemosensitive disease [101, 102]. The administration of donor lymphocytes (DLI) in relapse is associated with similar efficacy to a possible second allogeneic SCT [103]. The combination of DLI with HMA can increase efficacy [104].

Relapsed patients with FLT3 mutation who are **not suitable for intensive salvage therapy** should be treated with gilteritinib. FLT3 wild-type patients who have not yet received HMA ("HMA-naive") can be treated with HMA and venetoclax.

Relapsed patients without FLT3 mutation who are not suitable for SZT should preferably be treated in clinical trials. Alternatively, therapy with venetoclax in combination with HMA is recommended (off-label in relapse). It is associated with CR rates of 30-40%, but experience to date is limited to retrospective case series [105, 106]. The combination with LDAC (off-label) appears to achieve slightly lower response rates.

In 10-20% of AML patients, a mutation in the IDH1 or IDH2 gene is found at initial diagnosis. In cases of relapse, a CR/CRi rate of 35% and a median overall survival of approximately 9 months can be expected for ivosidenib in the case of an IDH1 mutation [107], and CR/CRi rates of 27% and a median survival of also 9 months can be expected for enasidenib in the case of an IDH2 mutation [108]. Based on these data from non-randomized studies, the FDA approved both IDH inhibitors in 2017 for monotherapy in relapsed or refractory AML with proven IDH1/2 mutations. Due to a lack of survival benefit in a randomized study of enasidenib versus azacitidine, LDAC, IDAC, or BSC in a very problematic patient population (patients >60 years of age in second or

third relapse ), monotherapy in relapse is not expected to be approved by the EMA [109], see Appendix Acute Myeloid Leukemia - Approval Status.

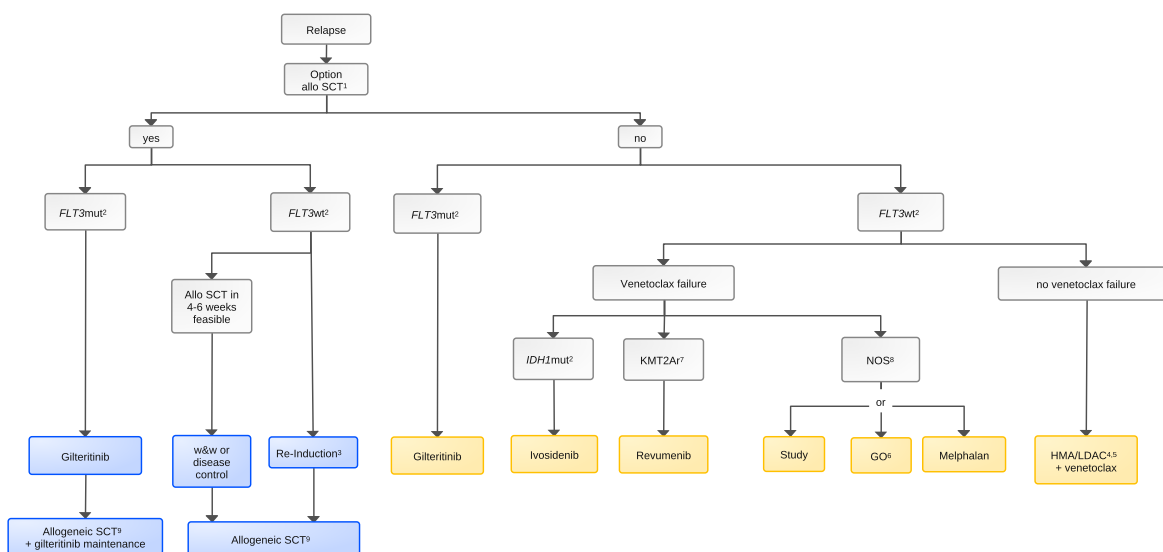
KMT2A rearrangements (KMT2Ar) occur in 5-15% of all AMLs and are associated with a poor prognosis [110]. Inhibition of the menin complex that arises in the course of this genetic alteration can achieve an antileukemic effect, which can be observed not only in KMT2Ar but also in NPM1-mutated AML. In contrast, there does not appear to be any pronounced menin inhibitor efficacy in KMT2A-PTD mutations.

Several orally available menin inhibitors are currently in clinical development. In the non-randomized AUGMENT-101 study, the use of the oral menin inhibitor revumenib achieved a response in 64% of 97 patients with multiple relapses of acute leukemia and KMT2Ar, including 42% with CRc [111]. Based on these results, Revumenib was approved by the FDA on November 15, 2024, for relapsed/refractory acute leukemia with KMT2Ar.

