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# Acute myeloid leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up<sup>†</sup>

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## Highlights

- This updated ESMO Clinical Practice Guideline provides key recommendations on the management of acute myeloid leukaemia (AML) including acute promyelocytic leukaemia (APL)
- Authorship includes a multidisciplinary group of experts from different institutions and countries in Europe

- A summary of recommendations is provided, including levels of evidence and grades of recommendation where applicable
- Recommendations take the approval status of AML drugs in Europe into account until the year 2019
- Detailed guidance on diagnosis, classification, response assessment, treatment and follow up is provided for adults with AML and APL

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## Incidence and epidemiology

Acute myeloid leukaemia (AML) incidence is age-dependent, rising markedly in patients aged  $\geq 60$  years. Ageing of the European population may therefore contribute to the reported increase in AML incidence in Europe from 3.48 in 1976 to 5.06 patients per 100 000 people in 2013 [1]. Across all age groups, the incidence of AML is higher in males than in females [2]. The median age at diagnosis is  $\sim 70$  years [2].

The 2016 World Health Organization (WHO) classification identifies distinct categories of AML (Supplementary Table S1) [3]. Notably, AML is primarily categorised by recurrent genetic abnormalities, with morphological classification reserved for patients not otherwise classifiable.

With advanced age, the relative incidence of AML with recurrent genetic abnormalities decreases [4], while the relative incidence of other AML categories [such as AML with myelodysplasia-related changes (MRC-AML) or therapy-related AML (tAML)] increases with age, comprising about 19% and 7% of AML cases, respectively [5-7].

## Survival of AML patients in Europe

The prognosis and long-term survival rates of patients <65 years have incrementally improved with time, largely based upon improved supportive care and increased utilisation of allogeneic haematopoietic cell transplantation (alloHCT). Despite this progress, age-standardised relative 5-year survival for adult patients diagnosed between 2000 and 2007 was as low as 17% (16.6–17.7) [8], mainly attributable to the minimal progress attained in AML patients >65 years.

## Diagnosis and molecular biology

Patients suspected of a diagnosis of AML must undergo prompt cytogenetic and molecular investigations to inform risk stratification and, increasingly, treatment strategies. It is vital to urgently differentiate acute promyelocytic leukaemia (APL) from other forms of AML by cytomorphology (dysplastic promyelocytes, binucleated blasts, faggot cells), signs of hyperfibrinolysis and molecular evidence of *PML-RARA* fusion.

AML is defined based on morphological inspection revealing a myeloid blast count of  $\geq 20\%$  out of 500 bone marrow (BM) cells [9], although counting fewer cells is sufficient in patients with high blast count [10]. Blast counts should include myeloblasts, monoblasts/promonocytes and megakaryoblasts, but not abnormal monocytes. According to the latest WHO classification, all nucleated cells in the BM serve as a denominator, even in cases where the BM is enriched with erythroid precursors [3]. Supplementary Table S2 lists all mandatory clinical and laboratory tests that should be carried out at presentation.

Past medical history should be carefully reviewed to reveal signs of an antecedent BM disease and previous exposure to radiation, chemotherapy (ChT) or leukaemogenic toxins such as benzene and organochlorine insecticides. Blood count results preceding AML diagnosis should be collected, but even if abnormal, are insufficient to make a definitive diagnosis of MRC-AML. A history of a myelodysplastic syndrome (MDS) or a myelodysplastic/myeloproliferative neoplasm or the presence of one of several MDS-related cytogenetic abnormalities, or  $\geq 50\%$

dysplastic cells in at least two cell lineages (except when combined with *NPM1* or double *CEBPA* mutations), is required for the diagnosis of MRC-AML [3]. Despite progress in immunophenotyping allowing recognition of dysplasia by aberrant flow cytometry patterns, cytomorphology remains the gold standard for MDS diagnosis [11].

We recommend a BM aspirate for cytology and cytochemistry, including Sudan Black B, myeloperoxidase and esterase staining, immunophenotyping and a trephine biopsy for histology at diagnosis. Cytochemistry is especially helpful whilst cytogenetic and molecular results are awaited [V, B]. A BM biopsy is mandatory in patients with dry-tap. Interpretation of morphological changes may be challenging. Presence of AML-related recurrent genetic abnormality [e.g. t(8:21)] overrules morphological uncertainties. Multiparameter flow cytometry (MFC), using a minimum of six colours and following an established flow cytometry protocol such as the European LeukaemiaNet (ELN) criteria for immunophenotypic leukaemia classification [12], is required for the diagnosis of specific entities, such as mixed phenotype acute leukaemia (MPAL), AML not otherwise specified (NOS) with minimal differentiation, acute megakaryoblastic leukaemia or blastic plasmacytoid dendritic cell neoplasm (BPDCN, positive for CD4, CD56, CD123 and TCL1) [13,14]. In general, genetic aberrations overrule immunophenotypic changes.

Cytogenetic classification should be based on the evaluation of at least 20 metaphases. An abnormal clone is reported only if at least 2/20 cells are identified as carrying the same karyotypic abnormality. Karyotype analysis may miss clinically-significant cryptic aberrations (e.g. *MLL/KMT2A*, inv(16), chromosome 3 aberrations) thus, complementary fluorescent *in situ* hybridisation (FISH) analysis is recommended and should be considered mandatory when conventional cytogenetic analysis fails.

Molecular studies to detect presence of mutations in the *FLT3* gene [internal tandem duplication (ITD) or tyrosine kinase domain (TKD)] should be carried out immediately to allow timely initiation of a FLT3 inhibitor. Additional molecular studies to measure the *FLT3*-ITD allelic ratio (AR), and detection of *NPM1*, *PML-RARA*, *RUNX1-RUNX1T1*, *CBFB-MYH11* and double *CEBPA* mutations should be carried out at

diagnosis given their prognostic significance. The presence of *TP53*, *RUNX1* and *ASXL1* mutations classifies patients to the adverse ELN risk group; testing is therefore advised. *IDH1* and *IDH2* should also be assessed for mutations to identify patients who may benefit from pharmacological inhibitors when these become available in Europe. If available, next-generation sequencing (NGS) of a panel of genes commonly mutated in AML provides important additional prognostic and therapeutic information.

The new WHO diagnosis of myeloid neoplasms with germline predisposition is often overlooked in patients with newly diagnosed AML (see Supplementary Table S1). Genetic counselling is recommended in case of a positive cancer family history or if an inherited condition potentially associated with leukaemia has been diagnosed in any relative. There are also specific medical conditions that should draw physicians' awareness regarding potential germline predisposition (Supplementary Table S3) [15]. All candidates for alloHCT and their siblings should undergo human leucocyte antigen (HLA) typing at diagnosis.

Sperm cryopreservation should be systematically proposed before starting ChT, especially in patients due to undergo alloHCT. In females, ovarian tissue cryopreservation (OTC) may be carried out before haematopoietic cell transplantation (HCT) if patients are in complete remission (CR) [16]. The main concern about the safety of autologous transplantation of ovarian fragments is possible contamination with leukaemic cells that may lead to AML recurrence [16]. Fertility preservation is further discussed in the section 'Follow-up, long-term implications and survivorship' in Supplementary Material.

## Classification and risk assessment

The initial assessment of newly diagnosed AML patients should focus on patient fitness for standard induction and consolidation ChT. Pre-existing heart, kidney, lung or liver disease, mental illness, an Eastern Cooperative Oncology Group (ECOG) performance score  $\geq 3$  and age  $\geq 75$  years are the strongest predictors for non-relapse induction-related mortality and should be considered to determine ineligibility to intensive induction and consolidation ChT [V, B] [17]. The risk of early death of older

AML patients upon induction ChT can be calculated using seven clinical parameters: body temperature, age, *de novo* versus secondary leukaemia, haemoglobin level, platelet count, fibrinogen level and serum concentration of lactate dehydrogenase [18]. The HCT-specific comorbidity index (HCT-CI) score predicts treatment-related mortality in patients treated with induction ChT, as well as transplant outcome [19,20]. The final decision concerning the role of intensive ChT is taken after careful consultation between an experienced clinician and the patient. The presence of extramedullary involvement should be evaluated clinically, although its prognostic value is debatable [21]. Extramedullary AML involvement has been found in 17% of patients when using positron emission tomography (PET) [22]. In case of any neurological signs or symptoms, diagnostic lumbar puncture should be carried out when blasts are reduced in peripheral blood, and cranial magnetic resonance imaging (MRI) [or computed tomography (CT) if MRI is unavailable] should be conducted. In APL patients, lumbar puncture should be delayed until recovery of bleeding diathesis.

In patients with hypoproliferative disease or those who can be safely treated with hydroxycarbamide cytoreduction, it may be feasible to await cytogenetic and molecular genetic results before commencing treatment, if these results are likely to influence the choice of therapeutic modalities.

Genetic classification of AML is essential to guide clinical decisions and predict prognosis. The 2017 ELN recommendations identify three risk groups, based on karyotype and mutational analysis (ELN favourable, intermediate and adverse risk, see Supplementary Table S4) [12]. The favourable-risk AML group comprises all patients in whom a relapse risk is predicted to be low if treated with induction and consolidation ChT alone. This group includes patients with mutated *NPM1* (*NPM1*<sup>mut</sup>) without *FLT3*-ITD or with *FLT3*-ITD presenting with AR <0.5, t(8;21)(q22;q22.1)/*RUNX1-RUNX1T1*, inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB-MYH11*, or presenting with double-mutant *CEBPA*. However, a large retrospective analysis showed that 3.6% of *NPM1*<sup>mut</sup>/*FLT3*-ITD<sup>low</sup> patients have adverse cytogenetic aberrations, which confer an equally poor prognosis as adverse cytogenetics in *NPM1*<sup>wildtype</sup> patients [23].

The intermediate-risk AML group comprises patients with molecular or cytogenetic abnormalities not classified as favourable or adverse, and includes patients with *NPM1*<sup>mut</sup> and a high AR of *FLT3*-ITD.

The adverse-risk AML group includes patients with complex cytogenetics and other poor-risk genetic aberrations [12]. All patients failing to achieve CR after 2 induction cycles should also be considered as adverse-risk patients, regardless of genetics/cytogenetics [24]. Accurate risk stratification plays a critical role in guiding selection of the optimal post-remission approach and of indications for alloHCT in first CR (CR1) [25]. A comprehensive risk classification integrating clinical, genetic and treatment data is available as an online tool that simulates the individual patient's risk and predicts outcome with and without alloHCT (<https://cancer.sanger.ac.uk/aml-multistage/>) [26].

