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SPECIAL ARTICLE

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

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INCIDENCE AND EPIDEMIOLOGY

Acute myeloid leukaemia (AML) incidence is age dependent, rising markedly in patients aged ≥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 ∼70 years.[2]

The 2016 World Health Organization (WHO) classification identifies distinct categories of AML (see supplementary Table S1, available at *Annals of Oncology* online).[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 the years 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 ≥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, available at *Annals of Oncology* online, 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

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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 ≥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 diagnosis of dysplasia and MDS.[11]

The authors 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 while 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 an 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 LeukemiaNet (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 the 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 an 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, available at *Annals of Oncology* online). 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, available at *Annals of Oncology* online).[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 'Follow-up, long-term implications and survivorship' section in supplementary Material, available at *Annals of Oncology* online.

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 ≥3 and age ≥75 years are the strongest predictors for nonrelapse 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, available at *Annals of Oncology* online).[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*^{mut}) 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*^{mut}/*FLT3*-ITD^{low} patients have adverse cytogenetic aberrations, which confer an equally poor prognosis as adverse cytogenetics in *NPM1*^{wildtype} 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*^{mut} 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 postremission 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_{MRD-}) were proposed (supplementary Table S5, available at *Annals of Oncology* online). ELN MRD recommendations recently proposed CR with molecular persistence at low copy numbers (CR_{MRDlow}) to account for *NPM1* and core binding factor leukaemia patients with positive MRD at low copy numbers ($<100-200$ copies/10^4 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. The authors 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, it is recommended to use CR_{MRD-}, CR, CRi and MLFS.

The authors 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, patients are considered 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 ≥ 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*^{mut}, *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 nonclonal 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 preemptive therapy at the time of molecular relapse, prior to the occurrence of haematological relapse.

When to assess response?

The authors 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 days 28 and 35 if haematological recovery is still lacking.

Morphological assessment of BM is recommended 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. 3-monthly differential blood counts are recommended 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 nonintensively, 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 cell (WBC) count $>100 \times 10^9$/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 are 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 nonintensive treatment (see 'Classification and risk assessment' section). 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, the authors recommend following the algorithm in Figure 1, which prioritises the recommended treatments. Schedules and doses are detailed in supplementary Table S6, available at *Annals of Oncology* online. For CBF-AML, the authors 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