GO is also approved in the US as monotherapy for CD33-positive AML relapses. Remission rates of around 30-40% have been reported for monotherapy in first relapse [112, 113]. Due to the risk of VOD, GO is not recommended in relapse after allogeneic SCT [114]. Alternatively, classic cytostatic drugs such as LDAC or melphalan can be used in cases of HMA failure.

For a summary of the therapeutic options in relapse and their prioritization, see Figure 4.

**Figure 4: Treatment algorithm for relapse therapy**



Legend:

█ curative therapy; █ non-curative therapy;

<sup>1</sup> SZT - stem cell transplantation

<sup>2</sup> mut - mutated; WT - wild-type intended therapy;

<sup>3</sup> Re-induction - renewed induction with cytostatic drugs or watch&wait/disease stabilization depending on disease kinetics and timely feasibility of allogeneic SZT

<sup>4</sup> HMA - hypomethylating agents

<sup>5</sup> LDAC - low-dose Ara-C

<sup>6</sup> GO - gemtuzumab ozogamicin

<sup>7</sup> KMT2Ar - KMT2A rearranged, not KMT2A-PTD

<sup>8</sup> NOS - not otherwise specified: without IDH1 mutation or KMT2Ar

<sup>9</sup> Aim for early reduction of immunosuppression and, if necessary, consider supplemental donor lymphocyte infusion (DLI)

### 6.1.3 Supportive care

The prognosis for newly diagnosed AML patients has improved significantly in recent decades, especially in the younger patient population. Given the marginal changes in cytostatic therapy—the combination of cytarabine plus anthracycline has been used since the 1970s, the 7+3

regimen dates back to the early 1980s, and high-dose cytarabine consolidation to the mid-1990s — this improvement in prognosis is due in no small part to improvements in supportive care [2, 3, 115, 116]. Essential components of supportive care include infection prophylaxis and therapy for immunosuppressed and stem cell transplant patients, transfusions, antiemesis, and therapy for gastrointestinal complications. For specific implementation, please refer to the separate German guidelines on supportive therapy (<https://www.onkopedia.com/onkopedia/guidelines>) and the hygiene requirements for immunosuppressed patients from the Robert Koch Institute ([http://www.rki.de/Content/Infekt/Krankenhaushygiene/Kommission/Downloads/Immunsuppr\\_Rili.html](http://www.rki.de/Content/Infekt/Krankenhaushygiene/Kommission/Downloads/Immunsuppr_Rili.html)).

## 6.3 Children and adolescents

### 6.3.1 Basics

The survival rate for children and adolescents with AML has improved in recent decades from an almost always fatal disease to more than 75% survival today. Nevertheless, AML remains one of the most threatening diagnoses in childhood. With an incidence of 7 per 1,000,000 children, approximately 100 to 120 children and adolescents are diagnosed with the disease each year in Germany [117].

The treatment of pediatric AML has been continuously refined through population-based therapy optimization studies. In Germany, Austria, Switzerland, Czechia, and Slovakia, this has been done by the AML-BFM study group. Internationally, various European (NOPHO, Scandinavia; AIOEP, Italy; LAME, France; MRC, Great Britain), American (COG, St. Jude), and Japanese study groups have contributed to the further development of therapy and the identification of prognostic factors [118].

While the improvements before 2000 were mainly achieved through the intensification of therapy accompanied by improvements in supportive treatment, risk stratification with the identification of high-risk patients with an indication for allogeneic stem cell transplantation in first complete remission has since become very important.

Only a small proportion of pediatric AML cases involve a genetic predisposition in children, with trisomy 21 and Fanconi anemia being the most notable examples. In children, the origin of leukemic development can begin as early as the prenatal period [119]. Leukemia-associated aberrations have already been detected in the metabolic screening charts of newborns [120].

A special model is myeloid leukemia in children with trisomy 21. The predisposition initially leads to a relatively increased megakaryopoiesis (trisomy 21 ~ 70% vs. normal ~30%) in fetal blood formation in utero. During the second trimester, an increased number of GATA1 (hematopoietic transcription factor) mutated megakaryoblastic clones become detectable, which can apparently become dominant in hematopoiesis in connection with other trisomy 21-related predispositions in fetuses. This proliferation is then diagnosed as transient leukemia (TL) in 5-10% of newborns. Factors that lead to myeloid leukemia in Down syndrome (ML-DS) in more than 20% of children within the first 4 years of life remain unclear. This phenotypically similar megakaryoblastic leukemia (AMKL) almost always has the same GATA1 mutation as TL [121]. In other subgroups, too, predisposition could play a relevant role, either through new mutations, polymorphisms, or predisposing germline mutations.