## Response assessment

### Defining response and treatment failure

The ELN has defined response categories to induction ChT [12]. In addition to conventional CR, CR with incomplete haematological recovery (CRi) and CR without measurable residual disease (CR<sub>MRD</sub>-) were proposed (Supplementary Table S5). ELN MRD recommendations recently proposed CR with molecular persistence at low copy numbers (CR<sub>MRDlow</sub>) to account for *NPM1* and core binding factor leukaemia patients with positive MRD at low copy numbers (<100-200 copies/10<sup>4</sup> ABL copies corresponding to <1-2% of target to reference gene or variant allele burden), who have completed their treatment and have a low risk of relapse despite MRD positivity. We recommend handling these patients the same way as patients with complete molecular remission. In addition, CR with partial haematological recovery (CRh) is proposed by other groups, to be used in the context of clinical studies [<5% blasts in the BM, without evidence of extramedullary disease, platelets  $\geq 50 \times 10^9/L$  and absolute neutrophil count (ANC)  $\geq 0.5 \times 10^9/L$ ]. The term CRp, also used in clinical studies, indicates a CR with platelets  $< 100 \times 10^9/L$  and with ANC recovery  $\geq 1.0 \times 10^9/L$ , but is now covered by CRi. Morphological leukaemia-free state (MLFS) consists of <5% BM blasts, absence of blasts with Auer rods, no extramedullary disease and a



lack of haematological recovery of both neutrophils and platelets where the BM may not be merely aplastic and at least 200 cells should be counted or cellularity at trephine biopsy should be at least 10%. By comparison, CRi requires recovery of at least one lineage (either ANC  $\geq 1.0 \times 10^9/L$  or platelets  $\geq 100 \times 10^9/L$ ). BM cellularity  $< 10\%$  should be defined as BM aplasia in patients without count recovery, and response assessment repeated after 2-4 weeks. It is unclear if prognosis differs between patients reaching CRi or MLFS. In clinical practice, we recommend using CR<sub>MRD</sub>-, CR, CRi and MLFS.

We introduce an operational definition of refractoriness for patients not achieving CR/CRi/MLFS after the first induction cycle: blast persistence after induction 1 defined by  $\geq 5\%$  blasts in BM. Consistent with ELN 2017 recommendations, we consider patients primary refractory to induction ChT if they have  $\geq 5\%$  blasts in BM after the second induction cycle. It was shown that patients with  $> 15\%$  BM blasts or  $< 50\%$  reduction of BM blasts after the first induction cycle constitute a group with an equally poor prognosis as patients with primary refractory disease and who may benefit from direct alloHCT [24].

Relapse is defined by BM blasts  $\geq 5\%$  in patients who have been in CR previously, or reappearance of blasts in the blood, or development of extramedullary AML [12,24]. Molecular relapse is defined by an increase of the MRD level of  $\geq 1 \log_{10}$  between two positive samples in a patient who previously tested negative.

### Measurable residual disease

Morphological enumeration of the blast percentage should be refined by immunophenotypic or molecular MRD assessment in patients with  $< 10\%$  blasts [27]. ELN recommendations on MRD assessment in AML specify its clinical use and technical requirements [28]. It is recommended to assess MRD by reverse transcriptase polymerase chain reaction (RT-PCR) for patients positive for *NPM1*<sup>mut</sup>, *RUNX1-RUNX1T1*, *CBFB-MYH11* or *PML-RARA* fusion genes;  $\sim 40\%$  of all AML patients. In the remaining patients, MRD should be assessed by MFC, which relies on antigens aberrantly expressed by leukaemic cells that can be found in  $> 90\%$  of AML patients. Many clinical studies have shown the strong prognostic impact of MRD, as measured by MFC, with levels  $\geq 0.1\%$  defined as positive [29-31]. Laboratories should report results of MRD studies according to recently published guidelines [28].

More than 90% of AML patients harbour a molecular marker that could potentially be used for MRD assessment by molecular methods. NGS enables simultaneous testing of multiple genes in a single assay [32], and sensitivity approaches  $10^{-4}$  with recent protocols [33]. Residual positivity for non-clonal haematopoiesis-related gene mutations (thus excluding *DNMT3A*, *TET2* and *ASXL1*) after 2 cycles of induction ChT and before alloHCT predicted AML relapse in a recent study, which also showed that NGS-MRD and MFC are complementary techniques [32]. However, NGS-MRD needs thorough standardisation and validation before recommendation for clinical use.

In APL patients, MRD assessment is recommended at the end of consolidation treatment, before starting maintenance. In non-high-risk APL patients treated with arsenic trioxide (ATO) and all-trans retinoic acid (ATRA), all patients were MRD-negative at the end of consolidation [34]. If MRD is negative in these patients, no further MRD assessment is recommended in view of the very low relapse risk [28]. In high-risk APL patients treated with ChT and ATRA, a variable proportion of 1%-5% of patients were MRD-positive at the end of consolidation [35]. Continuous MRD monitoring is therefore recommended in high-risk APL patients to predict impending haematological relapse and thereby prevent bleeding complications and to allow administration of pre-emptive therapy at the time of molecular relapse, prior to the occurrence of haematological relapse.

### **When to assess response?**

We recommend performing up to two BM assessments during the first cycle of standard induction ChT, the first between day 14 and day 21 as early response assessment to guide further treatment in case of insufficient response, and the second after recovery of BM to document CR. BM aspirates are usually sufficient, but trephine biopsy is recommended if smears are not evaluable. If a first response assessment gives an uncertain result, it is advisable to repeat BM aspirations until a clearer picture is obtained and the attainment of morphological CR can be more reliably assessed, at least when the non-attainment of CR would have therapeutic consequences. If a second induction cycle is applied, BM should be assessed after haematological recovery or between day 28 and 35 if haematological recovery is still lacking.

We recommend morphological assessment of BM before each consolidation cycle and before alloHCT. After the end of intensive induction and consolidation treatment, BM morphology may be repeated every 3 months for 24 months. We recommend 3-monthly differential blood counts for a total of 5 years after the end of treatment.

Assessment of MRD is recommended at diagnosis to establish the aberrant marker profile, after 2 cycles of ChT and after the end of treatment. In addition, molecular MRD may be assessed every 3 months after the end of treatment from BM or every 4-6 weeks from peripheral blood for 24 months in patients with a molecular marker. Flow cytometric MRD should be assessed from BM, while molecular MRD should be assessed from both blood and BM [28].

In patients treated non-intensively, response should be assessed at the very least after 4 cycles to diagnose refractory disease, and every 3 months thereafter if patients have no or incomplete recovery of at least one of the three blood lineages to identify refractory disease.

## **Treatment and outcome of newly diagnosed AML**

When a diagnosis of AML is made, a number of immediate decisions must be made. In patients in whom APL is suspected, immediate treatment with ATRA should be initiated, until confirmatory molecular and/or cytogenetic results are available [V, A]. In patients with non-APL AML with a white blood count (WBC)  $>100 \times 10^9/L$  and signs of leukostasis, the requirement for cytoreduction should be considered. This is achieved with 50-60 mg/kg hydroxycarbamide per day, or, if a patient cannot swallow, either with intravenous (i.v.) or subcutaneous cytarabine, or with i.v. daunorubicin. Leukapheresis for hyperleukocytosis should be avoided in APL patients because it may exacerbate coagulopathy [V, B]. In non-APL AML patients, the efficacy of leukapheresis to reduce early mortality was investigated in a meta-analysis and a propensity-matched study [36]. Early mortality was not reduced by leukapheresis which can thus not be generally recommended [II, C]. Nevertheless, if leukapheresis is applied, it should be accompanied by hydroxycarbamide, cytarabine or daunorubicin [37]. If central nervous system (CNS) involvement is diagnosed, the patient should be treated with intrathecal cytarabine twice weekly, with two injections beyond blast clearance from the cerebrospinal fluid (CSF), except in APL patients in

whom intrathecal treatment should be delayed until recovery of coagulopathy. Supportive care is essential for the patient and should include prophylaxis and management of tumour lysis syndrome, infection, hyperfibrinolysis, bleeding and eventual thrombosis. There is scant data to support the use of a gonadotropin-releasing hormone (GnRH) agonist in female AML patients for prevention of loss of fertility, but it can be used to avoid menorrhagia [38].

Based on eligibility criteria and patient preference, all AML patients must be assigned to either standard induction and consolidation ChT or non-intensive treatment (see section on 'Classification and risk assessment'). Patients should be encouraged to participate in clinical trials whenever possible.

### **First-line treatment of AML patients eligible for standard induction and consolidation ChT**

#### *Recommendations for induction ChT*

The recommended first-line treatment according to patient subgroups is shown in Figures 1 and 2. If a patient fulfils criteria for two or more novel drug combinations, we recommend following the algorithm in Figure 1, which prioritises the recommended treatments. Schedules and doses are detailed in Supplementary Table S6. For CBF-AML we recommend 7 days of cytarabine, 3 days of daunorubicin (7+3) and 1-3 days of gemtuzumab/ozogamicin (GO) in induction 1: 7+3+GO [II, A]. GO is approved for CD33-positive AML patients (defined by  $\geq 30\%$  blasts expressing CD33 in the pivotal trial) in combination with 7+3 induction ChT in induction 1, but not in induction 2 [39, 40]. Our recommendation is based primarily on the meta-analysis of five studies with GO, in which patients with CBF-AML (*RUNX1-RUNX1T1*- or *CBFB-MYH11*-positive AML) benefit most from the addition of GO [GO improved 6-year overall survival (OS) by 20.7% to an OS of 75.5% in this meta-analysis] [41]. GO is approved as a fractionated dose of 3 mg/m<sup>2</sup> on days 1, 4 and 7 based on the ALFA-0701 trial [39]. However, the ALFA-0701 trial contributed only 3.6% of the patients with favourable-risk cytogenetics to the meta-analysis (9/251 patients) [39,41]. The majority of patients with favourable-risk cytogenetics in the meta-analysis received only one dose of 3 mg/m<sup>2</sup> GO during induction cycle 1 (170/251 patients, 67.7%) [41]. Thus, the optimal dose for GO remains to be determined. Due to the risk of hepatic sinusoidal obstruction syndrome, a 2-month period was

recommended in the ALFA-0701 trial between the last dose of GO and alloHCT conditioning, but we recommend not to delay transplantation if GO was administered within 8 weeks before alloHCT.

If tAML or MRC-AML is diagnosed in patients  $\geq 60$  years, treatment with CPX-351 is recommended [I, A]. CPX-351 is approved for AML patients  $\geq 18$  years with tAML or MRC-AML and improved 2-year OS by 18.8% to 31.1% in patients  $\geq 60$  years [42]. CPX-351 is approved in Europe independent of age, although randomised or prospective data in younger patients have not been published. No benefit of CPX-351 over 7+3 was found in the subgroup of patients who had been previously treated with hypomethylating agents (HMAs) for MDS, who should preferably be treated in clinical trials [42]. We recommend CPX-351 also for *FLT3*-ITD- or *FLT3*-TKD-positive tAML or MRC-AML, as CPX-351 showed good efficacy in this subgroup [median OS (mOS) 10.25 versus 4.6 months], while very few MRC-AML and no tAML patients were treated in the RATIFY trial evaluating the *FLT3* inhibitor midostaurin.