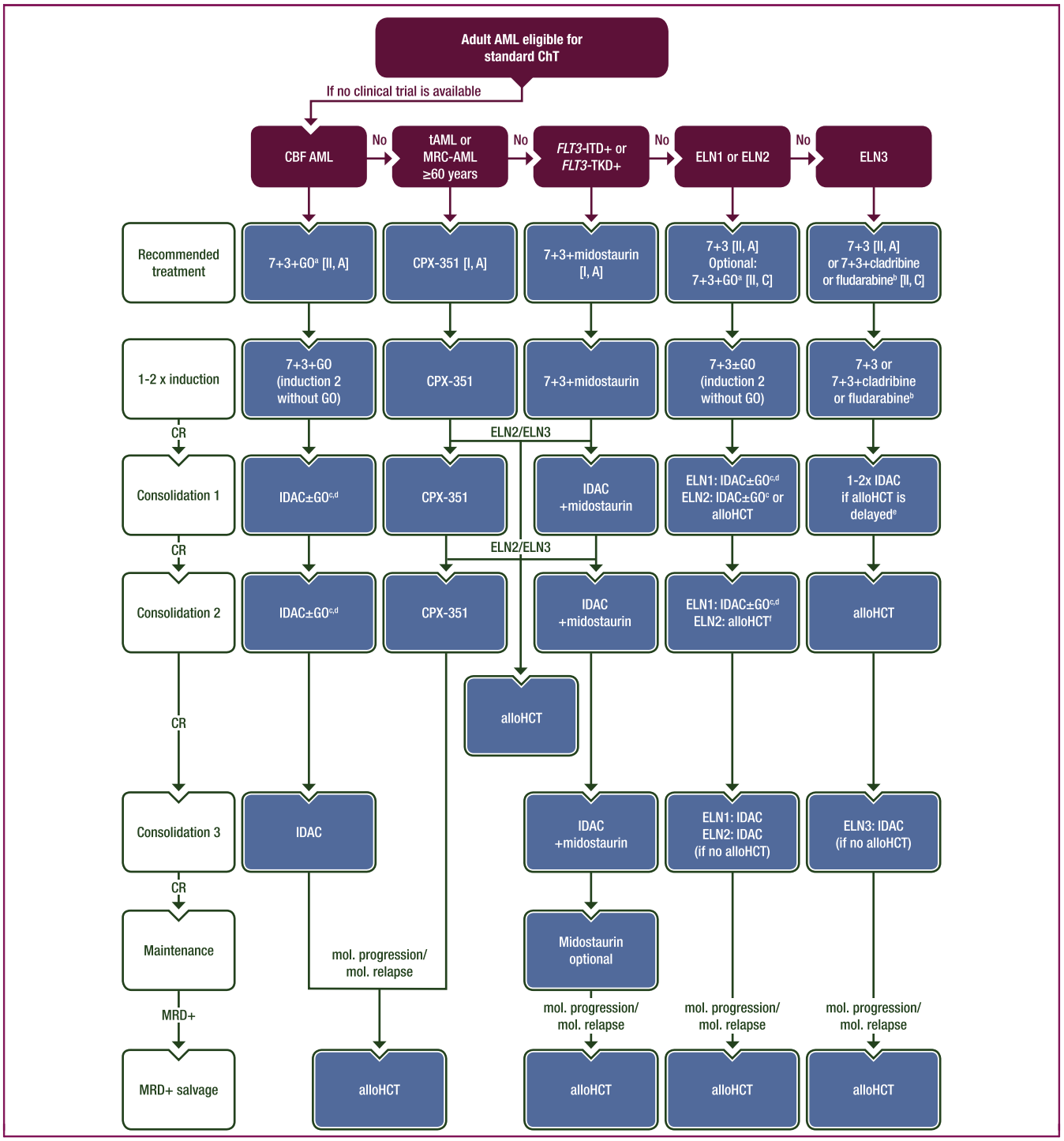

Figure 1. Treatment algorithm for first-line treatment in newly diagnosed AML patients eligible for standard induction and consolidation treatment.
7+3, 7 days of standard-dose cytarabine and 3 days of daunorubicin; 7+3+GO, 7 days of standard-dose cytarabine, 3 days of daunorubicin and 1–3 days of gemtuzumab 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; ELN1, 2, 3, European LeukaemiaNet favourable, intermediate and adverse risk, respectively; GO, gemtuzumab ozogamicin; IDAC, intermediate-dose cytarabine; ITD, internal tandem duplication; MACE, amsacrine, cytarabine, etoposide; MIDAC, mitoxantrone, intermediate dose cytarabine; mol., molecular; MRC-AML, acute myeloid leukaemia with myelodysplasia-related cytogenetic changes; MRD+, measurable residual disease-positive; tAML, therapy-related acute myeloid leukaemia; TKD, tyrosine kinase domain.
The subgroups are sorted hierarchically from left to right and the recommendations are also prioritised from left to right.
[a] GO if blasts are CD33+.
[b] Cladribine or fludarabine optional in patients ≤60 years; not approved for AML.
[c] GO optional in consolidation 1 and 2 of CD33+ CBF−, ELN1 and ELN2 patients; may restrict GO to patients <60–65 years.
[d] Alternatively autoHCT.
[e] Consider MACE/MIDAC if alloHCT is not possible.[39]
[f] IDAC or autoHCT, if alloHCT is not feasible.