### 6.3.2 Clinical characteristics

The symptoms of AML in children and adolescents are nonspecific and can be explained primarily by the displacement of normal hematopoiesis in the bone marrow or directly by high blast concentrations. The most noticeable symptoms are usually anemia-related pallor, increased

hematomas and petechiae in thrombocytopenia, or infections due to neutropenia and lymphopenia. High blast counts ( $>50\text{-}100 \times 10^9/\text{L}$ ) can lead to viscosity problems, often beginning with pulmonary symptoms, or to severe bleeding in cases of coagulation disorders.

Multiple skin infiltrations may be visible, particularly in monoblastic leukemias. Gingival hyperplasia should also prompt further hematological diagnosis. Other extramedullary manifestations, particularly in AML associated with translocation 8;21, can present as a mass in the orbit, but also as so-called myeloid sarcoma or chloroma at any other location.

### 6.3.3 Diagnosis

The diagnosis of AML is primarily made in the bone marrow, i.e., by analyzing bone marrow aspirate, see also [Table 1](#). In cases of AML with associated myelofibrosis, which is common in AMKL, a bone marrow biopsy may also be necessary. In cases of very high leukocyte counts with a high risk of bleeding, diagnosis is initially made from peripheral blood. The same applies to the initial mandatory lumbar puncture to rule out or confirm involvement of the central nervous system.

Despite advances in molecular genetic methods, primary morphological and immunophenotypic assessment remains highly important initially, as it allows rapid classification as AML. It is particularly relevant for the immediate identification of acute promyelocytic leukemia (APL, AML FAB M3) or monoblastic leukemia (here especially in differentiation from ALL). Both AML subtypes are considered emergencies that require immediate intervention.

APL has a significantly higher incidence among children of Mediterranean/Asian origin than among Northern Europeans ( $>20\%$  vs.  $5\%$ ), see also [Onkopedia Acute Promyelocytic Leukemia](#). Older children and adolescents are more frequently affected. Due to the very high risk of bleeding (including fatal cerebral hemorrhages) in the initial phase, APL is considered an emergency, especially if the leukocyte count is above  $10,000/\mu\text{l}$ . In this case, immediate therapy with differentiating all-trans retinoic acid (ATRA) must be administered.

In monoblast leukemia and the frequently accompanying hyperleukocytosis, rapid measures to inhibit proliferation (e.g., cytarabine therapy) must be initiated together with supportive care (rasburicase, hydration, correction of coagulation disorders) [[122](#), [123](#)].

### 6.3.4 Prognostic factors and risk groups

The stratification into risk groups as favorable, intermediate, and unfavorable is internationally established. The current risk groups are summarized in [Table 9](#). Despite many similarities with the prognosis groups for adult AML, there are significant differences. Guidelines for pediatric AML corresponding to the adult ELN are currently being developed. In most study groups, allocation is based on the genetic characteristics of the leukemic blasts. This is supplemented by the determination of the response to therapy using morphology and immunophenotyping.

A comprehensive analysis of the response to therapy by the AML-BFM study group was able to relativize the criteria for the prognostic relevance of complete remission. The retrospective study shows that no evidence of leukemia (NEL), i.e., morphological blast-free status after the first and second induction, alone allows for a sufficient prognostic statement, while the inclusion of hematological regeneration showed no additional benefit [[124](#)].