For the remaining patients, we recommend 7+3+midostaurin if they are *FLT3*-ITD- or *FLT3*-TKD-positive [I, A]. Midostaurin is approved for patients with a *FLT3*-ITD or *FLT3*-TKD mutation (defined by an AR  $\geq 0.05$ ) in combination with 7+3 induction ChT. The addition of midostaurin improved OS by 7.1% after 4 years to 51.4% [43].

If none of the previous markers is positive, we generally recommend 7+3 induction ChT [II, A]. The addition of GO to 7+3 may also be considered in younger CD33-positive patients with non-CBF AML with ELN favourable or intermediate risk [II, C]. In a meta-analysis, GO improved 6-year OS by 5.7% in patients with intermediate-risk cytogenetics to 39.6%. However, GO had no effect on 6-year OS in patients with adverse-risk cytogenetics (6-year OS 8.9%) and is not recommended in these patients [II, E] [41]. A large randomised study failed to show an event-free survival (EFS) benefit of additional GO in *NPM1*<sup>mut</sup> AML patients treated with induction ChT and ATRA [44].

In the remaining patients with ELN adverse risk, we recommend 7+3 ChT [II, A] with the option to add cladribine or fludarabine to induction ChT in patients up to age 60 (though cladribine and fludarabine are not approved for this indication) [II, C] [45]. Upfront treatment with 2 cycles of fludarabine, cytarabine, granulocyte-colony stimulating factor and idarubicin (FLAG-Ida) ChT improved relapse-free survival (RFS), but not OS in younger AML patients and may be considered in younger high-risk patients [I, C] [46]. There is limited data on the treatment of *BCR-ABL1*-positive

AML. Tyrosine-kinase inhibitor (TKI)-naïve patients should be treated with a second-line TKI with or without induction ChT [II, A] [47]. Non-responding patients should be treated with another TKI.

After the first induction cycle, response should be assessed between day 14 and day 21. Patients with  $\geq 5\%$  blasts in BM after induction 1 (blast persistence) should receive a second induction cycle, which may consist of the identical ChT as induction 1 or of a regimen containing intermediate-dose cytarabine (IDAC), e.g. FLAG-Ida [III, C]. As soon as patients achieve CR/CRi after one or two induction cycles, they should proceed to consolidation treatment [II, B] [48]. Patients not achieving CR/CRi after 2 cycles of induction ChT are defined as primary refractory and their treatment options are discussed below. The optimal ChT backbone for induction therapy consisting of cytarabine and an anthracycline is further discussed in Supplementary Material.

#### *Consolidation treatment with ChT or autologous HCT*

Patients in CR after induction ChT should undergo consolidation treatment either with ChT, autologous HCT (autoHCT) or alloHCT [I, A] (Figure 1). There is insufficient data to give a recommendation on the number of ChT cycles before auto/alloHCT, but the timing of alloHCT is usually determined by donor availability. Patients in CR with ELN favourable-risk AML should be consolidated with ChT [I, A], while autoHCT is an alternative and results in better RFS, but not OS, than ChT (e.g. in patients with CBF-AML or double-mutant *CEBPA* AML) [II, B] [49,50]. If CBF-AML patients are consolidated with ChT, we recommend 3 cycles with IDAC [II, B]. In CBF-AML patients, we consider the addition of 3 mg/m<sup>2</sup> GO given on day 1 in consolidation 1 and 2 as optional [II, C], as it remains unclear whether GO in consolidation contributes to the overall benefit (Figure 1) [51].

Patients in CR with ELN intermediate- or adverse-risk AML should undergo alloHCT, if feasible [II, A] [52,53]. If no suitable donor is available or if alloHCT is contraindicated, these patients should undergo consolidation ChT or autoHCT [49,54]. ELN intermediate-risk patients, 40-60 years old and in CR1, had comparable OS with autoHCT and alloHCT consolidation [54] and better OS with autoHCT compared with ChT [55]. A retrospective study reported better RFS and OS in patients receiving busulfan/melphalan conditioning before autoHCT compared with busulfan/cyclophosphamide conditioning [56].

Patients treated with CPX-351 during induction may receive up to 2 consolidation cycles with CPX-351 with a reduced dose and 2 instead of 3 days of application compared with induction ChT [42]. In *FLT3*-mutated patients, midostaurin is combined with consolidation ChT and up to 3 consolidation cycles should be applied in patients not undergoing alloHCT [43]. If non-CBF AML patients are treated with GO during induction, GO is optional in consolidation 1 and 2 in combination with cytarabine (Figure 1 and Supplementary Table S6) [39].

We recommend at least 2 consolidation cycles in CR patients not undergoing alloHCT with cytarabine 1.5 g/m<sup>2</sup> every 12 hours on days 1-3 in patients <60–65 years, and a dose reduction to 1 g/m<sup>2</sup> in patients ≥60–65 years, taking biologic age into consideration [II, A] [57].

If alloHCT is not feasible in younger patients with adverse-risk cytogenetics, consolidation with amsacrine, cytarabine, etoposide/mitoxantrone, cytarabine (MACE/MidAC) may be considered (OS 39% versus 0% after a median follow up of 5.6 years) [II, B] [46].

Extramedullary manifestations of AML/myeloid sarcoma may present at diagnosis and may be the sole manifestation of AML. If myeloid sarcoma is the only manifestation, we recommend induction ChT followed by alloHCT (Figure 1). Individual reports show that local radiotherapy (RT) can induce long-term remission in patients with persisting or relapsing extramedullary AML sites [58]. While RT can effectively induce local control, its effect on long-term outcome is poorly investigated [59].

#### *Consolidation treatment with alloHCT*

AML remains the most frequent indication for alloHCT. Key considerations before proceeding to alloHCT for consolidation in first or second CR include donor availability and patient fitness.

#### *Eligibility criteria*

In CR1, alloHCT is indicated in patients with intermediate or adverse risk ≤75 years, according to recommendations of ELN 2017 [12], European Society for Blood and Marrow Transplantation (EBMT) [60] and American Society of Blood and Marrow Transplantation (ASBMT) [61] [II, A]. BCR-ABL-positive patients should undergo



alloHCT as soon as they achieve remission. In older patients, comorbidities must be carefully evaluated. In this regard, the HCT-CI predicts non-relapse mortality (NRM) and OS and helps in the selection of patients [19]. Likewise, the combination of HCT-CI with the EBMT score translates into NRM prediction for patients undergoing reduced-intensity conditioning (RIC) alloHCT in CR1 [62].

### *Donor selection*

Nowadays, almost all patients will have a donor despite the decreasing number of siblings, as cord blood and haploidentical transplantation have become feasible [63]. Retrospective data comparing the different donor sources suggest similar leukaemia-free survival and OS probabilities in haploidentical transplant recipients who have received post-transplant cyclophosphamide, although results differ markedly according to the regimen used [64,65]. As patients need to be transplanted in due time, currently, the first priority is to select an HLA-identical donor (sibling or unrelated donor if the search time is <3 months from diagnosis, 10/10 or 9/10 HLA-match required), with second and third priority being an umbilical cord blood donor or haploidentical donor, depending on centre experience and patient's age [66]. In haploidentical transplants of AML patients  $\geq 40$  years, young donors are preferred, while in patients <40 years, neither the age of the donor nor the kinship have an impact on the outcome [67].

### *Conditioning regimens*

The aim of conditioning is to eradicate the disease and enable a graft-versus-leukaemia (GvL) effect with minimal NRM and low risk of relapse. Currently used myeloablative conditioning (MAC) regimens, with or without total body irradiation (TBI), are quite similar in dosing and schedules but are associated with considerable NRM and are therefore usually restricted to patients  $\leq 55$  years, if no comorbidities are present [68]. In younger fit patients, the myeloablative fludarabine/busulphan (Flu/Bu4) regimen is associated with less toxicity than busulphan/cyclophosphamide (Bu/Cy) [69]. Cy/TBI myeloablative regimens have been extensively used as a conditioning regimen in high-risk AML. However, there is no convincing data to demonstrate their superiority to a Bu/Cy or Flu/Bu4 regimen, both of which are widely utilised [70]. A TBI-based myeloablative regimen should be considered in rare patients with evidence of CNS disease at presentation or a myeloid sarcoma. In



contrast, RIC regimens use heterogeneous doses and schedules and rely more on the GvL effect. Despite large meta-analyses, it is currently not possible to define the optimal conditioning regimen for AML. In general, we recommend MAC for patients  $\leq 55$  years with HCT-CI  $\leq 2$  [I, A] and RIC for all other patients [II, B] [71]. Graft-versus-host disease (GvHD) prophylaxis is a critical part of alloHCT and we refer to the recommendations for a standardised prophylaxis and treatment of GvHD by the EBMT-ELN working group on GvHD [72].

#### *Maintenance treatment after intensive ChT or alloHCT*

Maintenance treatment is approved only for midostaurin in patients who are in CR after induction and consolidation ChT (but not after alloHCT). Exploratory analysis of the RATIFY trial failed to clarify whether midostaurin maintenance contributes to the OS benefit of midostaurin [73]; based on expert opinion, we currently do not favour this treatment after ChT consolidation [IV, D]. Importantly, midostaurin maintenance should not replace alloHCT in transplant candidates. Maintenance treatment with subcutaneous azacitidine in older AML patients who obtained CR after induction and consolidation treatment improved disease-free survival but not OS in a randomised study [74]. Recently, maintenance treatment with oral azacitidine (CC-486) showed improved survival in patients  $\geq 55$  years who obtained CR after intensive ChT, but is currently not approved [75].

The use of maintenance and pre-emptive treatment after alloHCT remains controversial. Therapeutic options include TKIs for *FLT3*-ITD-mutated AML, HMAs or donor lymphocyte infusions (DLIs). In a small randomised trial, maintenance with sorafenib after alloHCT in *FLT3*<sup>mut</sup> patients improved 2-year RFS in patients who were not pretreated with an FLT3 inhibitor [76]. The results of ongoing larger randomised trials are required before maintenance sorafenib or midostaurin can be recommended after alloHCT in patients with *FLT3*-ITD-positive AML [77].