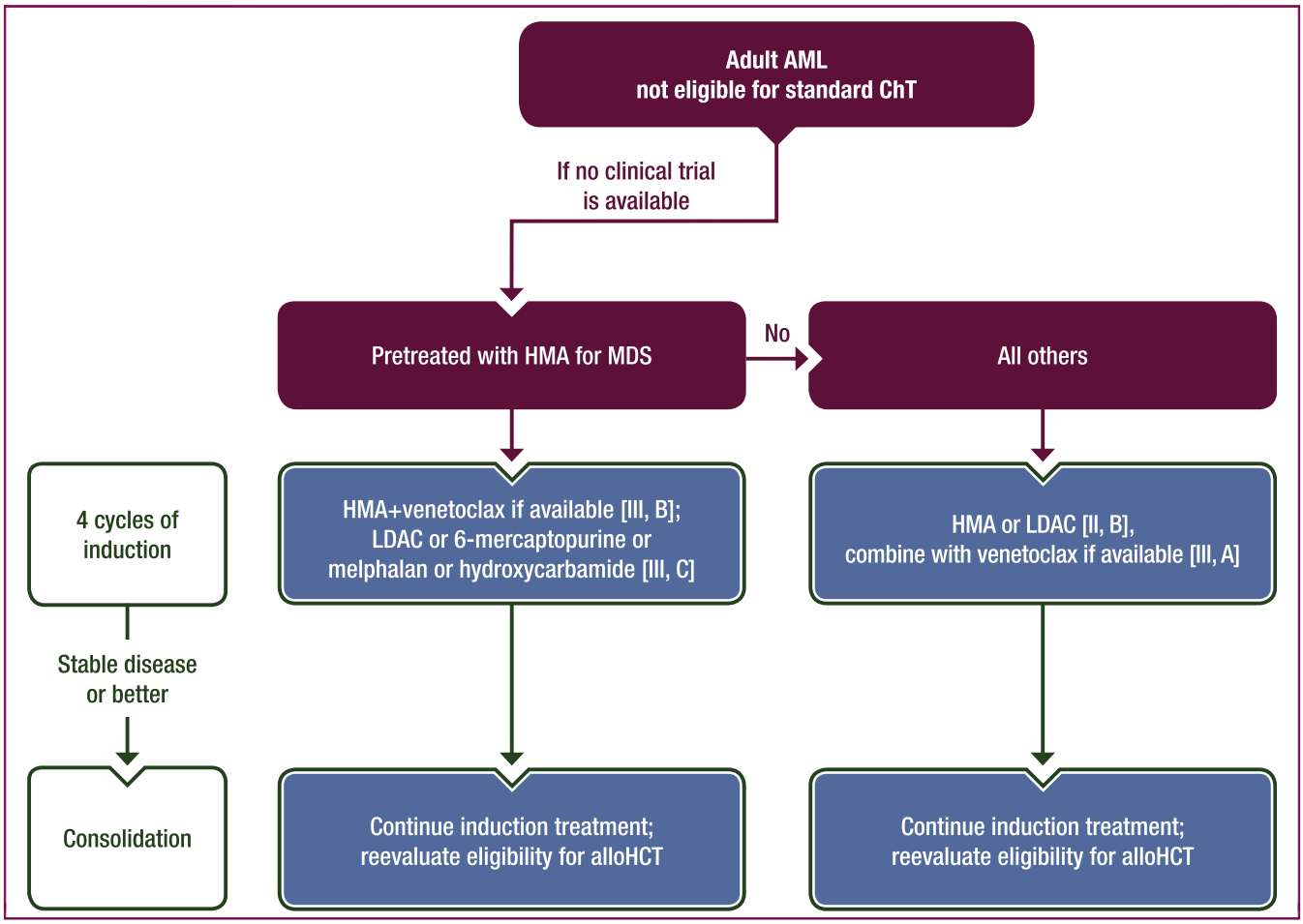

Figure 2. Treatment algorithm for first-line treatment in newly diagnosed AML patients not eligible for standard induction and consolidation treatment.
alloHCT, allogeneic haematopoietic cell transplantation; AML, acute myeloid leukaemia; ChT, chemotherapy; HMA, hypomethylating agent; LDAC, low-dose cytarabine; MDS, myelodysplastic syndrome.

(defined by ≥30% blasts expressing CD33 in the pivotal trial) in combination with 7 + 3 induction ChT in induction 1, but not in induction 2.[40,41] 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].[42] GO is approved as a fractionated dose of 3 mg/m^2 on days 1, 4 and 7 based on the ALFA-0701 trial.[40] However, the ALFA-0701 trial contributed only 3.6% of the patients with favourable-risk cytogenetics to the meta-analysis (9/251 patients).[40,42] The majority of patients with favourable-risk cytogenetics in the meta-analysis received only one dose of 3 mg/m^2 GO during induction cycle 1 (170/251 patients, 67.7%).[42] Thus, the optimal dose for GO remains to be determined. Because of 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 it is recommended not to delay transplantation if GO was administered within 8 weeks before alloHCT.