**Table 9: Risk groups for pediatric AML**

RISK Group	Genetic aberrations	Therapeutic response
STANDARD RISK (SR)	<ul style="list-style-type: none"> <li>• CBFβ               <ul style="list-style-type: none"> <li>◦ t(8;21)(q22;q22) with ≥ 2 log reduction in qPCR after induction 2</li> <li>◦ inv(16)(p13q22)/t(16;16)(p13;q22)</li> </ul> </li> <li>• NPM1 mutation</li> <li>• Biallelic CEBPα aberrations</li> <li>• t(16;21) <i>CBFA2T3/RUNX1</i></li> </ul> <p><i>and FLT3-ITD negative</i></p>	<ul style="list-style-type: none"> <li>• MRD &lt; 1% after induction 1</li> </ul> <p>t(8;21) /inv(16) and</p> <ul style="list-style-type: none"> <li>• MRD &gt;2 log decrease in qPCR after induction 2</li> </ul>
INTERMEDIATE RISK (IR)	<ul style="list-style-type: none"> <li>• Not SR and not HR</li> </ul>	<ul style="list-style-type: none"> <li>• MRD between 0.1% and &lt; 1% after induction 1 and MRD &lt; 0.1% after induction 2</li> </ul>
HIGH RISK (HR)	<ul style="list-style-type: none"> <li>• Complex karyotype (≥ 3 aberrations with one structural aberration) Leukemias with recurrent translocations are excluded</li> <li>• Monosomic karyotype, i.e. -7,-5/del(5q)</li> <li>• <i>11q23/KMT2A</i> rearrangements               <ul style="list-style-type: none"> <li>◦ t(4;11)(q21;q23) <i>KMT2A/AFF1</i></li> <li>◦ t(6;11)(q27;q23) <i>KMT2A/AFDN</i></li> <li>◦ t(10;11)(p12;q23) <i>KMT2A/MLLT10</i></li> <li>◦ t(9;11)(p21;q23) <i>KMT2A/MLLT3</i> with other cytogenetic aberrations</li> </ul> </li> <li>• t(16;21)(p11;q22) <i>FUS/ERG</i></li> <li>• t(9;22)(q34;q11.2) <i>BCR/ABL1</i></li> <li>• t(6;9)(p22;q34) <i>DEK/NUP214</i></li> <li>• t(7;12)(q36;p13) <i>MNX1/ETV6</i></li> <li>• inv3(q21q26)/t(3;3)(q21;q26) <i>RPN1/MECOM</i></li> <li>• 12p aberrations</li> <li>• FLT3-ITD with an AR ≥ 0.5, but in combination with recurrent translocations or an NPM1 mutation</li> <li>• <i>WT1</i> mutation and <i>FLT3-ITD</i></li> <li>• <i>inv(16)(p13q24) CBFA2T3/GLIS2</i></li> <li>• <i>T(5;11)(q35;p15.5) NUP98/NSD1</i> and <i>t(11;12)(p15;p13) NUP98/KDM5A</i></li> <li>•</li> <li>• Pure erythroblastic leukemia</li> </ul>	<ul style="list-style-type: none"> <li>• MRD ≥1% after induction 1 AND 1 or ≥0.1% after induction 2</li> <li>• If FLOW-MRD is not available: Blasts ≥5% of induction 1</li> </ul>

## 6.3.5 Therapy

### 6.3.5.1 Chemotherapy

The treatment of AML is based on intensive polychemotherapy, the most important components of which are cytarabine and anthracyclines. The improvements made in recent decades have been based primarily on the intensification of treatment in the induction phase. The prerequisite for this was, above all, improved supportive therapy in order to control the severe side effects and high frequency of infections, see also chapter 6.1.3.

In addition to these two substances, other cytostatic drugs used in the treatment of AML include etoposide, mitoxantrone, and thioguanine.

In recent years, additional substances have been introduced into the treatment of pediatric AML in order to achieve targeted therapy or therapy aimed at specific mechanisms [125, 126]. While additive treatment with the FLT3-ITD inhibitor sorafenib showed no additional effect in the AML-BFM, the COG was able to demonstrate benefits [127]. The recently presented data from the British-French MyChILD study, which demonstrated a significant improvement in event-free survival through the sequential administration of gemtuzumab ozagamicin, are certainly relevant [128].

### 6.3.5.2 Allogeneic stem cell transplantation

In addition to chemotherapy, allogeneic stem cell therapy can also be performed after remission of AML. The results of allogeneic stem cell transplantation have improved significantly in recent years. Nevertheless, SCT remains reserved for high-risk AML [129].

### 6.3.5.3 relapse

The treatment of AML relapse involves renewed induction therapy. In a global study conducted in 20 countries and 200 centers, the International AML Study Group achieved survival rates of 38% after relapse. In all cases, SCT was indicated in second remission. CBL-AML even had survival rates after relapse of approximately 60% [130]. Currently, additional therapy with gemtuzumab ozogamicin in combination with fludarabine/cytarabine (FLA) is recommended for relapse.