A phase I/II dose-finding study of oral azacitidine (CC-486) maintenance treatment after alloHCT in patients with AML or MDS showed encouraging results with a 1-year relapse/progression rate of 21% [78]. It is unclear whether prophylactic HMA treatment after alloHCT is beneficial to prevent relapse, as it may increase toxicity without therapeutic benefit in patients who can be cured with alloHCT alone. Pre-emptive treatment when mixed chimerism (MC) or MRD appears could prevent or

delay relapse in patients with AML and MDS [79]. Currently, we do not recommend maintenance with HMAs outside of clinical trials [V, D]. In BCR-ABL-positive patients we recommend TKI maintenance after alloHCT [V, B].

DLI, as pre-emptive treatment in patients with MRD or MC, or as prophylactic treatment before relapse or progression, is increasingly used in AML after alloHCT [80]. This is due to the poor efficacy of therapeutic DLIs when overt relapse occurs and increased use of RIC allografts. So far, there is no clear recommendation for the use of DLIs and important questions remain, such as time of administration, dose and use of DLIs as prophylactic or pre-emptive treatment.

### **First-line treatment of AML patients not eligible for standard induction and consolidation ChT**

The HMAs azacitidine and decitabine are currently the first choice in newly diagnosed unfit AML patients [II, B] (Figure 2, Supplementary Table S6 for dosing) [81,82]. While venetoclax in combination with azacitidine, decitabine or low-dose cytarabine (LDAC) is approved in the United States and Israel [83], and glasdegib in combination with LDAC is approved in the United States for newly diagnosed AML patients  $\geq 75$  years or with comorbidities that preclude use of intensive induction ChT [84], their approval is pending in most European countries. Although we consider venetoclax in combination with a HMA or LDAC to be superior to currently available first-line treatments for AML patients ineligible for standard induction ChT based on promising preliminary data, results of ongoing randomised trials are awaited before its use can be recommended with confidence [III, A].

A prospective randomised study comparing 5-day and 10-day decitabine treatment in newly diagnosed AML patients found almost identical CR and early mortality rates, EFS and OS between the two arms, which also extended to the subgroup of *TP53*<sup>mut</sup> patients [85]. Thus, if decitabine is chosen, we recommend the 5-day schedule [II, B]. No predictive markers are known to recommend one HMA over the other. HMA treatment is usually continued until disease progression or intolerance but may be terminated after at least 4 consecutive cycles if the patient has not responded or derived clinical benefit. Given the moderate effects of HMAs, LDAC remains an alternative to HMAs in the first-line treatment of AML patients who are ineligible for standard induction and consolidation ChT, except in patients with adverse-risk cytogenetics, where LDAC has very poor activity [II, B]. First-line treatment with

LDAC results in mOS of ~5 months [86]. A practical benefit of LDAC is its longer stability after being dissolved, allowing administration at home unlike azacitidine and decitabine. Patients with MDS progressing to AML during treatment with azacitidine constitute a significant therapeutic challenge. Current evidence shows that 21%–43% AML patients pretreated with HMAs and who received HMA and venetoclax achieved a response [87,88]. MDS patients progressing to AML under HMA treatment may be similarly sensitised to HMA by the addition of venetoclax [III, B]; LDAC or best supportive care with either 6-mercaptopurine or low-dose melphalan or hydroxycarbamide are remaining options, if no clinical trial is available [III, C]. Patients should be treated for at least 4 cycles and, in case of clinical benefit, should continue until progression or intolerance. Patients responding to initial treatment should be re-evaluated regarding their ability to undergo alloHCT using RIC, which may cure a proportion of these patients.

## **Treatment of primary refractory and relapsed AML**

Roughly 10%–20% of younger and 50% of older AML patients do not achieve CR after at least two courses of intensive induction therapy, and 50%–70% of patients who obtain CR will relapse [12]. The prognosis of primary refractory and relapsed AML patients remains poor and treatment is challenging. A primary consideration in the therapeutic approach of refractory or relapsed AML patients should be their suitability for intensive ChT and alloHCT. Mutation analysis for *FLT3* should be repeated in relapsed patients, as gilteritinib has been approved in Europe and the US in the relapse setting of *FLT3*-ITD- and *FLT3*-TKD-mutated patients [89]. Mutation analysis for *IDH1/2* will become relevant once the *IDH1/2*<sup>mut</sup> inhibitors ivosidenib/enasidenib become available in Europe.

### **Primary refractory and relapsed AML patients eligible for standard ChT and alloHCT**

The outcome of patients with primary refractory AML is dismal, with no realistic prospect of long-term survival after salvage ChT [90]; thus, alloHCT is the most effective treatment option providing long-term survival in 20%–30% of patients [III, B] [91]. Outcomes for patients with primary refractory AML may be better with a sequential transplant conditioning regimen, in which a combination of

cytarabine/amsacrine ChT is followed by a fludarabine-based RIC regimen (FLAMSA-RIC) [III,C] [92]. If a family or unrelated donor is not immediately available, either a haploidentical or cord blood donor alloHCT should be offered promptly. For fit patients with relapsed AML, the recommended treatment is salvage ChT followed by alloHCT [III, B] (Figure 3). Breems et al. developed a simplified prognostic score to predict the efficacy of salvage ChT in relapsed AML patients based on the length of the relapse-free interval after CR1, cytogenetics at diagnosis, age at relapse and previous alloHCT [93]. Many salvage regimens have been studied in an effort to improve CR rates in patients with relapsed AML. Commonly used salvage regimens are summarised in Supplementary Table S7 [94]. Due to the limited long-term effects, enrolment in clinical trials is strongly recommended. We recommend a salvage protocol based on high- or intermediate-dose cytarabine in combination with an anthracycline and, optionally, a purine analogue (e.g. FLAG-Ida) [II, B]. Patients with late relapse ( $\geq 12$  months after the end of first-line treatment) may also benefit from retreatment with the previously successful induction regimen.

AlloHCT should be considered for all fit, eligible patients who entered second CR [III, B], as it represents the only chance for long-term survival [95,96]. A second alloHCT or DLI may induce long-term survival in patients with relapse after the first alloHCT, particularly for those relapsing later than 5 months [IV, C] [97]. A Center for International Blood and Marrow Transplant Research (CIBMTR) retrospective study found survival probabilities at 3 years to be 4%, 12%, 26% and 38% for patients relapsing within 6 months, 6-24 months, 2-3 years or  $>3$  years after alloHCT [98]. Intensive ChT can induce a CR in a proportion of patients relapsing after an alloHCT, but is associated with considerable toxicity. HMAs, notably azacitidine, represent an important and less toxic alternative, particularly in patients relapsing  $>6$  months post alloHCT, as demonstrated in a recent large EBMT study [99]. Relapse of *FLT3*-mutated AML after alloHCT has a poor prognosis, but encouraging results have been reported using both gilteritinib and quizartinib as monotherapy [89,100]. Patients achieving a CR can proceed to a second alloHCT or DLI with potentially curative intent.

### **Primary refractory and relapsed AML patients not eligible for standard ChT**

The therapeutic options in unfit AML patients aim at controlling disease progression and minimising treatment-related mortality (TRM). In *FLT3*-mutated patients, we

recommend treatment with gilteritinib, which showed a favourable response rate and improved OS compared with ChT (mOS 9.3 versus 5.6 months) [I, A] [89]. Quizartinib also showed a survival benefit in relapsed/refractory *FLT3*-ITD-mutated patients but was not approved in Europe (mOS 6.2 versus 4.7 months) [100]. If the patient is considered ineligible, azacitidine or decitabine should be applied if LDAC was given in first line, and LDAC may be applied in favourable- and intermediate-risk patients if an HMA was given initially [IV, C] (Figure 3). In a cohort of 655 relapsed/refractory AML patients treated with azacitidine or decitabine, the CR/CRi rate was found to be 16.3% with mOS of 6.7 months, with no differences observed between agents [101]. If available, venetoclax in combination with HMA or LDAC is a promising second-line treatment with overall response rates of 21%–43% [87,88]. In *IDH1/IDH2*<sup>mut</sup> patients, inhibitors ivosidenib [102] and enasidenib [103], respectively, show considerable activity as single agents in relapsed/refractory patients, and will expand the treatment options once they become available. Differentiation syndrome occurs in up to 20% of patients treated with IDH-inhibitor monotherapy or when combined with HMAs and requires close monitoring and immediate initiation of dexamethasone treatment when suspected [104]. Eligibility for RIC alloHCT should be re-evaluated for patients who achieved CR. GO is not approved in Europe for refractory and relapsed AML patients and currently is not recommended as a salvage treatment. Older patients with hypocellular marrow may benefit from oral low-dose melphalan [V, C] [105]. Best supportive care with cytoreductive treatment (hydroxycarbamide, 6-mercaptopurine) should be offered for patients who cannot tolerate or who decline other treatments.

## Treatment of APL patients

ELN APL treatment guidelines were updated in 2019 and we largely follow these recommendations [106]. Treatment of APL patients should be centralised in hospitals with proven experience in APL treatment and haematological intensive care. Non-high-risk APL patients defined by a WBC count  $\leq 10 \times 10^9/\text{L}$  should be treated with ATO and ATRA (Figure 4 and Supplementary Table S6) [I, A]. Non-high-risk patients continuously receive ATO/ATRA until day 28, or up to day 60 if no CR/CRi is achieved by day 28. Missed doses due to adverse events should be appended to this schedule. As all patients will likely achieve CR it is sufficient to repeat BM assessment only after haematological recovery. Patients with CR/CRi are given time

for neutrophil and platelet recovery without treatment. Consolidation treatment with ATO/ATRA should be started as soon as possible after count recovery. Four 8-week consolidation cycles with ATO/ATRA are recommended (Supplementary Table S6) providing excellent cure rates to these patients [34,107]. Comparable cure rates can be also achieved with a more condensed infusion scheme of ATO [108]. If ATO is not available/affordable for first-line treatment, the classical combination of ATRA and anthracycline-based ChT is still an acceptable option, which however requires 2-year maintenance therapy with methotrexate and 6-mercaptopurine.

APL high-risk patients defined by a WBC count  $>10 \times 10^9/\text{L}$  may be treated with either ATRA plus ATO combined with an anthracycline (while ATO is not approved for high-risk APL) or with conventional ATRA plus anthracycline-based ChT [e.g. ATRA and idarubicin (AIDA)] [II, A] (see Supplementary Table S6). In the AIDA regimen, the induction and consolidation treatments are followed by a 2-year maintenance phase [109]. The combination of ATRA and ATO with idarubicin during induction followed by ATRA and ATO for consolidation and 2-year maintenance of ATRA, 6-mercaptopurine and methotrexate in a single-arm phase II trial resulted in excellent outcomes also in high-risk patients, suggesting good activity in this patient population [110].