If tAML or MRC-AML is diagnosed in patients aged ≥60 years, treatment with liposomal daunorubicin and cytarabine (CPX-351) is recommended [I, A]. CPX-351 is approved for AML patients ≥18 years of age with tAML or MRC-AML and improved 2-year OS by 18.8% to 31.1% in patients aged ≥60 years.[43] 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.[43] CPX-351 is also recommended 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, 7 + 3 + midostaurin is recommended 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 ≥0.05) in

combination with 7 + 3 induction ChT. The addition of midostaurin improved OS by 7.1% after 4 years to 51.4%.[44]

If none of the previous markers is positive, 7 + 3 induction ChT is generally recommended [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].[42] A large randomised study failed to show an event-free survival (EFS) benefit of additional GO in *NPM1*^{mut} AML patients treated with induction ChT and ATRA.[45]

In the remaining patients with ELN adverse risk, 7 + 3 ChT is recommended [II, A] with the option to add cladribine or fludarabine to induction ChT in patients up to 60 years (though cladribine and fludarabine are not approved for this indication) [II, C].[46] 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].[39] There are limited data on the treatment of *BCR-ABL1*-positive AML. Tyrosine-kinase inhibitor (TKI)-naive patients should be treated with a second-line TKI with or without induction ChT [II, A].[47] Nonresponding patients should be treated with another TKI.

After the first induction cycle, response should be assessed between day 14 and day 21. Patients with ≥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), for example, FLAG-Ida [III, C]. As soon as patients achieve CR/CRi after 1 or 2 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 later. The optimal ChT backbone for induction therapy consisting of cytarabine and an anthracycline is further discussed in supplementary Material, available at *Annals of Oncology* online.

Consolidation treatment with ChT or autologous HCT. Patients in CR after induction ChT should undergo consolidation treatment with either ChT, autologous HCT (autoHCT) or alloHCT [I, A] (Figure 1). There are 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, 3 cycles with IDAC are recommended [II, B]. In CBF-AML patients, the addition of 3 mg/m^2 GO given on day 1 in consolidation 1 and 2 is 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.[43] In *FLT3*-mutated patients, midostaurin is combined with consolidation ChT and up to 3 consolidation cycles should be applied in patients not undergoing alloHCT.[44] 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, available at *Annals of Oncology* online).[40]

At least 2 consolidation cycles are recommended in CR patients not undergoing alloHCT with cytarabine 1.5 g/m^2 every 12 hours on days 1—3 in patients <60—65 years of age, and a dose reduction to 1 g/m^2 in patients aged ≥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].[39]

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, induction ChT followed by alloHCT is recommended (Figure 1). Individual reports show that local 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 AML and age ≤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 nonrelapse 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 aged $\geq$40 years, young donors are preferred, while in patients $<$40 years of age, neither the age of the donor nor the kinship has 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 of age, if no comorbidities are present.[68] In younger fit patients, the myeloablative fludarabine/busulfan (Flu/Bu4) regimen is associated with less toxicity than busulfan/cyclophosphamide (Bu/Cy).[69] Cy/TBI myeloablative regimens have been extensively used as a conditioning regimen in high-risk AML. However, there are 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, MAC is recommended for patients aged $\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 the recommendations for a standardised prophylaxis and treatment of GvHD by the EBMT-ELN working group on GvHD should be followed.[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, this treatment after ChT consolidation is not recommended [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 of age 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 $FLT3^{mut}$ 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, maintenance with HMAs cannot be recommended outside of clinical trials [V, D]. In BCR-ABL-positive patients, TKI maintenance after alloHCT is recommended [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); see supplementary Table S6, available at *Annals of Oncology* online, 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 aged $\geq$75 years or those with comorbidities that preclude use of intensive induction ChT,[84] their approval is pending in most European countries. Although venetoclax in combination with an HMA or LDAC is considered 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- 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*^{mut} patients.[85] Thus, if decitabine is chosen, it is recommended to follow 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 United States 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^{mut} 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] (Figure 3).[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, available at *Annals of Oncology* online.[94] Because of the limited long-term effects, enrolment in clinical trials is strongly recommended. The authors 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 (≥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 azacytidine, represent an important and less toxic alternative, particularly in patients relapsing >6 months after 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, the authors