For some time now, all patients with a quantifiable genetic marker have been continuously monitored after remission in order to detect molecular relapse (increase >1 log level) at an early stage. In a few genetic subgroups (CBL), molecular relapse has been successfully treated with azacitidine monotherapy ( ), eliminating the need for re-induction therapy prior to the necessary stem cell transplantation. In the majority of cases, however, better combination therapies are required to prevent overt relapse [131].

### 6.3.5.4 Myeloid leukemia in trisomy 21

Children with trisomy 21 have a high risk of developing AML with the GATA1 mutation in the first 4 years of life (see chapter 6.3.1). In contrast to other AML, a reduction and adjustment of the intensity of therapy led to improved survival rates of around 90% in these children due to their increased sensitivity to toxicities. (Recommendations for Diagnosis and Treatment of Children with Transient Abnormal Myelopoiesis (TAM) and Myeloid Leukemia in Down Syndrome (ML-DS) – PubMed). In contrast, relapses of ML-DS are very severe and difficult to treat successfully, so an international recommendation has been developed [132].

Once the initial phase with its very high risk of bleeding had been overcome, APL already had a very good prognosis in the past [118]. As in adults, the current recommendation is a combination of ATRA and arsenic trioxide, see also [Onkopedia Acute Promyelocytic Leukemia](#).

### 6.3.5.5 Therapy-associated AML

AML is the most common secondary malignancy after previous radiation or chemotherapy. Myelomonoblastic AML occurs most frequently, usually associated with a t(9;11). Overall, the prognosis for therapy-associated AML remains poor. Experience over the last few decades shows that one or two induction blocks should achieve remission or at least blast-free status (morphologically), followed by allogeneic SCT. With this approach of limited chemotherapy, a survival rate of 30-40% has recently been achieved [133].

### 6.3.6 Late effects

Severe long-term effects in children and adolescents with AML manifest themselves in the form of secondary malignancies, cardiotoxicities, and, as a consequence of stem cell transplantation, chronic GvHD. The cumulative secondary malignancy rate after 20 years is approximately <2%. Overall, however, about half of all long-term survivors report chronic health problems. Severe, life-threatening diseases are about three times more common than in the comparison popula-

tion. Late cardiotoxicity must be expected in about 5% of patients, but it only manifests clinically in half of them. It is difficult to make statements about fertility. In girls who have only received chemotherapy, 14% show a significant reduction in anti-Müllerian hormone as a sign of impaired fertility [134, 135].

### **6.3.7 Outlook**

With the exception of APL, the newer, molecularly active substances have not yet been able to cure AML on their own. Only in a few cases do the treatment results appear to be improved by combination with conventional chemotherapy. Therefore, current treatment must continue to be optimized. This applies to risk stratification, supportive therapy, and chemotherapy or stem cell transplantation.

MDR-AML and some genetically determined high-risk groups in particular could benefit from the BCL-2 inhibitor venetoclax in combination with azacitidine.

Menin inhibitors are a promising development, with clinical trials initiated in patients with relapse due to KMT2A rearrangement, NPM1 mutation, KMT2A translocation, or UBTF tandem duplication.

Another approach, especially for high-risk patients, is cellular post-SCT therapies, e.g., with cytokine-induced killer (CIK) cells [136].

For molecular relapse, combinations of venetoclax/azacitidine with specific inhibitors (menin inhibitors, IDH inhibitors, FLT3 inhibitors) are in clinical development.

At the same time, research into the mechanisms of development and more targeted drugs with fewer side effects or alternative options such as immune and cell therapies must be intensified in order to make AML curable in all children and adolescents in the future.

The Leukemia & Lymphoma Society (LLS) global project on pediatric acute leukemias (PedAL) is working with its European partner ([EuPAL Foundation, Utrecht](#)) to develop treatment options and registries for relapsed AML in children and adolescents.

## **8 Follow-up and aftercare**

### **8.1 Follow-up**

During ongoing therapy, remission monitoring is generally performed at the following times:

- Two weeks after the start of induction I ("early puncture")
- after the end of induction therapy when blood counts have recovered
- before the start of each consolidation therapy
- after the end of post-remission therapy

### **8.2 follow-up**

AML patients who have undergone curative treatment should receive clinical and hematological follow-up care in order to detect relapse as early as possible. This requires regular clinical examinations as well as blood count and bone marrow checks. If relapse is clinically suspected or blood counts are abnormal, a bone marrow examination must be performed. Since most relapses occur within 18-24 months after remission is achieved, blood count checks every 1-3 months are recommended within the first two years, followed by every 3-6 months for years

3-5. For patients with a CBF fusion or NPM1 mutation, RT-qPCR-based MRD monitoring from peripheral blood (every 4-6 weeks) or bone marrow (every 3 months) is recommended [22].