To prevent differentiation syndrome, patients should be treated prophylactically with steroids as soon as they receive ATRA (e.g. prednisolone 0.5 mg/kg/day) and with hydroxycarbamide as soon as the WBC count increases above  $5-10 \times 10^9/\text{L}$ . Bleeding is the most frequent cause of early death in APL patients. Adequate support is recommended with fibrinogen or fresh frozen plasma and platelets to maintain levels above 1.0-1.5 g/L and  $>30-50 \times 10^9/\text{L}$ , respectively.

MRD assessment in APL patients is discussed in the 'Response assessment' section.

Patients relapsing after ATRA and ChT or relapsing  $>24$  months after the end of ATO/ATRA treatment should receive ATO/ATRA for reinduction and consolidation until achievement of second molecular remission [IV, B]. In the unlikely event of an early relapse (within 24 months) after treatment with ATO/ATRA, we recommend ATRA with ChT or, in patients not eligible for ChT, GO with or without ATO/ATRA [IV, B] (Figure 5) [111,112]. For patients in second molecular CR, autoHCT is recommended for consolidation [IV, B] [113]. For MRD-positive or refractory patients after salvage treatment, alloHCT is the preferred consolidation treatment. If alloHCT

is not feasible, treatment with GO, with or without ATO/ATRA, may be considered (Figure 5) [IV, C]. The CNS is involved in 10% of relapsing patients. Treatment of patients with CNS involvement should include ATO, which crosses the blood-brain barrier to some extent (CSF ATO levels were 17.7% of plasma levels) [114]. Due to the haemorrhagic risk, however, lumbar puncture should not be carried out in patients with haematological relapse and should be postponed in these cases to the end of induction.

## **Personalised medicine**

AML has long been the paradigm disease for personalised treatment approaches. Current and prospective use of biomarkers for personalised diagnosis, prognostication and treatment are shown in Supplementary Table S8.

## **Methodology**

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development <http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology>. The relevant literature has been selected by the expert authors. A summary of recommendations is shown in Supplementary Table S9. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S10. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty. This manuscript has been subjected to an anonymous peer review process.

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## References

1. E. Roman *et al.*, Myeloid malignancies in the real-world: Occurrence, progression and survival in the UK's population-based Haematological Malignancy Research Network 2004-15. *Cancer Epidemiol* **42**, 186-198 (2016).
2. G. Juliusson *et al.*, Prevalence and characteristics of survivors from acute myeloid leukemia in Sweden. *Leukemia* **31**, 728-731 (2017).
3. D. A. Arber *et al.*, The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* **127**, 2391-2405 (2016).
4. L. Bullinger, K. Dohner, H. Dohner, Genomics of Acute Myeloid Leukemia Diagnosis and Pathways. *J Clin Oncol* **35**, 934-946 (2017).
5. L. S. Granfeldt Ostgard *et al.*, Epidemiology and Clinical Significance of Secondary and Therapy-Related Acute Myeloid Leukemia: A National Population-Based Cohort Study. *J Clin Oncol* **33**, 3641-3649 (2015).



6. E. Hulegardh *et al.*, Characterization and prognostic features of secondary acute myeloid leukemia in a population-based setting: a report from the Swedish Acute Leukemia Registry. *Am J Hematol* **90**, 208-214 (2015).
7. S. Kayser *et al.*, The impact of therapy-related acute myeloid leukemia (AML) on outcome in 2853 adult patients with newly diagnosed AML. *Blood* **117**, 2137-2145 (2011).
8. R. De Angelis *et al.*, Survival variations by country and age for lymphoid and myeloid malignancies in Europe 2000-2007: Results of EURO CARE-5 population-based study. *European journal of cancer (Oxford, England : 1990)* **51**, 2254-2268 (2015).
9. J. W. Vardiman *et al.*, The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood* **114**, 937-951 (2009).
10. A. A. Abdulrahman *et al.*, Is a 500-Cell Count Necessary for Bone Marrow Differentials?: A Proposed Analytical Method for Validating a Lower Cutoff. *Am J Clin Pathol* **150**, 84-91 (2018).
11. M. C. Bene *et al.*, Immunophenotyping of acute leukemia and lymphoproliferative disorders: a consensus proposal of the European LeukemiaNet Work Package 10. *Leukemia* **25**, 567-574 (2011).
12. H. Dohner *et al.*, Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood* **129**, 424-447 (2017).
13. J. J. van Dongen *et al.*, EuroFlow antibody panels for standardized n-dimensional flow cytometric immunophenotyping of normal, reactive and malignant leukocytes. *Leukemia* **26**, 1908-1975 (2012).
14. U. Johansson *et al.*, Guidelines on the use of multicolour flow cytometry in the diagnosis of haematological neoplasms. British Committee for Standards in Haematology. *Br J Haematol* **165**, 455-488 (2014).
15. L. A. Godley, A. Shimamura, Genetic predisposition to hematologic malignancies: management and surveillance. *Blood* **130**, 424-432 (2017).
16. M. Shapira, H. Raanani, Y. Cohen, D. Meirou, Fertility preservation in young females with hematological malignancies. *Acta haematologica* **132**, 400-413 (2014).
17. F. Ferrara *et al.*, Consensus-based definition of unfit to intensive and non-intensive chemotherapy in acute myeloid leukemia: a project of SIE, SIES and GITMO group on a new tool for therapy decision making. *Leukemia* **27**, 997-999 (2013).
18. U. Krug *et al.*, Complete remission and early death after intensive chemotherapy in patients aged 60 years or older with acute myeloid leukaemia: a web-based application for prediction of outcomes. *Lancet* **376**, 2000-2008 (2010).
19. M. L. Sorror *et al.*, Development and Validation of a Novel Acute Myeloid Leukemia-Composite Model to Estimate Risks of Mortality. *JAMA Oncol* **3**, 1675-1682 (2017).
20. F. J. Giles *et al.*, The haematopoietic cell transplantation comorbidity index score is predictive of early death and survival in patients over 60 years of age receiving induction therapy for acute myeloid leukaemia. *Br J Haematol* **136**, 624-627 (2007).
21. C. Ganzel *et al.*, Extramedullary Disease in Adult Acute Myeloid Leukemia Is Common but Lacks Independent Significance: Analysis of Patients in ECOG-

- ACRIN Cancer Research Group Trials, 1980-2008. *J Clin Oncol* **34**, 3544-3553 (2016).
22. F. Stölzel *et al.*, The Prevalence of Extramedullary AML Detected By 18-FDG/PET-CT: Results from the Prospective PET-AML Trial. *Blood* **124**, 2270-2270 (2014).
  23. L. Angenendt *et al.*, Chromosomal Abnormalities and Prognosis in NPM1-Mutated Acute Myeloid Leukemia: A Pooled Analysis of Individual Patient Data From Nine International Cohorts. *J Clin Oncol*, Jco1900416 (2019).
  24. P. Ferguson *et al.*, An operational definition of primary refractory acute myeloid leukemia allowing early identification of patients who may benefit from allogeneic stem cell transplantation. *Haematologica* **101**, 1351-1358 (2016).
  25. J. J. Cornelissen *et al.*, The European LeukemiaNet AML Working Party consensus statement on allogeneic HSCT for patients with AML in remission: an integrated-risk adapted approach. *Nat Rev Clin Oncol* **9**, 579-590 (2012).
  26. M. Gerstung *et al.*, Precision oncology for acute myeloid leukemia using a knowledge bank approach. *Nat Genet* **49**, 332-340 (2017).
  27. S. D. Freeman *et al.*, Induction response criteria in acute myeloid leukaemia: implications of a flow cytometric measurable residual disease negative test in refractory adults. *Br J Haematol*, (2018).
  28. G. J. Schuurhuis *et al.*, Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. *Blood* **131**, 1275-1291 (2018).
  29. F. Buccisano *et al.*, Cytogenetic and molecular diagnostic characterization combined to postconsolidation minimal residual disease assessment by flow cytometry improves risk stratification in adult acute myeloid leukemia. *Blood* **116**, 2295-2303 (2010).
  30. W. Zeijlemaker *et al.*, Peripheral blood minimal residual disease may replace bone marrow minimal residual disease as an immunophenotypic biomarker for impending relapse in acute myeloid leukemia. *Leukemia* **30**, 708-715 (2016).
  31. S. D. Freeman *et al.*, Measurable Residual Disease at Induction Redefines Partial Response in Acute Myeloid Leukemia and Stratifies Outcomes in Patients at Standard Risk Without NPM1 Mutations. *J Clin Oncol* **36**, 1486-1497 (2018).
  32. M. Jongen-Lavrencic *et al.*, Molecular Minimal Residual Disease in Acute Myeloid Leukemia. *N Engl J Med* **378**, 1189-1199 (2018).
  33. F. Thol *et al.*, Measurable residual disease (MRD) monitoring by NGS before allogeneic hematopoietic cell transplantation in AML. *Blood* **132**, 1703-1713 (2018).
  34. U. Platzbecker *et al.*, Improved Outcomes With Retinoic Acid and Arsenic Trioxide Compared With Retinoic Acid and Chemotherapy in Non-High-Risk Acute Promyelocytic Leukemia: Final Results of the Randomized Italian-German APL0406 Trial. *J Clin Oncol* **35**, 605-612 (2017).
  35. D. Grimwade *et al.*, Prospective minimal residual disease monitoring to predict relapse of acute promyelocytic leukemia and to direct pre-emptive arsenic trioxide therapy. *J Clin Oncol* **27**, 3650-3658 (2009).
  36. S. Oberoi *et al.*, Leukapheresis and low-dose chemotherapy do not reduce early mortality in acute myeloid leukemia hyperleukocytosis: a systematic review and meta-analysis. *Leuk Res* **38**, 460-468 (2014).
  37. C. Rollig, G. Ehninger, How I treat hyperleukocytosis in acute myeloid leukemia. *Blood* **125**, 3246-3252 (2015).