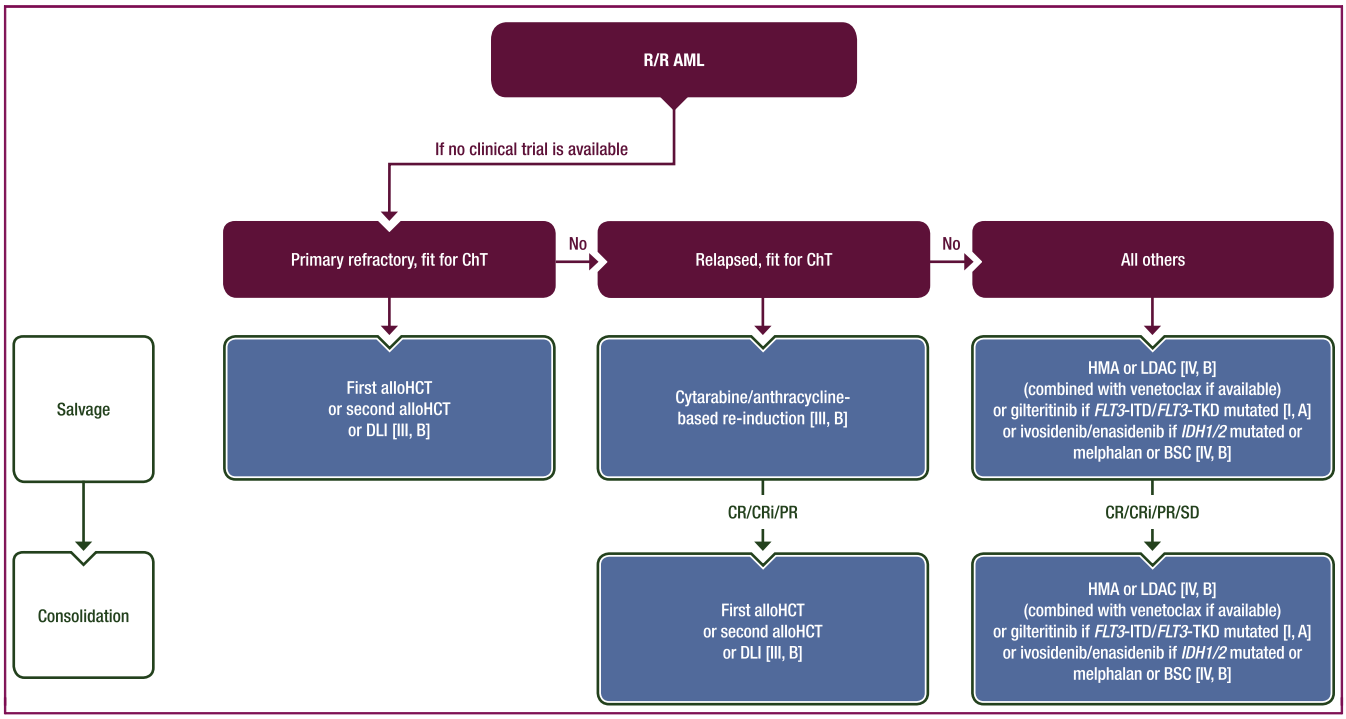

Figure 3. Treatment algorithm for second-line treatment in relapsed/refractory AML patients.
alloHCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukaemia; BSC, best supportive care; ChT, chemotherapy; CR, complete remission; CRi, complete remission with incomplete haematological recovery; DLI, donor lymphocyte infusion; HMA, hypomethylating agent; LDAC, low-dose cytarabine; PR, partial remission; R/R, relapsed/refractory; SD, stable disease.

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, B] (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*^{mut} 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

These recommendations largely follow the ELN APL treatment guidelines that were updated in 2019.[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 $\leq 10 \times 10^9$/l should be treated with ATO and ATRA (Figure 4 and supplementary Table S6, available at *Annals of Oncology* online) [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, available at *Annals of Oncology* online), 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.