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## 10 Active studies

<http://www.kompetenznetz-leukaemie.de/content/studien/studienregister/dlsr>

## 14 Links

A video on how to perform a bone marrow puncture was created by the Elisabethinen Hospital in Linz for training purposes and for patients (<https://www.youtube.com/watch?v=3RgGmErO50g>).

## 15 Authors' Affiliations

### **Prof. Dr. med. Francis Ayuketang Ayuk**

Universitätsklinikum Hamburg-Eppendorf  
 Klinik für Stammzelltransplantation  
 Martinistr. 52  
 20246 Hamburg  
[ayuketang@uke.de](mailto:ayuketang@uke.de)

### **Prof. Dr. med. Claudia Baldus**

Universitätsklinikum Schleswig-Holstein  
 Klinik für Innere Medizin II  
 Hämatologie und Onkologie  
 Arnold-Heller-Str. 3  
 24105 Kiel  
[Claudia.Baldus@uksh.de](mailto:Claudia.Baldus@uksh.de)

**Prof. Dr. med. Jan Braess**

Krankenhaus der Barmherzigen Brüder Regensburg  
Onkologisches Zentrum  
Prüfeninger Str. 86  
93049 Regensburg  
[jan.braess@barmherzige-regensburg.de](mailto:jan.braess@barmherzige-regensburg.de)

**Prof. Dr. med. Konstanze Döhner**

Universitätsklinikum Ulm  
Innere Medizin III  
Albert-Einstein-Allee 23  
89081 Ulm  
[konstanze.doehner@uniklinik-ulm.de](mailto:konstanze.doehner@uniklinik-ulm.de)

**Assoc. Prof. PD Dr. Karoline Gleixner**

**Prof. Dr. med. Michael Heuser**

Universitätsklinikum Halle (Saale)  
Innere Medizin IV  
Ernst-Grube-Str. 40  
06120 Halle  
[michael.heuser@uk-halle.de](mailto:michael.heuser@uk-halle.de)

**Prof. Dr. med. Jan-Henning Klusmann**

Klinik für Kinder- und Jugendmedizin  
Universitätsklinikum Frankfurt  
Theodor-Stern-Kai 7, Haus 32  
60590 Frankfurt am Main  
[KKJM-Direktor@unimedizin-ffm.de](mailto:KKJM-Direktor@unimedizin-ffm.de)

**Prof. Dr. med. Markus G. Manz**

Universitätsspital Zürich  
Zentrum für Hämatologie und Onkologie USZ  
Rämistr. 100  
CH-8091 Zürich  
[Markus.Manz@usz.ch](mailto:Markus.Manz@usz.ch)

**Prof. Dr. med. Jakob Passweg**

Universitätsspital Basel  
Hämatologie  
Petersgraben 4  
CH-4031 Basel  
[jakob.passweg@usb.ch](mailto:jakob.passweg@usb.ch)

**Prof. Dr. med. Dirk Reinhardt**

Universitätsklinikum Essen  
Klinik für Kinderheilkunde III  
Hufelandstr. 55  
45122 Essen  
[dirk.reinhardt@uk-essen.de](mailto:dirk.reinhardt@uk-essen.de)

**Prof. Dr. med. Christoph Röllig**

Universitätsklinikum Dresden  
Medizinische Klinik und Poliklinik I  
Fetscherstr. 74  
01307 Dresden  
[christoph.roellig@uniklinikum-dresden.de](mailto:christoph.roellig@uniklinikum-dresden.de)

**Prof. Dr. Richard F. Schlenk**

Nationales Centrum für Tumorerkrankungen (NCT)  
Marsilius Arkaden  
Turm West 9 Stock  
Im Neuenheimer Feld 330.3  
69120 Heidelberg  
[richard.schlenk@nct-heidelberg.de](mailto:richard.schlenk@nct-heidelberg.de)

**Prof. Dr. med. Armin Zebisch**

Abteilung für Hämatologie und Otto Loewi Forschungszentrum  
Medizinische Universität  
Auenbruggerplatz 38  
A-8036 Graz  
[armin.zebisch@medunigraz.at](mailto:armin.zebisch@medunigraz.at)

## **16 Disclosure of Potential Conflicts of Interest**

according to the rules of the responsible Medical Societies.