38. I. Demeestere *et al.*, No Evidence for the Benefit of Gonadotropin-Releasing Hormone Agonist in Preserving Ovarian Function and Fertility in Lymphoma Survivors Treated With Chemotherapy: Final Long-Term Report of a Prospective Randomized Trial. *J Clin Oncol* **34**, 2568-2574 (2016).
39. S. Castaigne *et al.*, Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. *Lancet* **379**, 1508-1516 (2012).
40. J. Lambert *et al.*, Gemtuzumab ozogamicin for de novo acute myeloid leukemia: final efficacy and safety updates from the open-label, phase III ALFA-0701 trial. *Haematologica* **104**, 113-119 (2019).
41. R. K. Hills *et al.*, Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. *Lancet Oncol* **15**, 986-996 (2014).
42. J. E. Lancet *et al.*, CPX-351 (cytarabine and daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia. *J Clin Oncol*, Jco2017776112 (2018).
43. R. M. Stone *et al.*, Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. *N Engl J Med* **377**, 454-464 (2017).
44. R. F. Schlenk *et al.*, Gemtuzumab Ozogamicin in *NPM1*-Mutated Acute Myeloid Leukemia (AML): Results from the Prospective Randomized AMLSG 09-09 Phase-III Study. *Blood* **132**, 81-81 (2018).
45. J. Holowiecki *et al.*, Cladribine, but not fludarabine, added to daunorubicin and cytarabine during induction prolongs survival of patients with acute myeloid leukemia: a multicenter, randomized phase III study. *J Clin Oncol* **30**, 2441-2448 (2012).
46. A. K. Burnett *et al.*, Optimization of chemotherapy for younger patients with acute myeloid leukemia: results of the medical research council AML15 trial. *J Clin Oncol* **31**, 3360-3368 (2013).
47. M. Baccarani *et al.*, European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood* **122**, 872-884 (2013).
48. J. M. Rowe *et al.*, Adult patients with acute myeloid leukemia who achieve complete remission after 1 or 2 cycles of induction have a similar prognosis: a report on 1980 patients registered to 6 studies conducted by the Eastern Cooperative Oncology Group. *Cancer* **116**, 5012-5021 (2010).
49. E. Vellenga *et al.*, Autologous peripheral blood stem cell transplantation for acute myeloid leukemia. *Blood* **118**, 6037-6042 (2011).
50. R. F. Schlenk *et al.*, The value of allogeneic and autologous hematopoietic stem cell transplantation in prognostically favorable acute myeloid leukemia with double mutant CEBPA. *Blood* **122**, 1576-1582 (2013).
51. A. K. Burnett *et al.*, Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: results of the MRC AML15 trial. *J Clin Oncol* **29**, 369-377 (2011).
52. J. J. Cornelissen *et al.*, Results of a HOVON/SAKK donor versus no-donor analysis of myeloablative HLA-identical sibling stem cell transplantation in first remission acute myeloid leukemia in young and middle-aged adults: benefits for whom? *Blood* **109**, 3658-3666 (2007).
53. J. Koreth *et al.*, Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials. *JAMA* **301**, 2349-2361 (2009).

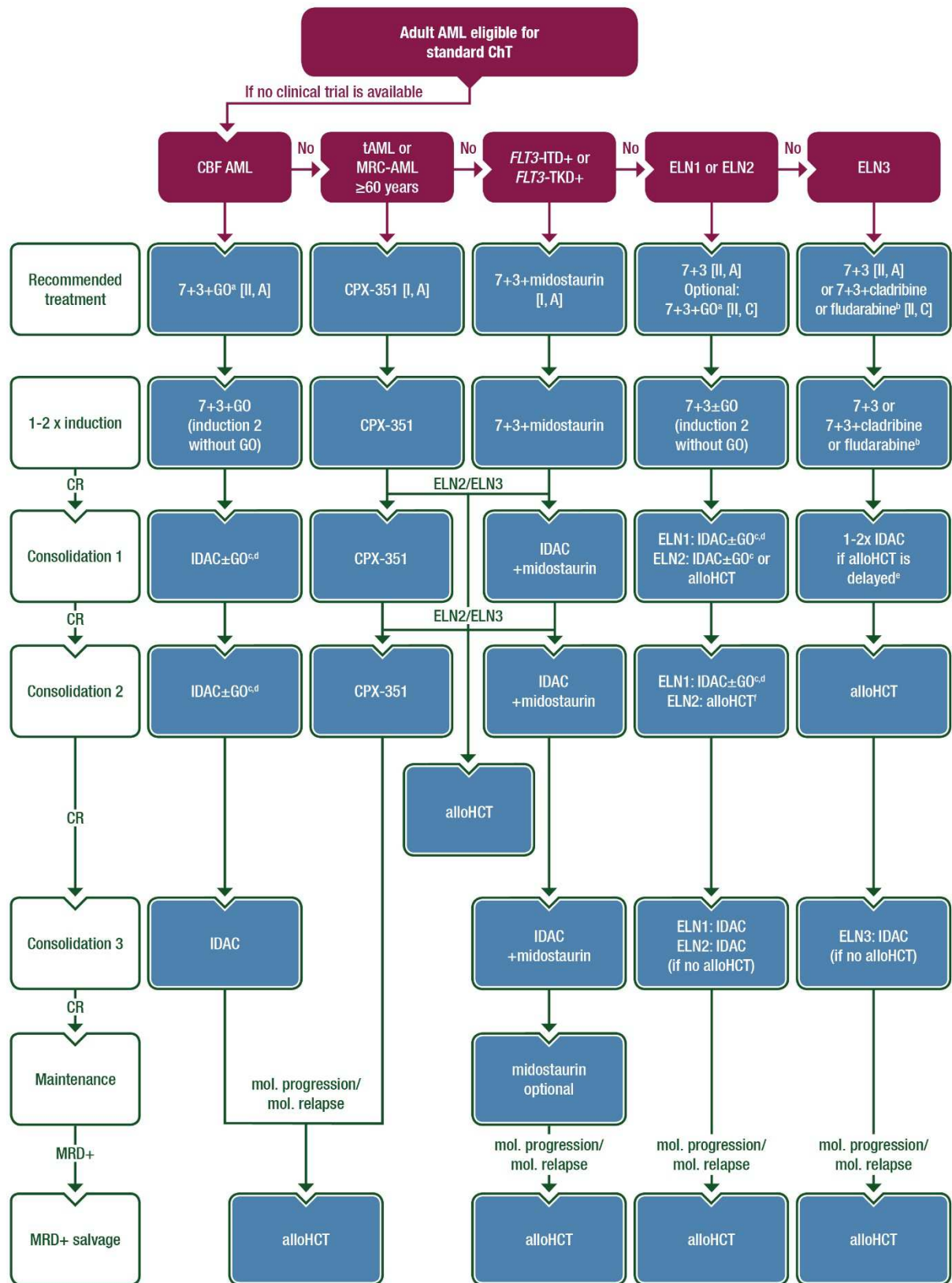
54. J. J. Cornelissen *et al.*, Comparative therapeutic value of post-remission approaches in patients with acute myeloid leukemia aged 40-60 years. *Leukemia* **29**, 1041-1050 (2015).
55. J. J. Cornelissen, D. Blaise, Hematopoietic stem cell transplantation for patients with AML in first complete remission. *Blood* **127**, 62-70 (2016).
56. N. C. Gorin *et al.*, Autologous stem cell transplantation for adult acute myelocytic leukemia in first remission-Better outcomes after busulfan and melphalan compared with busulfan and cyclophosphamide: A retrospective study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT). *Cancer* **123**, 824-831 (2017).
57. B. Lowenberg, Sense and nonsense of high-dose cytarabine for acute myeloid leukemia. *Blood* **121**, 26-28 (2013).
58. I. Cunningham, B. Kohno, 18 FDG-PET/CT: 21st century approach to leukemic tumors in 124 cases. *Am J Hematol* **91**, 379-384 (2016).
59. R. L. Bakst, M. S. Tallman, D. Douer, J. Yahalom, How I treat extramedullary acute myeloid leukemia. *Blood* **118**, 3785-3793 (2011).
60. R. F. Duarte *et al.*, Indications for haematopoietic stem cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2019. *Bone Marrow Transplant*, (2019).
61. N. S. Majhail *et al.*, Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant* **21**, 1863-1869 (2015).
62. J. Versluis *et al.*, Prediction of non-relapse mortality in recipients of reduced intensity conditioning allogeneic stem cell transplantation with AML in first complete remission. *Leukemia* **29**, 51-57 (2015).
63. T. M. Robinson, P. V. O'Donnell, E. J. Fuchs, L. Luznik, Haploidentical bone marrow and stem cell transplantation: experience with post-transplantation cyclophosphamide. *Semin Hematol* **53**, 90-97 (2016).
64. A. Ruggeri *et al.*, Comparison of outcomes after unrelated cord blood and unmanipulated haploidentical stem cell transplantation in adults with acute leukemia. *Leukemia* **29**, 1891-1900 (2015).
65. S. O. Ciurea *et al.*, Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia. *Blood* **126**, 1033-1040 (2015).
66. F. Milano *et al.*, Cord-Blood Transplantation in Patients with Minimal Residual Disease. *N Engl J Med* **375**, 944-953 (2016).
67. J. Canaani *et al.*, Donor age determines outcome in acute leukemia patients over 40 undergoing haploidentical hematopoietic cell transplantation. *Am J Hematol* **93**, 246-253 (2018).
68. B. L. Scott *et al.*, Myeloablative Versus Reduced-Intensity Hematopoietic Cell Transplantation for Acute Myeloid Leukemia and Myelodysplastic Syndromes. *J Clin Oncol* **35**, 1154-1161 (2017).
69. A. Rambaldi *et al.*, Busulfan plus cyclophosphamide versus busulfan plus fludarabine as a preparative regimen for allogeneic haemopoietic stem-cell transplantation in patients with acute myeloid leukaemia: an open-label, multicentre, randomised, phase 3 trial. *Lancet Oncol* **16**, 1525-1536 (2015).
70. Y. S. Jethava *et al.*, Conditioning regimens for allogeneic hematopoietic stem cell transplants in acute myeloid leukemia. *Bone Marrow Transplant* **52**, 1504-1511 (2017).
71. C. Craddock, Conditioning intensity in HCT for AML: the jury is still out. *Lancet Haematol* **5**, e132-e133 (2018).