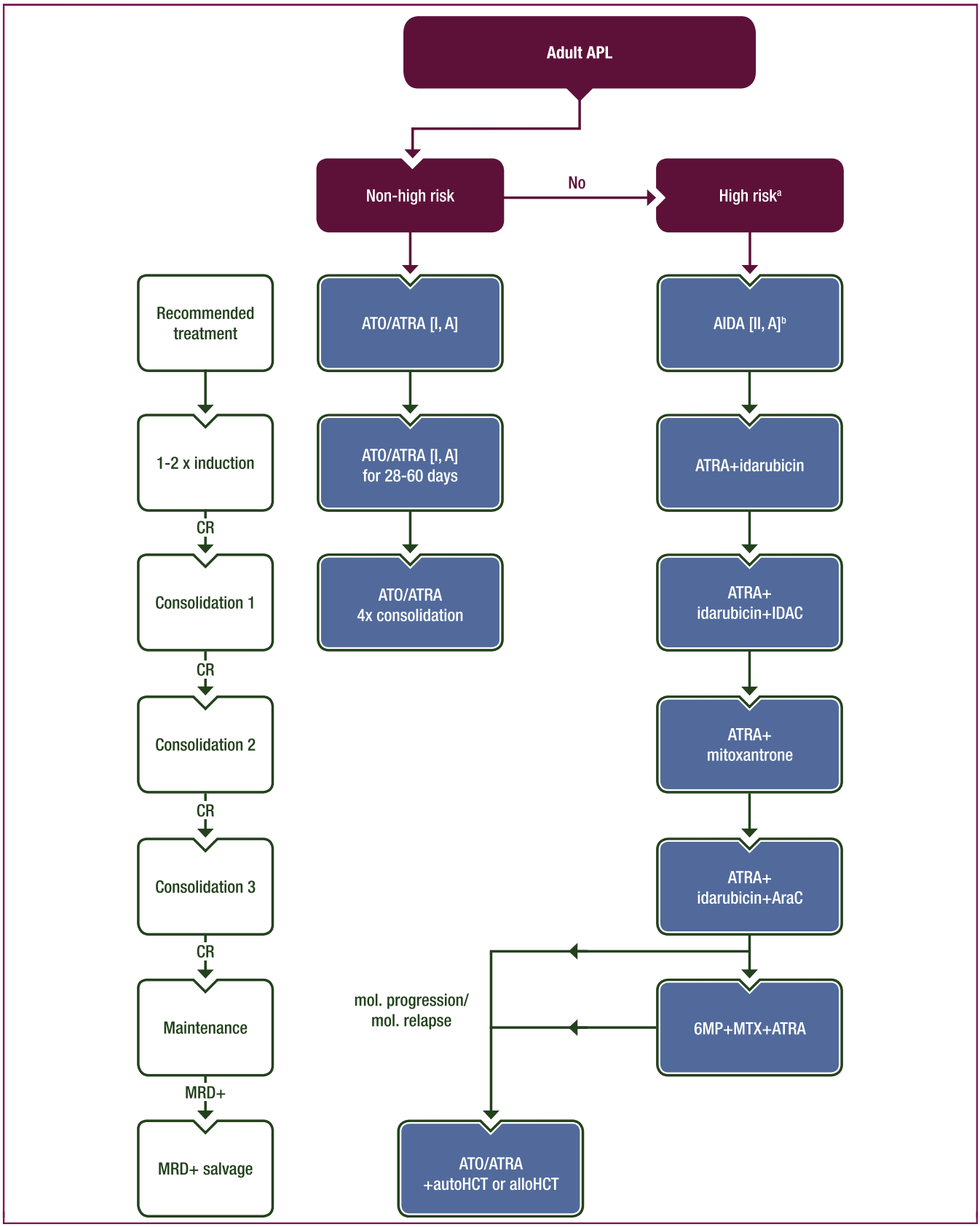

Figure 4. Treatment algorithm for first-line treatment in newly diagnosed APL patients.
6MP, 6 mercaptopurine; AIDA, all-*trans* retinoic acid and idarubicin; alloHCT, allogeneic haematopoietic cell transplantation; autoHCT, autologous haematopoietic cell transplantation; APL, acute promyelocytic leukaemia; 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.
[a] Defined by a WBC count $>10 \times 10^9$/l.
[b] Alternatively ATO/ATRA/ChT, but ATO is not approved for high-risk APL.