72. T. Ruutu *et al.*, Prophylaxis and treatment of GVHD: EBMT-ELN working group recommendations for a standardized practice. *Bone Marrow Transplant* **49**, 168-173 (2014).
73. R. A. Larson *et al.*, An Analysis of Maintenance Therapy and Post-Midostaurin Outcomes in the International Prospective Randomized, Placebo-Controlled, Double-Blind Trial (CALGB 10603/RATIFY [Alliance]) for Newly Diagnosed Acute Myeloid Leukemia (AML) Patients with FLT3 Mutations. *Blood* **130**, 145-145 (2017).
74. G. Huls *et al.*, Azacitidine maintenance after intensive chemotherapy improves DFS in older AML patients. *Blood Advance online publication*, (2019).
75. A. H. Wei, LBA-3 The QUAZAR AML-001 Maintenance Trial: Results of a Phase III International, Randomized, Double-Blind, Placebo-Controlled Study of CC-486 (Oral Formulation of Azacitidine) in Patients with Acute Myeloid Leukemia (AML) in First Remission. (2019).
76. A. Burchert *et al.*, Sorafenib As Maintenance Therapy Post Allogeneic Stem Cell Transplantation for FLT3-ITD Positive AML: Results from the Randomized, Double-Blind, Placebo-Controlled Multicentre Sormain Trial. *Blood* **132**, 661-661 (2018).
77. R. F. Schlenk *et al.*, Midostaurin added to chemotherapy and continued single-agent maintenance therapy in acute myeloid leukemia with FLT3-ITD. *Blood* **133**, 840-851 (2019).
78. M. de Lima *et al.*, CC-486 Maintenance after Stem Cell Transplantation in Patients with Acute Myeloid Leukemia or Myelodysplastic Syndromes. *Biol Blood Marrow Transplant* **24**, 2017-2024 (2018).
79. U. Platzbecker *et al.*, Measurable residual disease-guided treatment with azacitidine to prevent haematological relapse in patients with myelodysplastic syndrome and acute myeloid leukaemia (RELAZA2): an open-label, multicentre, phase 2 trial. *Lancet Oncol* **19**, 1668-1679 (2018).
80. G. Orti *et al.*, Donor lymphocyte infusions in AML and MDS: Enhancing the graft-versus-leukemia effect. *Exp Hematol* **48**, 1-11 (2017).
81. H. Dombret *et al.*, International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood* **126**, 291-299 (2015).
82. H. M. Kantarjian *et al.*, Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. *J Clin Oncol* **30**, 2670-2677 (2012).
83. C. D. DiNardo *et al.*, Venetoclax combined with decitabine or azacitidine in treatment-naïve, elderly patients with acute myeloid leukemia. *Blood* **133**, 7-17 (2019).
84. J. E. Cortes *et al.*, Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. *Leukemia* **33**, 379-389 (2019).
85. N. J. Short *et al.*, A Randomized Phase II Trial of 5-Day Versus 10-Day Schedules of Decitabine for Older Patients with Previously Untreated Acute Myeloid Leukemia. *Blood* **130**, 2577-2577 (2017).
86. A. K. Burnett *et al.*, A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. *Cancer* **109**, 1114-1124 (2007).

87. C. D. DiNardo *et al.*, Clinical experience with the BCL2-inhibitor venetoclax in combination therapy for relapsed and refractory acute myeloid leukemia and related myeloid malignancies. *Am J Hematol* **93**, 401-407 (2018).
88. R. Ram *et al.*, Venetoclax in patients with acute myeloid leukemia refractory to hypomethylating agents-a multicenter historical prospective study. *Ann Hematol* **98**, 1927-1932 (2019).
89. A. E. Perl *et al.*, Gilteritinib or Chemotherapy for Relapsed or Refractory FLT3-Mutated AML. *N Engl J Med* **381**, 1728-1740 (2019).
90. D. Revesz *et al.*, Salvage by timed sequential chemotherapy in primary resistant acute myeloid leukemia: analysis of prognostic factors. *Ann Hematol* **82**, 684-690 (2003).
91. C. Craddock *et al.*, Factors predicting outcome after unrelated donor stem cell transplantation in primary refractory acute myeloid leukaemia. *Leukemia* **25**, 808-813 (2011).
92. C. Schmid *et al.*, Long-term survival in refractory acute myeloid leukemia after sequential treatment with chemotherapy and reduced-intensity conditioning for allogeneic stem cell transplantation. *Blood* **108**, 1092-1099 (2006).
93. D. A. Breems *et al.*, Prognostic index for adult patients with acute myeloid leukemia in first relapse. *J Clin Oncol* **23**, 1969-1978 (2005).
94. J. E. Megias-Vericat, D. Martinez-Cuadron, M. A. Sanz, P. Montesinos, Salvage regimens using conventional chemotherapy agents for relapsed/refractory adult AML patients: a systematic literature review. *Ann Hematol* **97**, 1115-1153 (2018).
95. A. K. Burnett *et al.*, Curability of patients with acute myeloid leukemia who did not undergo transplantation in first remission. *J Clin Oncol* **31**, 1293-1301 (2013).
96. M. Wattad *et al.*, Impact of salvage regimens on response and overall survival in acute myeloid leukemia with induction failure. *Leukemia* **31**, 1306-1313 (2017).
97. C. Schmid *et al.*, Donor lymphocyte infusion in the treatment of first hematological relapse after allogeneic stem-cell transplantation in adults with acute myeloid leukemia: a retrospective risk factors analysis and comparison with other strategies by the EBMT Acute Leukemia Working Party. *J Clin Oncol* **25**, 4938-4945 (2007).
98. C. Schmid *et al.*, Treatment, risk factors, and outcome of adults with relapsed AML after reduced intensity conditioning for allogeneic stem cell transplantation. *Blood* **119**, 1599-1606 (2012).
99. C. Craddock *et al.*, Clinical activity of azacitidine in patients who relapse after allogeneic stem cell transplantation for acute myeloid leukemia. *Haematologica* **101**, 879-883 (2016).
100. J. E. Cortes *et al.*, Quizartinib versus salvage chemotherapy in relapsed or refractory FLT3-ITD acute myeloid leukaemia (QuANTUM-R): a multicentre, randomised, controlled, open-label, phase 3 trial. *Lancet Oncol* **20**, 984-997 (2019).
101. M. Stahl *et al.*, Hypomethylating agents in relapsed and refractory AML: outcomes and their predictors in a large international patient cohort. *Blood advances* **2**, 923-932 (2018).
102. C. D. DiNardo *et al.*, Durable Remissions with Ivosidenib in IDH1-Mutated Relapsed or Refractory AML. *N Engl J Med* **378**, 2386-2398 (2018).
103. E. M. Stein *et al.*, Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. *Blood* **130**, 722-731 (2017).

104. A. T. Fathi *et al.*, Differentiation Syndrome Associated With Enasidenib, a Selective Inhibitor of Mutant Isocitrate Dehydrogenase 2: Analysis of a Phase 1/2 Study. *JAMA Oncol*, (2018).
105. A. M. Whittle, S. Feyler, D. T. Bowen, Durable second complete remissions with oral melphalan in hypocellular Acute Myeloid Leukemia and Refractory Anemia with Excess Blast with normal karyotype relapsing after intensive chemotherapy. *Leukemia research reports* **2**, 9-11 (2013).
106. M. A. Sanz *et al.*, Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet. *Blood* **133**, 1630-1643 (2019).
107. F. Lo-Coco *et al.*, Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. *N Engl J Med* **369**, 111-121 (2013).
108. A. K. Burnett *et al.*, Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a randomised, controlled, phase 3 trial. *Lancet Oncol* **16**, 1295-1305 (2015).
109. F. Lo-Coco *et al.*, Front-line treatment of acute promyelocytic leukemia with AIDA induction followed by risk-adapted consolidation for adults younger than 61 years: results of the AIDA-2000 trial of the GIMEMA Group. *Blood* **116**, 3171-3179 (2010).
110. H. J. Lland *et al.*, Use of arsenic trioxide in remission induction and consolidation therapy for acute promyelocytic leukaemia in the Australasian Leukaemia and Lymphoma Group (ALLG) APML4 study: a non-randomised phase 2 trial. *The Lancet. Haematology* **2**, e357-366 (2015).
111. F. Lo-Coco *et al.*, Gemtuzumab ozogamicin (Mylotarg) as a single agent for molecularly relapsed acute promyelocytic leukemia. *Blood* **104**, 1995-1999 (2004).
112. Y. Abaza *et al.*, Long-term outcome of acute promyelocytic leukemia treated with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab. *Blood* **129**, 1275-1283 (2017).
113. C. Ganzel *et al.*, Autologous transplant remains the preferred therapy for relapsed APL in CR2. *Bone Marrow Transplant* **51**, 1180-1183 (2016).
114. W. Y. Au, S. Tam, B. M. Fong, Y. L. Kwong, Determinants of cerebrospinal fluid arsenic concentration in patients with acute promyelocytic leukemia on oral arsenic trioxide therapy. *Blood* **112**, 3587-3590 (2008).





**Figure 1. Treatment algorithm for first-line treatment in newly diagnosed AML patients eligible for standard induction and consolidation treatment.**

The subgroups are sorted hierarchically from left to right and the recommendations are also prioritised from left to right.

<sup>a</sup>GO if blasts are CD33+.

<sup>b</sup>Cladribine or fludarabine optional in patients  $\leq 60$  years, not approved for AML.

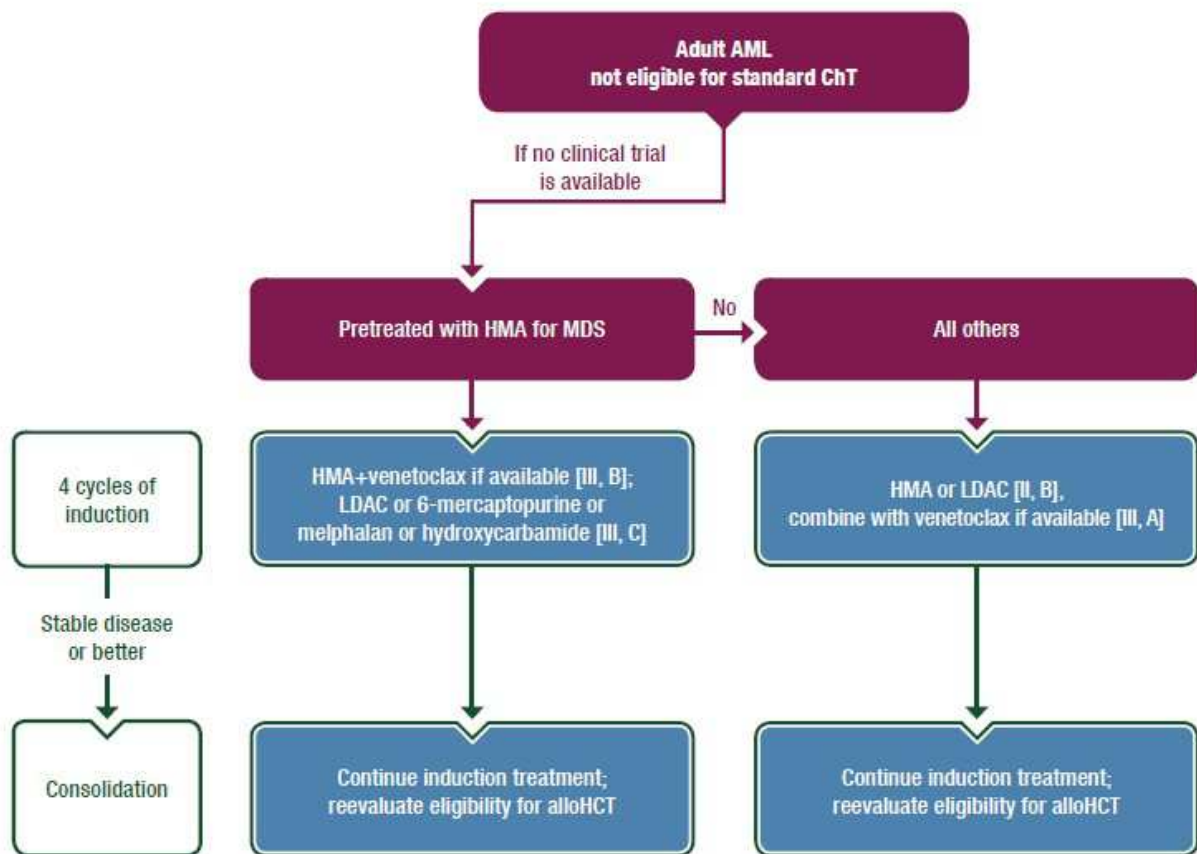
<sup>c</sup>GO optional in consolidation 1 and 2 of CD33+ CBF-, ELN1 and ELN2 patients, may restrict GO to patients <60-65 years.