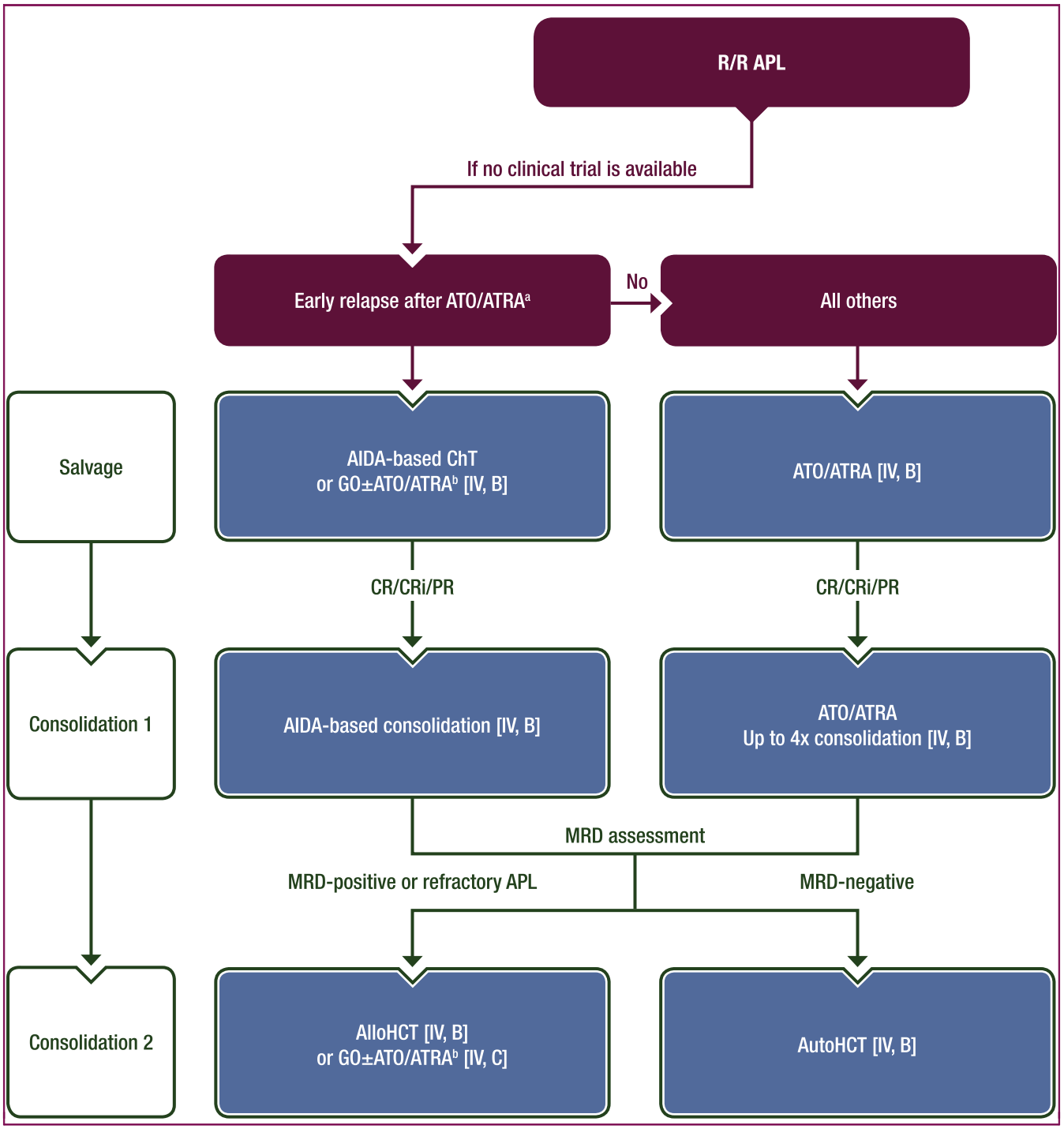

Figure 5. Treatment algorithm for second-line treatment in relapsed/refractory APL patients.
AIDA, all-*trans*-retinoic acid and idarubicin; alloHCT, allogeneic hematopoietic cell transplantation; APL, acute promyelocytic leukaemia; ATO, arsenic trioxide; ATRA, all-*trans*-retinoic acid; autoHCT, autologous 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.
[a] Early relapse is defined as relapse within 24 months after the end of the primary treatment.
[b] GO ± ATO/ATRA in patients who are unfit for alloHCT; GO is not approved in this indication.

APL high-risk patients defined by a WBC count >10 × 10^9/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, available at *Annals of Oncology* online). 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/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/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] Because of 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 uses of biomarkers for personalised diagnosis, prognostication and treatment are shown in supplementary Table S8, available at *Annals of Oncology* online.

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, available at *Annals of Oncology* online. Levels of evidence and grades of recommendation have been applied using the system shown in supplementary Table S10, available at *Annals of Oncology* online.[115] 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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