<sup>d</sup>Alternatively autoHCT.

<sup>e</sup>Consider MACE/MIDAC if alloHCT is not possible [46].

<sup>f</sup>IDAC or autoHCT, if alloHCT is not feasible.

7+3, seven days of standard-dose cytarabine and three days of daunorubicin; 7+3+GO, seven days of standard-dose cytarabine, three days of daunorubicin and one to three days of gemtuzumab/ozogamicin; alloHCT, allogeneic haematopoietic cell transplantation; AML, acute myeloid leukaemia; autoHCT, autologous haematopoietic cell transplantation; CBF, core binding factor; ChT, chemotherapy; CPX-351, liposomal daunorubicin and cytarabine; CR, complete remission; GO, gemtuzumab-ozogamicin; MRC-AML, acute myeloid leukaemia with myelodysplasia-related cytogenetic changes; ELN1, 2, 3, European LeukaemiaNet favourable, intermediate and adverse risk, respectively; IDAC, intermediate-dose cytarabine; ITD, internal tandem duplication; MACE, amsacrine, cytarabine, etoposide; MIDAC, mitoxantrone, intermediate dose cytarabine; mol., molecular; MRD+, measurable residual disease-positive; tAML, therapy-related acute myeloid leukaemia; TKD, tyrosine kinase domain.

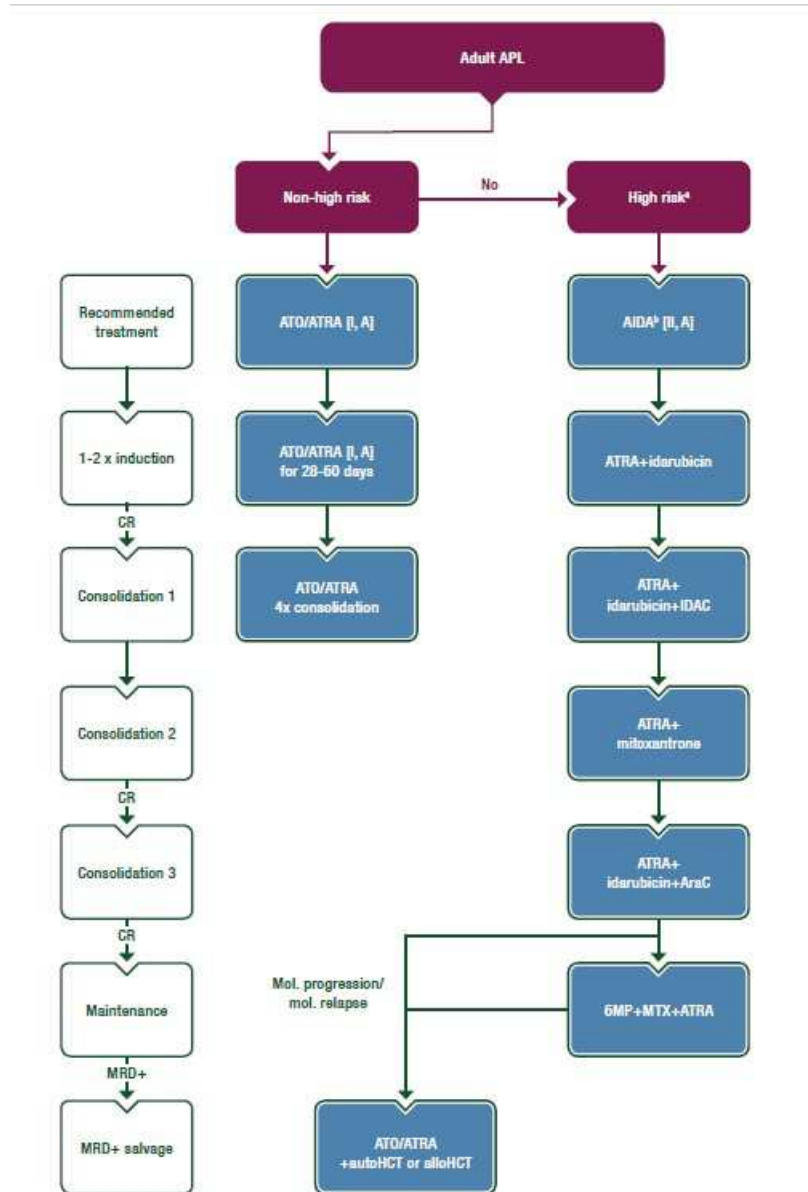


**Figure 2. Treatment algorithm for first-line treatment in newly diagnosed AML patients not eligible for standard induction and consolidation treatment.**

alloHCT, allogeneic haematopoietic cell transplantation; AML, acute myeloid leukaemia; ChT, chemotherapy; HMA, hypomethylating agent; LDAC, low-dose cytarabine; MDS, myelodysplastic syndrome.



infusion; HMA, hypomethylating agent; LDAC, low-dose cytarabine; PR, partial remission; R/R, relapsed/refractory; SD, stable disease.

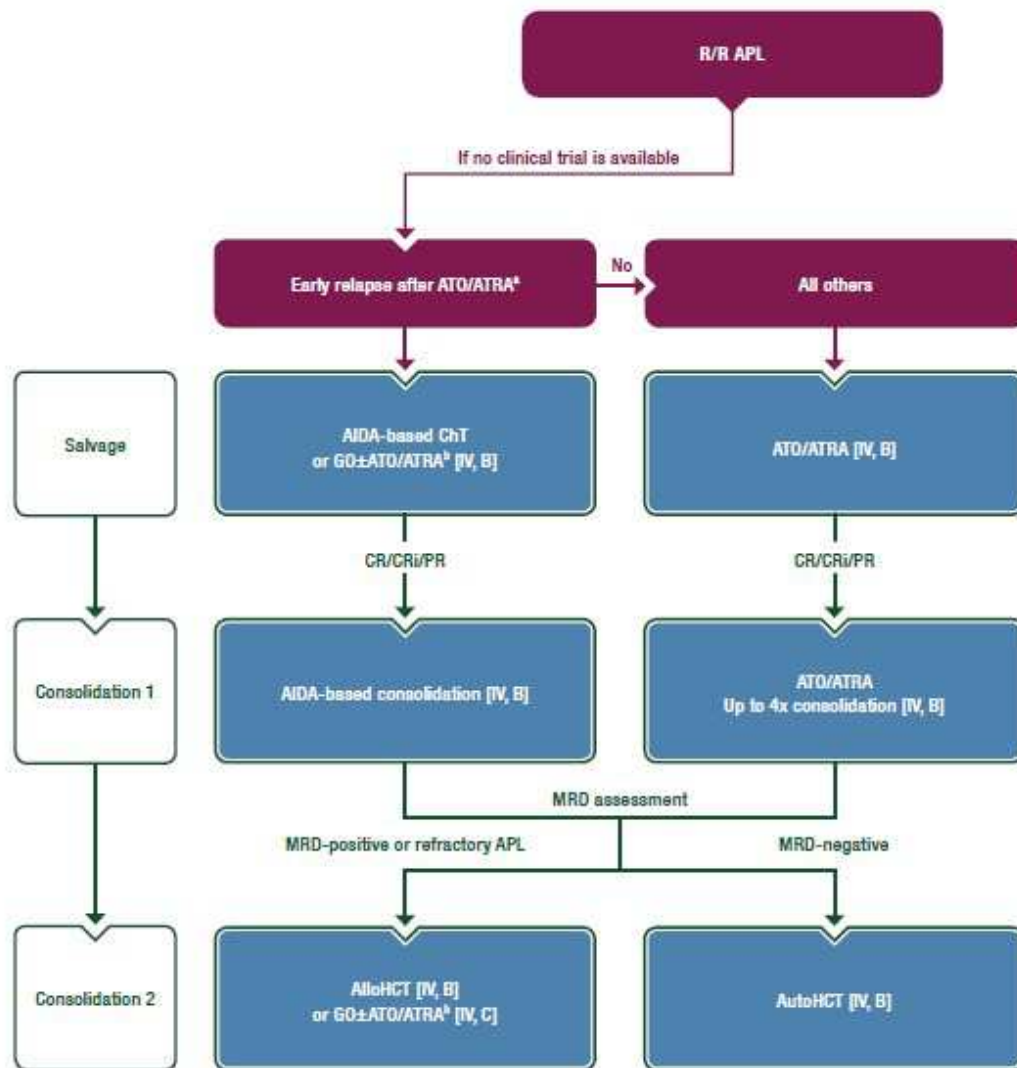


**Figure 4. Treatment algorithm for first-line treatment in newly diagnosed APL patients.**

<sup>a</sup>Defined by a WBC count  $>10 \times 10^9/L$ .

<sup>b</sup>Alternatively ATO/ATRA/ChT, but ATO is not approved for high-risk APL.

6MP, 6 mercaptopurine; AIDA, all-trans retinoic acid and idarubicin; alloHCT, allogeneic haematopoietic cell transplantation; autoHCT, autologous haematopoietic cell transplantation; APL, acute promyelocytic leukaemia; AraC, cytarabine; ATO, arsenic trioxide; ATRA, all-trans retinoic acid; ChT, chemotherapy; CR, complete remission; IDAC, intermediate-dose cytarabine; mol, molecular; MRD+, measurable residual disease-positive; MTX, methotrexate; WBC, white blood cell.



**Figure 5. Treatment algorithm for second-line treatment in relapsed/refractory APL patients**

<sup>a</sup>Early relapse is defined as relapse within 24 months after the end of the primary treatment.

<sup>b</sup>GO ± ATO/ATRA in patients who are unfit for alloHCT; GO is not approved in this indication.

AIDA, all-trans retinoic acid and idarubicin; alloHCT, allogeneic hematopoietic cell transplantation; APL, acute promyelocytic leukaemia; ATO, arsenic trioxide; ATRA, all-trans retinoic acid; autoHCT, autologous hematopoietic cell transplantation; ChT, chemotherapy; CR, complete remission; CRi, complete remission with incomplete haematological recovery; GO, gemtuzumab-ozogamicin; MRD, measurable residual disease; PR, partial remission; R/R, relapsed/refractory.

